

PATENT SPECIFICATION

(11) 1 293 590

NO DRAWINGS

- (21) Application No. 55209/69 (22) Filed 11 Nov. 1969
 (21) Application No. 33211/70 (22) Filed 8 July 1970
 (23) Complete Specification filed 10 Nov. 1970
 (45) Complete Specification published 18 Oct. 1972
 (51) International Classification C07D 99/14; A61K 21/00 // C07C 119/16; C07D 41/04
 (52) Index at acceptance
 C2A 1C2A 1C2B 1C2C 2C1
 C2C 181—198—280 200 20Y 215 246 247 250 251 25Y
 290 29X 29Y 30Y 313 315 31Y 326 328 339 342
 34Y 364 366 368 36Y 372 379 3A13C10B 3A13C6C
 3A5C1C2 3A5H 440 561 566 581 624 62X 659 65Y
 73Y HA KQ KV MG NV QZ ZM

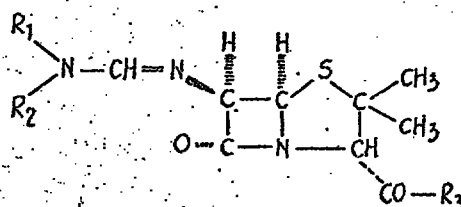
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(54) NEW PENICILLANIC ACID DERIVATIVES

(71) We, LØVENS KEMISKE FABRIK PRODUKTIONS-AKTIESELSKAB, a Company incorporated under the Laws of Denmark, of 2750 Ballerup, Denmark, 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 hitherto unknown derivatives of 6-aminopenicillanic acid, to pharmaceutically acceptable salts thereof, and to methods for the production of these new compounds.

The compounds of the invention have the general formula:



(I)

in which R_1 and R_2 each represent the same or different substituents and each represents an unsubstituted or substituted aliphatic hydrocarbon radical, a mono- or bicyclic aryl radical, an aralkyl radical, a cycloalkyl radical, a cycloalkyl-alkyl radical, a heterocyclic radical or a heterocyclically substituted alkyl radical, or R_1 and R_2 when taken together with the nitrogen atom represent a ring system; and R_3 represents a hydroxyl group, or a substituted hydroxyl group.

In particular, R_1 and R_2 may each represent an aliphatic hydrocarbon radical in which the carbon chain can be straight or branched, saturated or unsaturated, e.g. a methyl, ethyl, propyl, isopropyl, butyl, sec.butyl, tert.butyl, pentyl, hexyl, dodecyl, allyl, butenyl, pentenyl or propargyl radical; a mono- or bicyclic aryl radical, e.g. a phenyl or naphthyl radical; an aralkyl radical, such as a mono- or bicyclic aralkyl radical, e.g. a benzyl phenylethyl, or a 1- or 2-naphthylmethyl radical; a cycloalkyl or cycloalkyl-alkyl radical, in which the cycloalkyl group can have from 3 to 10 ring members and can be saturated or have one or two double bonds, e.g. a cyclopentyl, cyclohexyl, 1-adamantyl, 1-bicyclo(2,2,2)octyl, cyclopentenyl, cyclohexenyl, cyclopentylmethyl, cyclohexylmethyl, cyclopentenylethyl or cyclohexenylmethyl radical; a heterocyclic radical or a heterocyclically substituted alkyl radical in which the heterocyclic part may be fully or partly hydrogenated and can have from 5 to 10 atoms in the ring and can contain oxygen, sulphur, or nitrogen atoms, e.g. a pyridyl, pyrazinyl, pyrimidyl, pyrrolidyl, piperidyl, morpholinyl, thiazinyl, furyl, thienyl or quinolyl

radical, in all of which the hetero atoms may be placed in any of the available positions; R_1 and R_2 , when taken together with the nitrogen atom, may represent a saturated heterocyclic ring having from 5 to 9 carbon atoms optionally substituted with an alkyl group containing 1 to 6 carbon atoms or may represent a heterocyclic radical having from 5 to 10 atoms and optionally containing other hetero atoms in the ring, such as sulphur, oxygen or nitrogen, forming fully or partly hydrogenated ring systems, e.g. a piperidyl, morpholinyl, hexahydro-1H-azepin-1-yl, or hexahydro-1(2H)-azocinnyl radical. Preferably, R_1 and R_2 , taken together, represent a pentamethylene, hexamethylene or heptamethylene radical. The radicals R_1 and R_2 may be further substituted with one or more halogen atoms, or alkyl, hydroxy, alkoxy, alkylthio, acyl, carboxy, carbalkoxy, carbamyl, carbamido, cyano, sulphonyl, amino- or substituted amino radicals.

In particular, R_3 may represent a hydroxyl group, or a substituted hydroxyl group OR_4 , in which R_4 stands for an alkyl radical, an aryl radical, an aralkyl radical, a cycloalkyl-alkyl radical, an alkyl radical substituted with one or more halogen atoms, or alkoxy, alkanoyl, aroyl, cyano or carbalkoxy radicals, e.g. a methyl, ethyl, phenyl, benzyl, β,β,β -trichloroethyl, methoxymethyl, acetonyl, phenacyl, cyanomethyl, carbethoxymethyl, or dicarbethoxymethyl radical; R_4 may further represent an acyloxymethyl radical, the acyl part of which is an aliphatic, alicyclic, aromatic, ar-aliphatic or heterocyclic acyl radical, such as an acetyl, propionyl, butyryl, pivaloyl, cyclohexylacetyl, benzoyl, phenylacetyl, picolinyl, nicotinyl, furylacetyl or thienylacetyl radical. R_3 is preferably a hydroxyl group or an alkanoyloxymethoxy group, especially one having 3 to 8 carbon atoms.

The compounds of formula I may be isolated as such or in the form of a salt with a pharmaceutically acceptable acid, such as hydrochloric acid, phosphoric acid, nitric acid, p-toluenesulphonic acid, acetic acid, propionic acid, citric acid, tartaric acid or maleic acid. When R_3 stands for a hydroxyl group, the compounds of formula I may be isolated as the ammonium (zwitterion) or as a salt, e.g. an alkali metal salt or an ammonium or amine salt, or a salt with a strong acid.

The invention comprises all possible isomeric forms of the compounds of formula I, depending upon the different substituents, the 6-aminopenicillanic acid moiety having the configuration as obtained by a fermentation process.

The compounds of the present invention possess strong antibacterial activity, especially on gram-negative bacteria and the toxicity is extremely low. This effect is quite unexpected, since hitherto only derivatives of 6-amino-penicillanic acid substituted in the 6-amino group with an acyl group have shown an antibacterial effect. The effect on penicillin-sensitive, gram-positive bacteria is less than that of benzylpenicillin and α -aminobenzylpenicillin, whereas the effect on gram-negative bacilli, e.g. coli and salmonella species, is many times higher than that of e.g. benzyl penicillin and α -aminobenzylpenicillin. Table A below shows the antibacterial spectrum of 6-[(hexahydro-1H-azepin-1-yl)-methylencamino]-penicillanic acid, hydrochloride, dihydrate (in the Table called FL 1060) as compared with α -aminobenzylpenicillin (in the Table called Amp.) and benzylpenicillin (in the Table called G—Pen.). IC_{50} means the concentration required for 50% inhibition.

TABLE A

gram pos. and gram neg. strains	IC_{50} (μ g./ml.)		
	FL 1060	Amp.	G-Pen.
Staph. aureus, penicillin sensitive	5.0	0.025	0.016
— " — penicillinase producing	> 100	130	100
Diplococcus pneumoniae EA	3.2	0.01	0.01
Streptococcus pyogenes	0.50	0.013	0.008
Streptococcus faecalis E13	> 100	0.79	3.2

TABLE A — continued.

gram pos. and gram neg. strains	IC ₅₀ (ag./ml.)		
	FL 1060	Amp.	G-Pen.
<i>Corynebacterium xerosis</i> FF	1.6		0.013
<i>Listeria Monocytogenes</i> FT	50	0.10	0.10
<i>Erysipelothrix insidiosa</i> FU	20	0.040	0.025
<i>Bacillus subtilis</i> KA2	5.0	0.025	0.010
—, — <i>megatherium</i> KD	0.50		0.016
<i>Pseudomonas aeruginosa</i>	>100	>100	>100
<i>Vibrio comma</i>	0.40	0.40	0.79
<i>Alcaligenes faecalis</i>	0.63	0.50	1.6
<i>Escherichia coli</i> , average of 36 strains	0.089	2.2	32
—, — HA2 Leo Strain	0.016	2.0	32
<i>Klebsiella pneumoniae</i> , average of 12 strains	0.65	26	29
<i>Proteus</i> , average of 8 strains	0.23	1.3	5.4
<i>Salmonella paratyphi</i> A	0.13	0.4	3.2
—, — <i>schottmuelleri</i>	0.063	0.63	3.2
—, — <i>typhimurium</i>	0.063	0.50	2.5
—, — <i>abortusovae</i>	0.040	0.25	2.5
—, — <i>hirschfeldii</i>	0.016	0.079	0.13
—, — <i>chlorerae</i>	0.16	0.32	1.6
—, — <i>typhosa</i>	0.079	0.32	2.0
—, — <i>enteritidis</i>	0.16	0.40	2.5
<i>Shigella dysenteriae</i>	0.16	0.63	5.0
—, — <i>flexneri</i>	0.050	0.79	10

* In Table B below the activity of a number of the compounds of the invention against the Escherichia coli HIA2 Leo strain of Table A is shown:

TABLE B

Example No.	R ₁	R ₂	R ₃	IC ₅₀ µg./ml.
16	ethyl	ethyl	OH	0.10
18	ethyl	iso-propyl	OH	0.05
23	methyl	cyclo-pentyl	OH	0.05
24	methyl	cyclo-hexyl	OH	0.13
28	methyl	benzyl	OH	0.50
	• R ₁ R ₂ N—			
37	piperidyl-1		OH	0.05
40	4-methyl-piperidyl-1		OH	0.05
41	2,6-dimethyl-piperidyl-1		OH	0.08
44	hexahydro-1 (2H)-azocinnyl		OH	0.016

The compounds of Table B are obtained by enzymatic hydrolysis of the corresponding esters described in the Examples mentioned by treatment with a 20 per cent mouse serum at 37°C. for 90 minutes.

These *in vitro* experiments indicate activities up to 2000 times the activity of benzylpenicillin and 100 times the activity of α-amino-benzylpenicillin on coli bacteria, and for salmonella bacteria the corresponding figures are 50 times and 10 times, respectively. For certain medical purposes it will be advantageous to use the free acids or their salts, whereas it for other purposes will be more favourable to use the easily hydrolyzable esters, which in the organism will be chemically or enzymatically hydrolyzed to the corresponding free acids. In other cases, the less hydrolyzable esters will be preferred in order to obtain particular distribution in the body.

For instance, in some cases acyloxymethyl esters are absorbed more efficiently after oral administration than the corresponding free acids. After absorption, these esters are hydrolyzed under the influence of enzymes present in the blood and tissues with the liberation of the corresponding free acids, which generally have a more pronounced antibacterial activity than the esters.

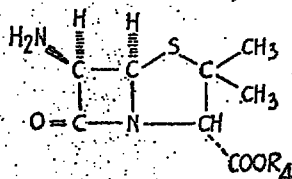
The toxicity of the compounds is, as mentioned before, very low. When 600 mg./kg. of pivaloyloxymethyl 6-[(hexahydro-1H-azepin-1-yl)-methylenecamino]-penicillanate were given orally to rats for 55 days or 200 mg./kg. of that compound were given orally to dogs for 47 days, no toxic symptoms were observed on macroscopic, biochemical or haematological examinations.

The invention also comprises methods for the preparation of the above described compounds. In one method, the compounds are prepared by reacting a reactive derivative of an amide or a thioamide of the general formula II:



in which R₁ and R₂ have the meanings defined before and R₃ is an oxygen or sulphur

atom, with a 6-aminopenicillanic acid derivative of the general formula III:



(III)

in which R_4 has the meaning defined before, or with a silyl ester of 6-aminopenicillanic acid. In the latter case, the reaction must be followed by a solvolysis to provide the compounds of the invention in which R_4 is OH, which also may be obtained by cleavage of the other esters.

The starting materials of formula II are known or can be prepared by conventional methods for preparing analogous compounds.

The amides of formula II can be transformed by well-known methods into reactive derivatives such as acid amide halides, acid amide dialkyl sulphate complexes or acid amide acetals. The acid amide halides are preferably the chlorides or bromides, and they can be prepared by treating the amides with halogenating agents. It is preferred to use halogenating agents which, throughout the reaction, form gaseous by-products, such as phosgene, oxalyl halides, or thionyl halides, but others may also be used. The reaction can be performed in an inert, dry, organic solvent, e.g. ether or toluene, in which the amide halide will in most cases be insoluble and from which it can be isolated by filtration after the reaction is completed. The acid amide halides are hygroscopic and rather unstable and are therefore preferably used in the next step without purification.

The acid amide dialkyl sulphate complexes can be prepared by treating the amides with a dialkyl sulphate, preferably dimethyl sulphate, under well-known conditions. By treating the acid amide dialkyl sulphate complexes with a sodium C_1 to C_6 alcoholate, e.g. sodium methoxide, acid amide acetals of the general formula II a:



in which R_1 and R_2 have the meanings defined above and R_6 is an alkyl group containing 1 to 6 carbon atoms, are formed, which acetals may also be used in the next step.

When acid thioamides are used as starting materials, a reactive derivative in form of an acid thioamide alkyl halide complex can be formed by treatment with an alkyl halide, e.g. a C_1 to C_6 alkyl iodide. This reaction is well known from the chemical literature.

The reaction conditions for the reaction between the amide derivative and the compound of formula III depend on the reaction components used in the process. When an acid amide acetal is used in the reaction with the compound of formula III, the reaction temperature depends upon the reaction components. The reaction is performed in inert organic solvent, for instance ether. When an acid amide halide, a dialkyl sulphate complex, or a thioamide alkyl halide complex is used, the reaction is also performed in an inert organic solvent, which is dry and free from traces of alcohol, preferably chloroform, in which the reaction components are soluble, but solvents in which the starting materials are insoluble, e.g. ether, may also be used. The reaction is performed with cooling and in the presence of at least one equivalent of a tertiary amine, for example trimethylamine, triethylamine, N,N-diisopropylethylamine or N-methylmorpholine. In the case where one equivalent of a tertiary amine is used, the reaction product will be obtained as a salt when an acid amide halide is used, and as an R_1, R_2 -amidinopenicillanic acid when a dialkyl sulphate complex or a thioamide alkyl halide complex is used. When two or more equivalents of the tertiary amine are used, an R_1, R_2 -amidinopenicillanic acid is obtained which can, if desired, be transformed into a salt.

The reaction time depends upon the reactants, the temperature and the solvents used in the process. In the case where R_3 stands for a hydroxyl group, it is preferred

to protect the carboxyl group as a trimethylsilyl ester or a dimethylsilyl diester which, after the reaction can easily be cleaved again. This reaction is preferably performed with an acid amide acetal reactant. The preparation of the silyl esters of 6-aminopenicillanic acid is known from the literature. The silyl esters of the amidinopenicillanic acid are preferably cleaved by hydrolysis or alcoholysis under mild conditions.

In another method, the compounds of the present invention can be prepared by reacting an amine of the formula HNR_1R_2 with a reactive derivative of a 6-formamidopenicillanic acid ester. Such a reactive derivative is for instance obtained by reacting a compound of formula III with a 1,1-dihalodimethyl ether, preferably 1,1-dichlorodimethyl ether, in the presence of a tertiary organic base. The reaction can be performed without isolation of the intermediate formed by the process, which in the example mentioned above is presumed to be a methoxymethylene derivative of the compound of formula III. The reactions are performed below or at room temperature and in the presence of an inert solvent, e.g. chloroform.

The reaction products of formula I can be purified and isolated in conventional manner and may be obtained either in the free state or in the form of a salt. The free acid ($\text{R}_3=\text{OH}$) can also be obtained from some of the esters by an enzymatic hydrolysis or a mild hydrogenolysis, and, if the free acid is the reaction product, the esters can be prepared therefrom by methods known from the literature.

Some of the compounds of formula III are known compounds and may be prepared by esterification of 6-aminopenicillanic acid or a protected 6-aminopenicillanic acid, such as the δ -trityl derivative thereof. The trityl group may be split off after the reaction under conditions not affecting the lactam ring. They can also be prepared by esterification of the generally industrially used penicillins, whereafter the acyl side chain can be split off chemically or enzymatically under such conditions that the ester group is not affected.

The compounds of formula I are well tolerated compounds. In the case where R_3 is a hydroxyl group the compounds are preferably used for parenteral administration in the form of an aqueous, sterile solution. In the case where esters are used, they are preferably administered orally either as such, or in form of one of their salts, and may be mixed with a solid carrier. In such compositions, the proportion of therapeutically active material to carrier substance can vary between 1% and 95%. The compositions can either be worked up to pharmaceutical forms of presentation such as tablets, pills or dragees, or can be filled in medical containers such as capsules, or, in the case of mixtures, can be filled into bottles. Pharmaceutical organic or inorganic solid or liquid carriers suitable for oral, enteral or topical administration can be used to make up the composition. Gelatine, lactose, starch, magnesium stearate, talc, vegetable and animal fats and oils, gum, polyalkylene glycol, or other known carriers for medicaments are all suitable as carriers. Furthermore, the compositions may contain other pharmaceutically active components which can appropriately be administered together with the compounds of the invention in the treatment of infectious diseases, such as other suitable antibiotics. Another object of the invention resides in the selection of a dose of the compounds of the invention which can be administered so that the desired activity is achieved without simultaneous secondary effects.

The compounds are conveniently administered in dosage units containing not less substance than corresponding to from 0.025 g. to 1 g. of the free acid of formula I ($\text{R}_3=\text{OH}$) and preferably to from 0.05 to 0.5 g. By the term "dosage unit" is meant a unitary, i.e. a single dose capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically stable unit dose, comprising either the active material as such or a mixture of it with a solid pharmaceutical carrier. A preferred preparation for oral treatment comprises from 10 to 50 mg. of a compound of the invention in the form of an ester which is hydrolysable in the human body per ml. of a carrier in which the compound is presented.

In the form of a dosage unit, the compound may be administered once or more times a day at appropriate intervals, always depending, however, on the condition of the patient.

Thus a daily dose will preferably amount to from 0.2 to 5.0 g. of the compound of the invention calculated as free acid.

The favourable high blood levels obtained after oral administration of a single dose of 200 mg. of pivaloyloxymethyl 6-[(hexahydro-1H-azepin-1-yl)-methylene-amino]-penicillanate hydrochloride in 200 ml. water to 4 fasting persons appear from Table C, in which the figures show the serum concentrations in $\mu\text{g./ml.}$ of the corresponding acid.

TABLE C

Person	µg. per ml. serum					Urinary excretion in per cent of administered dose		
	Hours							
	1/4	1/2	1	2	4	0—6	6—24	0—24
DR	3.2	6.4	4.2	1.7	0.34	43	6.6	50
GK	2.1	3.8	4.2	2.0	0.29	53	2.7	56
BB	2.1	3.8	3.5	1.6	<0.42	55	0.81	56
LT	2.1	5.1	3.3	1.3	0.34	45	1.1	46

The invention will be further described in the following non-limiting Examples:

Example 1.

Pivaloyloxymethyl 6-[(hexahydro-1H-azepin-1-yl)-methylenecarbamoyl]-penicillanate
12.7 g. of N-formylhexamethylencimine were dissolved in 250 ml. of dry ether. While stirring and cooling, 8.5 ml. of oxalyl chloride in 50 ml. of dry ether were added dropwise, whereafter the mixture was stirred overnight at room temperature. The precipitated amide chloride was filtered off and washed with dry ether, and was placed in an exsiccator.

27.5 g. of pivaloyloxymethyl 6-aminopenicillanate tosylate was suspended in 1500 ml. of ethyl acetate with continuous stirring and cooling in an ice bath and 950 ml. of ice-cold aqueous sodium bicarbonate (2 per cent) were added. The ethyl acetate layer was separated and was shaken with 750 ml. of ice-water containing 25 ml. of aqueous sodium bicarbonate (2 per cent), whereafter it was dried over magnesium sulphate at 0°C. After filtration, the solution was evaporated to dryness *in vacuo*. The residue was dissolved in a solution of 15.5 ml. of dry triethylamine in 75 ml. of dry alcohol-free chloroform. To this solution, 10 g. of the above prepared amide chloride dissolved in 75 ml. of dry alcohol-free chloroform were added dropwise at a temperature of about -20°C. After standing for half an hour at -20°C., the temperature was raised to 0°C. within 15 minutes and the solution was evaporated to dryness *in vacuo*. The residue was stirred with 750 ml. of ether. Undissolved triethylamine hydrochloride was filtered off, and the filtrate was again evaporated to dryness *in vacuo*. The residue was reprecipitated from acetone (200 ml.) — water (150 ml.). After recrystallization from cyclohexane an analytically pure product was obtained with a melting point of 118.5—119.5°C. and $[\alpha]_D^{20}$: +231° (c=1, 96% ethanol).

The starting material N-formylhexamethylencimine was prepared from hexamethylencimine and chloral and had a boiling point of 111—112°C./10 mm Hg.

Example 2.

Pivaloyloxymethyl 6-(N,N-dimethylformamidino-N')-penicillanate hydrochloride.
5.8 g. of chlorodimethylformiminium chloride were dissolved in 40 ml. of dry alcohol-free chloroform. At a temperature of -30° to -40°C., this solution was added dropwise to a solution of 13.3 g. of pivaloyloxymethyl 6-aminopenicillanate and 12.4 ml. of triethylamine in 75 ml. of dry, alcohol-free chloroform while stirring. The temperature was raised to 0°C. within 1 hour. The solution was evaporated *in vacuo* and the residue was treated with 200 ml. of dry ether. After filtration from triethylamine hydrochloride, the filtrate was evaporated *in vacuo*. The oily residue was dissolved in 40 ml. of isopropanol. At 0°C. and while stirring, 4 ml. of a solution of dry hydrogen chloride in isopropanol (9N) was added dropwise. Thereafter 150 ml. of ether was added. After filtration, washing with ether and recrystallization from acetone-ether, the compound was obtained in analytically pure form having a melting point of 146°C. $[\alpha]_D^{20}$: +209° (c=1, 96% C₂H₅OH).

Example 3.

Pivaloyloxymethyl 6-[(hexahydro-1H-azepin-1-yl)-methyleneamino]-penicillanate.

To a solution of pivaloyloxymethyl 6-aminopenicillanate (3.3 g.) and triethylamine (2.8 ml.) in dry chloroform (35 ml.) was added 1,1-dichlorodimethyl ether (1.1 g.) at 0°C. After 20 hours at room temperature, 1.1 ml. of hexamethyleneimine was added and the solution was kept at 0°C. overnight. The solution was evaporated *in vacuo* and the residue was triturated with water (75 ml.). The aqueous phase was removed by decantation. The residue was dissolved in dilute hydrochloric acid (pH~3) and filtered and the filtrate was made alkaline with sodium bicarbonate (pH~7.5). The precipitate was sucked off and was washed with water to yield a product with a melting point of 117–119°C. The IR spectrum was identical with that of the product of Example 1.

Example 4.

Cyanomethyl 6-(N,N-diethylformamidino-N')-penicillanate oxalate.

A. *Cyanomethyl 6-aminopenicillanate p-toluenesulphonate.*

To a stirred suspension of 6-aminopenicillanic acid (43.3 g.) in dimethylformamide (400 ml.) at room temperature was added triethylamine (35 ml.) and chloroacetonitrile (25.5 ml.), and stirring was continued at room temperature for 24 hours. The mixture was diluted with 400 ml. of ethyl acetate and filtered; and the solid was washed with ethyl acetate. The filtrate was diluted with 800 ml. of ethyl acetate, extracted four times with 200 ml. of water and dried over magnesium sulphate. After filtration an 0.5 M solution of p-toluenesulphonic acid in ethyl acetate (320 ml.) was added with stirring. The precipitate was filtered off and washed with ethyl acetate and ether. Recrystallization from methanol-ethyl acetate afforded a colourless analytically pure product, melting at 154.5–156°C. (dec.) $[\alpha]_D^{25}$: +146° (c=1, 96% C₂H₅OH).

B. *Chlorodiethylformiminium chloride.* 1.7 ml. of oxalyl chloride dissolved in 10 ml. of dry ether were slowly added to a solution of 2.2 ml. of diethylformamide in 50 ml. of dry ether at 0°C. with stirring. After stirring at room temperature for 3/4 hour, the precipitate was quickly filtered with suction, washed with dry ether and stored in an exsiccator.

C. *Cyanomethyl 6-(N,N-diethylformamidino-N')-penicillanate oxalate.* Cyanomethyl 6-aminopenicillanate was liberated from 4.7 g. of its p-toluenesulphonate according to the procedure of Example 1 and dissolved in 15 ml. of dry, alcohol-free chloroform. Dry triethylamine (3.1 ml.) was added and the solution was cooled to -30°C. A solution of 1.7 g. of crude amide chloride from step B in 15 ml. of dry, alcohol-free chloroform was slowly added at -20°C. to -30°C., with stirring. In the course of 3/4 hour the temperature was allowed to rise to 0°C. The solution was evaporated *in vacuo* and the residue triturated with 200 ml. of ether. After filtration and evaporation *in vacuo* of the filtrate, the residue was dissolved in 200 ml. of ether and treated with "Dicalite" (Registered Trade Mark) filter aid (diatomaceous earth). A solution of 0.85 g. of anhydrous oxalic acid in 50 ml. of ether was slowly added to the filtrate with stirring. When the precipitate had settled, the supernatant liquor was decanted and the precipitate stirred with fresh ether. After filtration, the product was recrystallized twice from acetone-ether to yield the analytically pure material melting at 121–122.5°C. $[\alpha]_D^{25}$: +214° (c=1, 96% C₂H₅OH).

Example 5.

γ -Phenylpropyl 6-[(hexahydro-1H-azepin-1-yl)-methyleneamino]-penicillanate hydrochloride

A. *γ -Phenylpropyl 6-aminopenicillanate.* To a stirred suspension of 6-aminopenicillanic acid (21.6 g.) in dimethylformamide (200 ml.), triethylamine (11.4 ml.) and γ -bromophenylpropane (22.0 g.) were added at room temperature, and stirring was continued at room temperature for 18 hours. 200 ml. of ethyl acetate were added and the mixture filtered. The filtrate was diluted with 400 ml. of ethyl acetate, extracted four times with 100 ml. of water and dried over magnesium sulphate. After evaporation *in vacuo*, the oily residue was dissolved in a mixture of water and ether (200 ml. of each) with stirring and ice-cooling. By slow addition of dilute hydrochloric acid, the pH was adjusted to 3 to 4. The aqueous phase was separated, made alkaline to a pH of about 7.5 by addition of sodium bicarbonate and extracted with ether. After drying, the ether was evaporated *in vacuo* to leave the crude ester as an oil.

B. γ -Phenylpropyl 6-[(hexahydro-1H-azepin-1-yl)-methylenecamino]-penicillanate hydrochloride. 2.2 g. of the crude ester and 2.0 ml. of dry triethylamine were dissolved in 15 ml. of dry, alcohol-free chloroform and cooled to -60°C . with stirring. A solution of 1.2 g. of the amide chloride described in Example 1 in 10 ml. of dry, alcohol-free chloroform was slowly added. The temperature was raised to 0°C . during 1 hour, whereupon the solution was evaporated *in vacuo*. After trituration with 80 ml. of ether, the solid formed was filtered off. The filtrate was extracted with 80 ml. of water with stirring and ice-cooling, while the pH of the aqueous phase was lowered to about 3. The aqueous phase was separated, made alkaline with sodium bicarbonate and extracted with ether. After drying, the ether was evaporated *in vacuo*. The oily residue was dissolved in 10 ml. of isopropanol and treated with 0.35 ml. of a solution of dry hydrogen chloride in isopropanol (9N), with stirring and ice-cooling. The precipitate was filtered off and washed with a little isopropanol. Two recrystallizations from methanol-ether yielded an analytically pure product melting at 163.5°C . $[\alpha]_{\text{D}}^{20} : +201$ ($c=1$, 96% $\text{C}_2\text{H}_5\text{OH}$).

Example 6.

6-[(Hexahydro-1H-azepin-1-yl)-methylenecamino]-penicillanic acid

A solution of the amide chloride described in Example 1 (4.6 g.) in dry, alcohol-free chloroform (20 ml.) was added slowly to a solution of trimethylsilyl 6-aminopenicillanate (7.2 g.) and triethylamine (3.5 ml.) in dry, alcohol-free chloroform (50 ml.) with stirring and cooling to -70°C . The temperature was raised to 0°C . during $1\frac{1}{2}$ hours. The solution was evaporated to dryness *in vacuo* and the residue was triturated with dry ether (200 ml.). The precipitate was filtered off and washed with dry ether. The filtrate was diluted with ether (200 ml.). 2-Butanol (2.8 ml.) was added dropwise with stirring and cooling to 0°C . The stirring was continued for $1/4$ hour at 0°C ., whereupon the precipitate was filtered off, washed with ether and dried. It was a white, amorphous powder, soluble in water. Paper chromatography was performed using the descending technique on "Whatman" (Registered Trade Mark) No. 1 paper with the solvent system n-butanol-ethanol-water (4:1:5). The R_f value was 0.5.

NMR spectrum (D_2O):

$\text{C}_6(\text{CH}_3)_2$	3 H	s	at 1.58
	3 H	s	at 1.71
$(\text{CH}_2)_4$	8 H	m	at 1.4—2.0
$\text{N}(\text{CH}_2)_2$	4 H	m	at 3.45—3.90
C_3H	1 H	s	at 4.34
C_5H	1 H	d	at 5.62, ($J=4.0$)
C_6H	1 H	d	at 5.47, ($J=4.0$)
$\text{N}-\text{CH}=\text{N}$	1 H	broad s	at 8.03

The chemical shifts are given as ppm in δ values with sodium 2,2,3,3-tetradeutero-3-trimethylsilylpropionate (0 ppm) as internal standard. Coupling constants (J) are in cps.

Example 7.

Butyl 6-(N,N-diethylformamidino-N')-penicillanate hydrochloride

A. Butyl 6-aminopenicillanate tosylate.

To a stirred suspension of 6-aminopenicillanic acid (21.7 g.) in dimethylformamide (200 ml.) at room temperature were added triethylamine (16.8 ml.), n-butyl bromide (21.4 ml.), and a catalytic amount of triethylammonium iodide. Stirring was continued at room temperature for 24 hours. Ethyl acetate (200 ml.) was added and the mixture filtered. The solid was washed with ethyl acetate. The filtrate was diluted

with ethyl acetate (400 ml.), extracted four times with water (100 ml.) and dried over magnesium sulphate. After evaporation *in vacuo*, the reddish oil was dissolved in water (250 ml.) with stirring and ice-cooling, the pH being adjusted to 3.5 by slow addition of dilute hydrochloric acid. The aqueous phase was separated, filtered, made alkaline to a pH of 7.5 by the addition of sodium bicarbonate and extracted with ether (200 ml.). After drying over magnesium sulphate, the ethereal phase was treated with a solution of p-toluenesulphonic acid (9.5 g.) in ether (250 ml.) with cooling and stirring. The precipitate was filtered off and washed with ether. The melting point of the crude product was 139–140°C.

B. Butyl 6-(N,N-diethylformamidino-N')-penicillanate hydrochloride.

Butyl 6-aminopenicillanate was liberated from 4.9 g. of the tosylate, according to the procedure of Example 1 for pivaloyloxymethyl 6-amino-penicillanate tosylate, and dissolved in 15 ml. of dry, alcohol-free chloroform. Dry triethylamine (3.1 ml.) was added and the solution cooled to -30°C . A solution of chlorodiethylformiminium chloride (1.7 g.) in chloroform (15 ml.) was slowly added at -20°C . to -30°C . with stirring. In the course of 3/4 hour the temperature was raised to 0°C . The solution was evaporated *in vacuo* and the residue triturated with ether (200 ml.). The triethylammonium chloride formed was filtered off and the filtrate evaporated *in vacuo*. The residue was dissolved in water (200 ml.) by the addition of dilute hydrochloric acid until a pH of about 3.5 was attained. After filtration with "Dicalite" filter aid, the pH was brought to 7.5 by the addition of sodium bicarbonate. The oily phase was extracted with ether (200 ml.), dried and evaporated *in vacuo*. To the residue in isopropanol (10 ml.), was added 1 ml. of dry hydrogen chloride in isopropanol (8.5 N) with cooling and stirring. Addition of ether (150 ml.) precipitated the hydrochloride with a melting point of 126–130°C. After recrystallizations from acetone-ether and isopropanol-ether the compound was obtained in analytically pure form having a melting point of 140.5–141°C.

$[\alpha]_{\text{D}}^{20}$: +241° (c=1, 96% $\text{C}_2\text{H}_5\text{OH}$).

Example 8.

Pivaloyloxymethyl 6-(N,N-dimethylformamidino-N')-penicillanate hydrochloride.

A solution of pivaloyloxymethyl 6-aminopenicillanate (3.3 g.) and 1,1-dimethoxytrimethylamine (1.2 g.) in ether (30 ml.) was slowly evaporated at room temperature for 1 hour and thereafter at 40°C . for 3 hours. The oily residue was dissolved in dilute hydrochloric acid (pH~3), filtered and the filtrate treated with sodium bicarbonate (pH~7.5). The liberated base was taken up in ether, which was dried and evaporated. To the oily residue dissolved in isopropanol (10 ml.) was added 0.36 ml. of dry hydrogen chloride (8.5 N) in isopropanol and thereafter ether (100 ml.). The precipitate had a melting point of 130–144°C. A recrystallization from acetone-ether raised the melting point to 143–146°C. The IR spectrum was identical with that of the product of Example 2.

Example 9:

Pivaloyloxymethyl 6-[(hexahydro-1H-azepin-1-yl)-methyleneamino]-penicillanate.

To a solution of pivaloyloxymethyl 6-aminopenicillanate (3.3 g.) and N,N-diisopropylethylamine (1.7 ml.) in dry chloroform (35 ml.) at 0°C . were added 2.5 g. of the N-formylhexamethylenimine-dimethyl sulphate complex prepared according to the method of Brederick et al. (Chem. Ber. 101, 41 (1968)). After 20 hour at $0-5^{\circ}\text{C}$., the solution was evaporated and the residue crystallized from acetone-water yielding a product with a melting point of 115–117°C. The IR spectrum was identical with that of the product of Example 1.

Example 10.

Pivaloyloxymethyl 6-[(hexahydro-1H-azepin-1-yl)-methyleneamino]-penicillanate hydrochloride.

The product of Example 9 (36 g.) was suspended in isopropanol (165 ml.) with stirring and ice-cooling. 9.7 ml. of a solution of dry hydrogen chloride (8.5 N) in isopropanol were added and the hydrochloride crystallized spontaneously from the resulting solution. Ether (350 ml.) was added. After filtration and recrystallization from methanol-diisopropyl ether an analytically pure product was obtained with a melting point of 172–173°C.

$[\alpha]_{\text{D}}^{20}$: +219° (c=1, N HCl).

Example 11.

Pivaloyloxymethyl 6[(hexahydro-1H-azepin-1-yl)-methyleneamino]-penicillanate hydroiodide.

To a solution of the hydrochloride of Example 10 (2.6 g.) in 15 ml. of water was added sodium iodide (0.8 g.) in water (5 ml.). The precipitate was sucked off, washed with water, and dried. After recrystallizations from isopropanol-ether and ethanol-ether the analytically pure product had a melting point of 153—154°C. $[\alpha]_D^{20}$: +182° (c=1, 96% C₂H₅OH).

Example 12.

β,β,β -Trichloroethyl 6-[(hexahydro-1H-azepin-1-yl)-methyleneamino]-penicillanate.

A. β,β,β -Trichloroethyl 6-aminopenicillanate hydrochloride. To a solution of phosphorus pentachloride (11.1 g.) in dry, alcohol-free chloroform (110 ml.) was added quinoline (12 ml. with stirring. At -20°C., β,β,β -trichloroethyl benzylpenicillanate (14.8 g.) was added and stirring was continued at -15°C. for 20 minutes. At -40°C., n-propanol (37 ml.) was added during 2—3 minutes. The temperature rose to -15°C. and was kept there for 15 minutes. The solution was poured onto a mixture of petroleum ether (330 ml.), saturated aqueous sodium chloride (88 ml.) and water (16 ml.), while stirring and cooling with ice-water. The mixture was seeded and stirred for 30 minutes. The aqueous phase was removed and the precipitate in the organic phase was isolated by filtration. After washing with a little isopropanol and with ether, the compound had $[\alpha]_D^{20}$: +153° (c=1, 0.1 N HCl). The analytically pure compound was obtained by liberating the free base with sodium bicarbonate and reprecipitating the salt with hydrogen chloride in isopropanol. After recrystallization from ethanol ether, it had a melting point of 153.5—155.5°C. $[\alpha]_D^{20}$: +160° (c=1, 0.1 N HCl).

B. β,β,β -Trichloroethyl 6-[(hexahydro-1H-azepin-1-yl)-methyleneamino]-penicillanate. A solution of the amide chloride described in Example 1 (1.0 g.) in pure chloroform (15 ml.) was added slowly to a solution of the above prepared crude ester (1.9 g.) and triethylamine (2.2 ml.) in pure chloroform (15 ml.) at -20°C. with stirring. The temperature was raised to 0°C. during 45 minutes, whereupon the solution was evaporated *in vacuo*. The residue was triturated with ether (100 ml.) and the solid formed was filtered off. The filtrate was evaporated *in vacuo* and the oily residue was triturated with water (50 ml.). The solid was isolated by filtration and recrystallized from acetone-water and isopropanol-water yielding an analytically pure product with a melting point of 99—101°C. $[\alpha]_D^{20}$: +214° (c=1, 96% C₂H₅OH).

Example 13.

6-(N,N-Di-n-butylformamidino-N')-penicillanic acid hydrate

A solution of N-(dimethoxymethyl)-dibutylamine (4.9 g.) in dry ether (100 ml.) was slowly added to a solution of trimethylsilyl 6-aminopenicillanate (7.0 g.) in ether (500 ml. at -30°C. with stirring. The temperature was raised to 0°C. during half an hour. Water (25 ml.) was added over 10 minutes. The aqueous phase was separated and the ethereal phase extracted with 25 ml. of water. The combined aqueous phases were freeze-dried. The solid product thus obtained was triturated with water (10 ml.) at 0°C., filtered and air-dried. It melted with decomposition at 106°C. and was analytically pure. $[\alpha]_D^{20}$: +261° (c=1, 0.1 N HCl).

Example 14

6-[(Hexahydro-1H-azepin-1-yl)-methyleneamino]-penicillanic acid hydrochloride dihydrate. A solution of benzyl 6-[(hexahydro-1H-azepin-1-yl)-methyleneamino]-penicillanate hydrochloride (4.3 g.) in methanol (70 ml.) was hydrogenated with palladium on charcoal catalyst (10%, 4.3 g.) at room temperature and under one atmosphere of hydrogen for 21 minutes. After filtration of the catalyst, the filtrate was evaporated *in vacuo*. The oily residue was dissolved in 95% isopropanol (28 ml.). After filtration with "Dicalite" filter aid and washing with isopropanol (15 ml.), diisopropyl ether (50 ml.) was added. The precipitate was filtered off, washed with diisopropyl ether, and air-dried. The melting point was 87—89°C. (dec.). $[\alpha]_D^{20}$: +238° (c=1, H₂O).

Example 15.

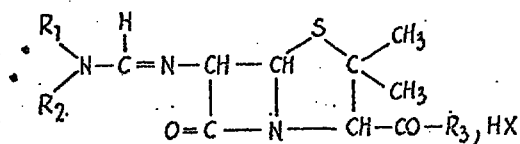
Pivaloyloxymethyl 6-[(hexahydro-1H-azepin-1-yl)-methyleneamino]-penicillanate.

A. *Methyl iodide complex of N-thioformylhexamethyleneimine.* To a solution of N-thioformylhexamethyleneimine (2.9 g.) in dry ether (10 ml.) was added methyl iodide (1.4 ml.) with stirring and cooling. The suspension formed was stirred for half an hour and filtered. The precipitate was washed with ether and placed in an exsiccator. The melting point of the crude product was 120—122°C.

B. *Pivaloyloxymethyl 6-[(hexahydro-1H-azepin-1-yl)-methyleneamino]-penicillanate.* To an ice-cold solution of pivaloyloxymethyl 6-aminopenicillanate (3.3 g.) and N,N-diisopropylethylamine (1.7 ml.) in pure chloroform (35 ml.) was added the above-prepared iodide (2.9 g.). After 20 hours at 0—5°C. the solution was evaporated *in vacuo* and the residue crystallized from acetone-water yielding a product with a melting point of 119—120°C. The IR spectrum was identical with that of the product of Example 1.

Examples 16 to 47

Following procedures analogous to those described in the foregoing Examples 1, 2, 4, 5, 7 and 12, the compounds of Table I according to formula V were obtained, either in the form of the free base or the acid (HX) addition salt thereof.



V

TABLE I

Ex. No.	R ₁	R ₂	R ₃	HX
16	ethyl	ethyl	pivaloyloxymethoxy	HNO ₃
17	propyl	propyl	— " —	HNO ₃
18	ethyl	isopropyl	— " —	HNO ₃
19	isopropyl	isopropyl	— " —	HNO ₃
20	allyl	allyl	— " —	HCl
21	methyl	n-butyl	— " —	HNO ₃
22	ethyl	tert.butyl	— " —	HCl
23	methyl	cyclopentyl	— " —	
24	methyl	cyclohexyl	— " —	
25	ethyl	cyclohexyl	— " —	
26	methyl	cycloheptyl	— " —	
27	methyl	cyclohexylmethyl	— " —	
28	methyl	benzyl	— " —	
29	methyl	p-chlorobenzyl	— " —	HNO ₃
30	ethyl	2-chlorooctyl	— " —	HCl
31	methyl	phenyl	— " —	
32	methyl	bornyl	— " —	HCl
33	n-heptyl	n-heptyl	— " —	(COOH) ₂

TABLE I continued

Ex. No.	R ₁	R ₂	R ₃	HX
34	methyl	methyl	benzoyloxymethoxy	HCl
35	methyl	methyl	phenacycloxy	(COOH) ₂
	R ₁ R ₂ N—		R ₃	HX
36	pyrrolidyl-1		pivaloyloxymethoxy	HNO ₃
37	piperidyl-1		— „ —	
38	2-methyl-piperidyl-1		— „ —	HNO ₃
39	3-methyl-piperidyl-1		— „ —	
40	4-methyl-piperidyl-1		— „ —	
41	2,6-dimethyl-piperidyl-1		— „ —	
42	hexahydro-1H-azepin-1-yl		benzoyloxy	HCl
43	— „ —		cyanomethoxy	HCl
44	hexahydro-1(2H)-azocinnyl		pivaloyloxymethoxy	
45	1,2,3,4-tetrahydro-isoquinolyl-2		— „ —	
46	4-methyl-piperazinyl-1		— „ —	(HNO ₃) ₂
47	morpholinyl-4-		— „ —	HNO ₃

In Table II below are listed the physical constants of the compound of Table I and the reaction conditions are shown:

TABLE II

Ex. No.	Amide halide preparation					Rotation [α] _D ²⁰ in ethanol (96%)
	Halogenation agent	Solvent	Reaction time in h.	Recrystallized from	M.P. °C.	
16	(COCl) ₂	Ether	1	Acetone-ether	145—145.5	+202
17	(COCl) ₂	Ether	2	Acetone-ether	* 121—122	+196
18	(COCl) ₂	Ether	1	Acetone-ether	140.5	+198
19	(COCl) ₂	Ether	2	Methanol-ether	158.3—158.4	+177
20	COCl ₂	Toluene	2	Ethanol-ether	131—131.5	+205
21	(COCl) ₂	Ether	2	Ethylacetate-ether	124—125	+188
22	(COCl) ₂	Ether	16	Isopropanol-ether	163.5—164.5	+195
23	(COCl) ₂	Ether	20	Cyclohexane	87 — 88	+219
24	(COCl) ₂	Ether	5	Ethanol-water	73.5—74	+202
25	(COCl) ₂	Ether	17	Ethanol-water	73.5—74	+211
26	(COCl) ₂	Ether	3—4	Petroleum	97—99	+201
27	(COCl) ₂	Ether	3.5	Ethanol-water	75—76	+216
28	(COCl) ₂	Ether	2	Acetone-water	102—104	+213
29	(COCl) ₂	Ether	16	Methanol-ether	163.5	+183

TABLE II (Continued)

Ex. No.	Amide halide preparation			Reaction time in h.	Recrystallized from	M.P. °C.	Rotation $[\alpha]_D^{20}$ in ethanol (96%)
	Halogenating agent	Solvent					
30	(COCl) ₂	Ether		2	Ethanol-ether	120	+183
31	COCl ₂	Toluene		19	Acetone-water	87.5—88.5	+119
32	(COCl) ₂	Ether		0.5	Methanol-ether	191—191.5	+161
33	(COCl) ₂	Ether		0.5	Acetone-water	80—84	+155
34	(COCl) ₂	Ether		0.5	Ethanol-ether	158—160	+209
35	(COCl) ₂	Ether		0.33	Ethanol-ether	127—128	+201
36	(COCl) ₂	Ether		17.5	Ethanol-ether	116.5—117	+182
37	(COCl) ₂	Ether		20	Isopropanol-water	102—103	+206
38	(COCl) ₂	Ether		20	Acetone-ether	156.5—157	+172
39	(COCl) ₂	Ether		20	Petrolether	70—71	+209
40	(COCl) ₂	Ether		20	Acetone-water	96.5—97.5	+218
41	(COCl) ₂	Ether		20	Acetone-water	91—93	+205
42	(COCl) ₂	Ether		3.5	Ethanol-acetone-ether	177.5—178	+226

TABLE II (Continued)

Ex. No.	Amide halide preparation			Reaction time in h.	Recrystallized from	M.P.°C.	Rotation $[\alpha]_D^{20}$ in ethanol (96%)
	Halogenation agent	Solvent					
43	(COCl) ₂	Ether		3.5	Acetonitrile-ether	163.5-164	+237
44	(COCl) ₂	Ether		16	Cyclohexane	125.5	+222
45	(COCl) ₂	Ether		16.5	Cyclohexane	112-113	+210
46	COCl ₂	Toluene		2	Methanol-ether	156.5-157	+136
47	(COCl) ₂	Ether		19	Methanol-ether	148.5	+167

Example 48.

6-[(Hexahydro-1H-azepin-1-yl)-methylencaminol]-penicillanic acid dihydrate.

A. 1-Hexamethylenciminecarboxaldehyde dimethyl acetal was prepared from the N-formylhexamethylencimine-dimethyl sulphate complex by reaction with sodium methoxide according to the method of Brederick et al (Chem. Ber. 101, 41 (1968)). The boiling point was 83-84°C./12 mm Hg.

B. 6 - [(Hexahydro - 1H - azepin - 1 - yl) - methylencaminol] - penicillanic acid dihydrate. A solution of the above-mentioned acid amide acetal (4.1 g.) in dry ether (100 ml.) was slowly added to a solution of trimethylsilyl 6-aminopenicillanate (6.8 g.) in ether (500 ml.) at -30°C. with stirring. The temperature was raised to 0° within half an hour and water (300 ml.) was added. The stirring was continued for ten minutes, whereafter the aqueous phase was separated, extracted with ether and freeze-dried. The solid product was crystallized from methanol-acetone. It melted with decomposition from 135 to 142°C.

Example 49.

6-[(Hexahydro-1H-azepin-1-yl)-methylencaminol]-penicillanic acid.
16.7 g. of benzyl 6-[(hexahydro-1H-azepin-1-yl)-methylencaminol]-penicillanate hydrochloride was suspended in ethyl acetate (550 ml.) with continuous stirring and

cooling in an ice bath. A solution of sodium bicarbonate (14.3 g.) in water (400 ml.) was added. The organic phase was separated and extracted with water (350 ml.). After drying, the organic phase was evaporated *in vacuo*.

The oily residue was dissolved in methanol (150 ml.) and hydrogenated with palladium on charcoal catalyst (10%, 11.4 g.) at room temperature and under one atmosphere of hydrogen until the absorption of hydrogen ceased (about 15 minutes). The catalyst was filtered off and washed with methanol. The filtrate was evaporated *in vacuo*. The oily residue was crystallized from methanol (15 ml.) — acetone (190 ml.). The precipitate was filtered off, washed with acetone ($\times 10$ ml.) and dried in a vacuum exsiccator. The melting point was 156°C. (dec.). $[\alpha]_D^{20}$: +285° ($c=1$; 0.1N HCl).

Example 50.

Acetoxymethyl 6-(N,N-dimethylformamidino-N')-penicillanate hydrochloride.

Acetoxymethyl 6-aminopenicillanate was liberated from 5.1 g. of the p-toluene-sulphonate according to the procedure of Example 1 and dissolved in dry chloroform (30 ml.). Dry triethylamine (2.8 ml.) was added and the solution cooled to -40°C. A solution of chlorodimethylformiminium chloride (1.3 g.) in dry chloroform (15 ml.) was slowly added with stirring at -20°C. In the course of 3/4 hour the temperature was allowed to rise to 0°C. The solution was evaporated *in vacuo* and the residue triturated with ether (200 ml.). After filtration, 1.0 ml. of a solution of dry hydrogen chloride in isopropanol (8 N) was added at 0°C. with stirring. An amorphous product was obtained.

NMR spectrum (10% w/v CDCl₃):

$C_{(2)}(CH_3)_2$	3 H	s	at	1.54
	3 H	s	at	1.74
$OCOCH_3$	3 H	s	at	2.13
$N(CH_3)_2$	6 H	broad s	at	3.43
$C_{(3)}H$	1 H	s	at	4.58
$C_{(5)}H + C_{(6)}H$	2 H	s	at	5.65
OCH_2O	2 H	ABq	at	5.83 ($J=5.5$)
$N-CH=N$	1 H	broad line	at	8.13

In this and the following Examples the chemical shifts are given as ppm in δ values with TMS (0 ppm) as internal standard. Coupling constants (J) are in cps.

Example 51.

Pivaloyloxymethyl 6-(N-ethyl-N- β -ethoxyethylformamidino-N')-penicillanate.

A. N-Ethyl-N- β -ethoxyethylformamide was prepared from formamide by reaction with chloral. The boiling point was 102—104°C./11 mm. Hg.

B. Chloro-(ethyl- β -ethoxyethyl)-formiminium chloride. 3.4 ml. of oxalyl chloride dissolved in dry ether (20 ml.) were slowly added to a solution of N-ethyl-N- β -ethoxyethylformamide (5.8 g.) in dry ether (60 ml.) at 0°C. with stirring. After stirring at room temperature for one hour, the ether was decanted from the oily amide chloride which was triturated with ether twice and stored in an exsiccator.

C. Pivaloyloxymethyl 6-(N-ethyl-N- β -ethoxyethylformamidino-N')-penicillanate. 5 g. of the crude amide chloride were dissolved in dry chloroform (30 ml.) and added dropwise to a solution of pivaloyloxymethyl 6-aminopenicillanate (6.6 g.) and triethylamine (7 ml.) in dry chloroform (30 ml.) at -30° to -40°C. with stirring. The temperature was raised to 0°C. within 3/4 hour. The solution was

Example 49.
6-[(Hexahydro-1H-azepin-1-yl)-methylencamino]-penicillanic acid.
16.7 g. of benzyl 6-[(hexahydro-1H-azepin-1-yl)-methylencamino]-penicillanate hydrochloride was suspended in ethyl acetate (550 ml.) with continuous stirring and

evaporated *in vacuo* and the residue was treated with ether (400 ml.). After filtration from triethylamine hydrochloride, the filtrate was evaporated *in vacuo*. The oily residue was dissolved in 350 ml. of dilute hydrochloric acid at a pH of about 3. After filtration with "Dicalite" filter aid (diatomaceous earth) the filtrate was made alkaline with sodium bicarbonate to a pH of about 7.5 and extracted with ether. After drying, the ether was removed *in vacuo* leaving an oil which could not be crystallized.

NMR spectrum (10% w/v CDCl_3):

$\text{N}-\text{CH}_2-\text{CH}_3$	3 H	t	at	1.13 ($J=6.5$)
OCH_2CH_3	3 H	t	at	1.17 ($J=6.5$)
$\text{C}(\text{CH}_3)_3$	9 H	s	at	1.20
$\text{C}_{(2)}(\text{CH}_3)_2$	3 H	s	at	1.49
	3 H	s	at	1.65
$\left. \begin{array}{l} -\text{CH}_2-\text{N}-\text{CH}_2- \\ \quad \quad \quad \text{OCH}_2 \end{array} \right\}^*$	6 H	m	at	3.1 — 3.7
$\text{C}_{(3)}\text{H}$	1 H	s	at	4.38
$\text{C}_{(6)}\text{H}$	1 H	dd	at	5.04 ($J=4.0$, $J=1$)
$\text{C}_{(5)}\text{H}$	1 H	d	at	5.47 ($J=4.0$)
OCH_2O	2 H	ABq	$\left\{ \begin{array}{l} 5.75 (J=5.5) \\ 5.88 (J=5.5) \end{array} \right.$	
$\text{N}-\text{CH}=\text{N}$	1 H	d	at	7.60 ($J=1$)

*overlapping bands

Example 52.

Pivaloyloxymethyl 6-(N-butyl-N- β -cyanoethylformamidino-N')-penicillanate.

10 A. *N*-Butyl- β -formamidopropionitrile was prepared by formylation of β -N-butyl-aminopropionitrile with chloral. The boiling point was 114—115°C./0.4 mm. Hg. 10

15 B. *Chloro*-(butyl- β -cyanoethyl)-formiminium chloride. 1.7 ml. of oxalyl chloride dissolved in dry ether (10 ml.) was slowly added to a solution of N-butyl- β -formamidopropionitrile (3.1 g.) in dry ether (30 ml.) at 0°C. with stirring. After stirring at room temperature for two hours, the ether was decanted from the oily amide chloride. The crude amide chloride was treated with fresh ether twice and kept in an exsiccator. 15

20 C. *Pivaloyloxymethyl 6* - (N - butyl - N - β - cyanoethylformamidino - N')-penicillanate. A solution of the crude amide chloride (2.3 g.) in dry chloroform (15 ml.) was added dropwise to a solution of pivaloyloxymethyl 6-aminopenicillanate (3.3 g.) and triethylamine (3.1 ml.) in dry chloroform at -20°—-30°C. with stirring. The temperature was kept at -20°C. for half an hour and then raised to 0°C. in the course of a quarter of an hour. The solvent was removed *in vacuo* and the residue triturated with ether (200 ml.). After filtration from triethylammonium chloride, the filtrate was concentrated to a volume of 50 ml. *in vacuo* and extracted with 75 ml. of dilute hydrochloric acid (pH~3). The aqueous phase was filtered with "Dicalite" and made alkaline to a pH of about 7.5. The oily product was extracted with ether. The ethereal phase was dried and evaporated *in vacuo* leaving an oil which did not crystallize. 25

NMR spectrum (10% w/v CDCl_3):

$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$	3 H	t	at	0.94 (J=6)
$\text{C}(\text{CH}_3)_3$	9 H	s	at	1.23
$\text{C}_{(2)}(\text{CH}_3)_2$	3 H	s	at	1.51
	3 H	s	at	1.65
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$	4 H	m	at	1.20—1.60
CH_2CN	2 H	t	at	2.79 (J=6.5)
CH_2NCH_2	4 H	m	at	3.10—3.70
$\text{C}_{(3)}\text{H}$	1 H	s	at	4.41
$\text{C}_{(6)}\text{H}$	1 H	dd	at	5.03 (J=4, J=1)
$\text{C}_{(5)}\text{H}$	1 H	d	at	5.50 (J=4)
OCH_2O	2 H	ABq	[d	5.77 (J=6.0)
			[d	5.90 (J=6.0)]
$\text{N}-\text{CH}=\text{N}$	1 H	d	at	7.62 (J=1)

Example 53.

Pivaloyloxymethyl 6-(N-methyl-N-carbomethoxymethylformamidino-N')-penicillanate.

5 A. *Chloro-(methyl-carbomethoxymethyl)-formiminium chloride*. 3.0 g. of phosgene in dry benzene (16 ml.) were slowly added to a solution of methyl N-formyl-N-methyl-glycinate (2.0 g.) in dry benzene (15 ml.) at 0°C . with stirring. The reaction mixture was stirred overnight at room temperature and evaporated *in vacuo*. The oily residue was triturated twice with ether and kept in an exsiccator.

10 B. *Pivaloyloxymethyl 6-(N-methyl-N-carbomethoxymethylformamidino-N')-penicillanate*.

A solution of the crude amide chloride (2.4 g.) in dry chloroform (15 ml.) was slowly added to a solution of pivaloyloxymethyl 6-aminopenicillanate (3.3 g.) and triethylamine (3.4 ml.) in dry chloroform (15 ml.) at -20° — -30°C . with stirring. The temperature was raised to 0°C . during 3/4 hour and the solvent removed *in vacuo*. The residue was treated with ether (200 ml.). The precipitate was filtered off and the filtrate concentrated to a volume of 50 ml. *in vacuo*. This solution was extracted with dilute hydrochloric acid (75 ml., pH~3) and the aqueous phase filtered with "Dicalite". By addition of sodium bicarbonate to a pH of about 7.5, an oil was formed, which was taken up in ether. The ethereal phase was dried and evaporated to leave an oil which did not crystallize.

NMR spectrum (10% w/v CDCl_3):

$\text{C}(\text{CH}_3)_3$	9 H	s	at	1.23
$\text{C}_{(2)}(\text{CH}_3)_2$	3 H	s	at	1.50
	3 H	s	at	1.65
$\text{N}-\text{CH}_3$	3 H	s	at	2.97
OCH_3	3 H	s	at	3.73
NCH_2CO	2 H	ABq	at	4.00
$\text{C}_{(3)}\text{H}$	1 H	s	at	4.38
$\text{C}_{(6)}\text{H}$	1 H	dd	at	5.08 ($J=4.4$, $J=1$)
$\text{C}_{(5)}\text{H}$	1 H	d	at	5.47 ($J=4.4$)
OCH_2O	2 H	ABq	[d	5.77 ($J=5.5$)]
			[d	5.89 ($J=5.5$)]
$\text{N}-\text{CH}=\text{N}$	1 H	d	at	7.67 ($J=1$)

Example 54.

Pivaloyloxymethyl 6-(N-methyl-N-carbamylmethylformamidino-N')-penicillanate.

To an ice-cold solution of pivaloyloxymethyl 6-aminopenicillanate (6.6 g.) and triethylamine (5.6 ml.) in dry chloroform (70 ml.) was added 1,1-dichlorodimethyl ether (2.3 g.) with stirring. The solution was kept overnight at room temperature and then cooled to 0°C . Sarcosinamide (1.8 g.) was added. The reaction mixture was kept for 48 hours at 0°C ., whereupon the solvent was removed *in vacuo*. The residue was distributed between ether (75 ml.) and dilute hydrochloric acid (75 ml., pH~3). The aqueous phase was separated and extracted with ether (25 ml.) and then made alkaline (to a pH of about 7.5) with sodium bicarbonate. The oily product was taken up in ether, which was dried and evaporated *in vacuo*. The residue did not crystallize.

NMR spectrum (10% w/v CDCl_3)

$\text{C}(\text{CH}_3)_3$	9 H	s	at	1.22
$\text{C}_{(2)}(\text{CH}_3)_2$	3 H	s	at	1.51
	3 H	s	at	1.65
NCH_3	3 H	s	at	2.99
NCH_2CO	2 H	ss	at	3.92
$\text{C}_{(3)}\text{H}$	1 H	s	at	4.43
$\text{C}_{(6)}\text{H}$	1 H	dd	at	5.05 ($J=4.1$, $J=1$)
$\text{C}_{(5)}\text{H}$	1 H	d	at	5.52 ($J=4.1$)
OCH_2O	[1 H	ABq		5.88 ($J=5.5$)]
	[1 H			5.78 ($J=5.5$)]
$\text{N}-\text{CH}=\text{N}$	1 H	d	at	7.66

Example 55.

Pivaloyloxymethyl 6-(N-ethyl-N-β-hydroxyethylformamidino-N')-penicillanate.

Pivaloyloxymethyl 6-aminopenicillanate (6.6 g.) was treated with 1,1-dichloro-dimethyl ether and triethylamine as in Ex. 54. To the ice-cold solution was added 2-ethylaminocethanol (1.8 g.). After 48 hours at 0°C. the solution was evaporated *in vacuo* and the residue was triturated with acetone (25 ml.) Triethylamine hydrochloride was filtered off and the filtrate was evaporated *in vacuo*. The residue was distributed between ether (75 ml.) and dilute hydrochloric acid (75 ml., pH~2.5). The aqueous phase was separated and made alkaline to a pH of about 7.5. The oily reaction product was taken up in ether. Drying and evaporation *in vacuo* gave an oil which did not crystallize.

NMR (10% w/v CDCl₃)

$\text{CH}_3\text{CH}_2\text{N}$	3 H	t	at	1.17 (J=7)
$\text{C}(\text{CH}_3)_3$	9 H	s	at	1.22
$\text{C}_{(2)}(\text{CH}_3)_2$	3 H	s	at	1.49
	3 H	s	at	1.65
* $\text{CH}_3\text{CH}_2\text{N}$	2 H	q	at	3.28 (J=7)
* $\text{N}-\text{CH}_2-\text{CH}_2\text{OH}$	2 H	m	at	3.5
* $\text{N}-\text{CH}_2-\text{CH}_2\text{OH}$	2 H	m	at	3.7
$\text{C}_{(3)}\text{H}$	1 H	s	at	4.43
$\text{C}_{(6)}\text{H}$	1 H	dd	at	4.98 (J=4.1, J ~ 0.8)
$\text{C}_{(6)}\text{H}$	1 H	d	at	5.49 (J=4.1)
OCH_2O	[1 H 1 H]	ABq d	d	5.77 (J=5.5) 5.88 (J=5.5)
$\text{N}-\text{CH}=\text{N}$	1 H	d	at	7.67 (J ~ 0.9)

*partly overlapped by other bands

Example 56.

Pivaloyloxymethyl 6-(N-methyl-N-carbethoxymethylformamidino-N')-penicillanate.

Pivaloyloxymethyl 6-aminopenicillanate (6.6 g.) was treated with 1,1-dichloro-dimethyl ether and triethylamine as described in Ex. 54. Ethyl N-methylglycinate (2.3 g.) was added to the ice-cold solution. The reaction mixture was kept in an ice-box for 48 hours and then worked up as in Ex. 55. The product was an oil which did not crystallize.

NMR spectrum (10% w/v CDCl_3)

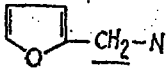
$\text{C}(\text{CH}_3)_3$	9 H	s	at	1.22
OCH_2CH_3	3 H	t	at	1.28
$\text{C}_{(2)}(\text{CH}_3)_2$	3 H	s	at	1.51
	3 H	s	at	1.66
NCH_3	3 H	s	at	2.98
NCH_2CO	2 H	ABq	at	4.01
OCH_2CH_2	2 H	q	at	4.23 (J=7)
$\text{C}_{(3)}\text{H}$	1 H	s	at	4.39
$\text{C}_{(6)}\text{H}$	1 H	dd	at	5.12 (J=4.2, J=1)
$\text{C}_{(6)}\text{H}$	1 H	d	at	5.48 (J=4.2)
OCH_2O	[1 H 1 H]	ABq	d d	5.78 (J=5.8) 5.87 (J=5.8)
$\text{N}-\text{CH}=\text{N}$	1 H	d	at	7.69 (J=1)

Example 57.

Pivaloyloxymethyl 6-(N-methyl-N-furfurylformamidino-N')-penicillanate.

By following the procedure of Example 55 but replacing 2-ethylaminoethanol with N-methylfurfurylamine (2.3 ml.) an oil was obtained which did not crystallize.

NMR spectrum (10% w/v CDCl_3)

$\text{C}(\text{CH}_3)_3$	9 H	s	at	1.22
$\text{C}_{(2)}(\text{CH}_3)_2$	3 H	s	at	1.51
	3 H	s	at	1.66
NCH_3	3 H	s	at	2.84
	2 H	bs	at	4.35
$\text{C}_{(3)}\text{H}$	1 H	s	at	4.40
$\text{C}_{(6)}\text{H}$	1 H	dd	at	5.10 ($J=4.5$, $J=1$)
$\text{C}_{(6)}\text{H}$	1 H	d	at	5.48 ($J=4.5$)
OCH_2O	[1 H 1 H]	ABq d	d	5.77 ($J=5$) 5.81 ($J=5$)
	2 H	m	at	6.2—6.4
	1 H	m	at	7.3—7.4
$\text{N}-\text{CH}=\text{N}$	1 H	d	at	7.69 ($J=1$)

Example 58.

Pivaloyloxymethyl 6-[(4'-dimethylcarbamylpiperazinyl-1')-methyleneamino]-penicillanate.

By following the procedure of Example 55 but replacing 2-ethylaminoethanol with 1-dimethylcarbamylpiperazine (3.1 g.), an amorphous solid was obtained which could not be crystallized.

NMR spectrum (10% w/v CDCl₃)

C(CH ₃) ₃	9 H	s	at	1.22
C ₍₂₎ (CH ₃) ₂	3 H	s	at	1.51
	3 H	s	at	1.66
N(CH ₃) ₂	6 H	s	at	2.85
NCH ₂	8 H	m	at	3.0 — 3.6
C ₍₃₎ H	1 H	s	at	4.38
C ₍₆₎ H	1 H	dd	at	5.07 (J=4.5, J=1)
C ₍₅₎ H	1 H	d	at	5.48 (J=4.5)
OCH ₂ O	[1 H] d		at	5.77 (J=6)
	[1 H] ABq		at	5.90 (J=6)
N—CH=N	1 H	d	at	7.63 (J=1)

Example 59.

Preparation of tablets containing pivaloyloxymethyl 6[(hexahydro-1H-azepin-1-yl)-methylenecamino]-penicillanate, hydrochloride.

Ingredients:

Pivaloyloxymethyl 6[(hexahydro-1H-azepin-1-yl)-methylenecamino]-penicillanate, hydrochloride	g.	350
Polyvinylpyrrolidone		10
Corn starch		40
Magnesium stearate		4

The pivaloyloxymethyl ester is screened through a sieve with 1.0 mm. mesh openings. Thereafter the powder is wetted with a solution of polyvinylpyrrolidone in 150 ml. of a solvent composed of 1 part of ethanol (96%) and 19 parts of acetone. The moist mass is passed through a sieve with 1.0 mm. mesh openings and then dried at 30°C. on trays or other convenient drying equipment, such as a "fluidized bed" drying cupboard.

When the solvent has evaporated, the granules are sifted through a sieve with 0.7 mm. mesh openings, and are finally mixed with the corn starch and magnesium stearate.

The granulate is compressed into tablets of 0.40 g. weight using punches and dies of 12 mm. diameter yielding 1000 tablets each containing 0.35 g. of the pivaloyloxymethyl ester.

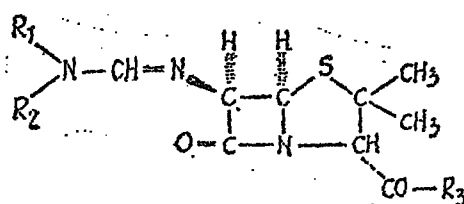
Example 60.

A pharmaceutical preparation for injection.

In a sterile vial is placed a single dose of 250 mg. of sterilized 6[(hexahydro-1H-azepin-1-yl)-methylenecamino]-penicillanic acid. For administration by injection the compound is dissolved in 5 ml. of sterile water.

WHAT WE CLAIM IS:—

1. An amidino-penicillanic acid derivative of the general formula:



(I)

NMR spectrum (10% w/v CDCl₃)

C(CH ₃) ₃	9 H	s	at	1.22
C ₍₂₎ (CH ₃) ₂	3 H	s	at	1.51
	3 H	s	at	1.66
N(CH ₃) ₂	6 H	s	at	2.85
NCH ₂	8 H	m	at	3.0 — 3.6
C ₍₃₎ H	1 H	s	at	4.38
C ₍₆₎ H	1 H	dd	at	5.07 (J=4.5, J=1)
C ₍₅₎ H	1 H	d	at	5.48 (J=4.5)
OCH ₂ O	[1 H] ABq d		at	5.77 (J=6)
	[1 H] ABq d		at	5.90 (J=6)
N—CH=N	1 H	d	at	7.63 (J=1)

Example 59.

Preparation of tablets containing pivaloyloxymethyl 6[(hexahydro-1H-azepin-1-yl)-methylenecamino]-penicillanate, hydrochloride.

Ingredients:

Pivaloyloxymethyl 6[(hexahydro-1H-azepin-1-yl)-methylenecamino]-penicillanate, hydrochloride	350
Polyvinylpyrrolidone	10
Corn starch	40
Magnesium stearate	4

The pivaloyloxymethyl ester is screened through a sieve with 1.0 mm. mesh openings. Thereafter the powder is wetted with a solution of polyvinylpyrrolidone in 150 ml. of a solvent composed of 1 part of ethanol (96%) and 19 parts of acetone. The moist mass is passed through a sieve with 1.0 mm. mesh openings and then dried at 30°C. on trays or other convenient drying equipment, such as a "fluidized bed" drying cupboard.

When the solvent has evaporated, the granules are sifted through a sieve with 0.7 mm. mesh openings, and are finally mixed with the corn starch and magnesium stearate.

The granulate is compressed into tablets of 0.40 g. weight using punches and dies of 12 mm. diameter yielding 1000 tablets each containing 0.35 g. of the pivaloyloxymethyl ester.

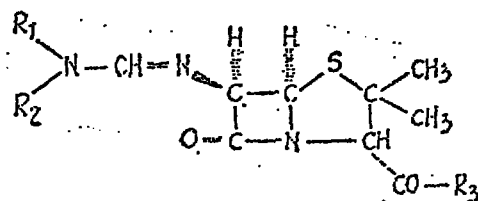
Example 60.

A pharmaceutical preparation for injection.

In a sterile vial is placed a single dose of 250 mg. of sterilized 6[(hexahydro-1H-azepin-1-yl)-methylenecamino]-penicillanic acid. For administration by injection the compound is dissolved in 5 ml. of sterile water.

WHAT WE CLAIM IS:—

1. An amidino-penicillanic acid derivative of the general formula:



(I)



* C L M S *

wherein R_1 and R_2 each represent an unsubstituted or substituted aliphatic hydrocarbon radical, a mono- or bicyclic aryl radical, an aralkyl radical, a cycloalkyl radical, a cycloalkyl-alkyl radical, a heterocyclic radical or a heterocyclically substituted alkyl radical, or R_1 and R_2 , when taken together with the nitrogen atom, represent a ring system; and R_3 represents a hydroxyl group, or a substituted hydroxyl group: and pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1, wherein R_1 and R_2 when taken together with the nitrogen atom represent a saturated heterocyclic ring having from 5 to 9 carbon atoms optionally substituted with an alkyl group containing 1 to 6 carbon atoms, and R_3 is a hydroxyl group or an alkanoyloxymethoxy group.

3. A compound as claimed in claim 1, wherein R_1 and R_2 when taken together with the nitrogen atom represent a heterocyclic radical having from 5 to 10 atoms and optionally containing other hetero atoms in the ring, and R_3 is a hydroxyl group or an alkanoyloxymethoxy group having from 3 to 8 carbon atoms.

4. A compound as claimed in claim 3, wherein R_1 and R_2 , when taken together, represent a pentamethylene, hexamethylene or heptamethylene radical.

5. 6-[(hexahydro-1H-azepin-1-yl)-methyleneamino]-penicillanic acid and the pivaloyloxymethyl ester thereof.

6. 6[(piperidyl-1)-methyleneamino]-penicillanic acid and the pivaloyloxymethyl ester thereof.

7. 6[(hexahydro-1(2H)-azocinnyl)-methyleneamino]-penicillanic acid and the pivaloyloxymethyl ester thereof.

8. A compound as claimed in claim 1 in which R_1 and R_2 each represent an alkyl or cycloalkyl radical and R_3 represents a hydroxyl group, and esters thereof.

9. 6-(N-ethyl-N-isopropyl-formamidino-N')-penicillanic acid and the pivaloyloxymethyl ester thereof.

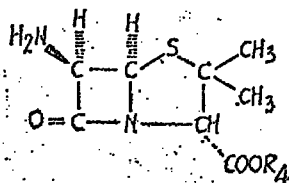
10. 6-(N-methyl-N-cyclopentyl-formamidino-N')-penicillanic acid and the pivaloyloxymethyl ester thereof.

11. An amidino-penicillanic acid derivative of the general formula defined in claim 1, substantially as hereinbefore described in any one of Examples 1 to 58 of the foregoing Examples.

12. A process for the preparation of a compound of the formula defined in claim 1, wherein a reactive derivative of an amide or a thioamide of the general formula II:



in which R_1 and R_2 have the meanings defined in claim 1 and R_3 stands for an oxygen or sulphur atom, is reacted with a 6-aminopenicillanic acid derivative of the general formula III:



(III)

in which $COOR_4$ is an ester group, or with a silyl ester of 6-aminopenicillanic acid, whereafter, if desired, the reaction is followed by a cleavage of the ester to the free acid.

13. A process for the preparation of a compound of the formula defined in claim 1, wherein an amine of the formula HNR_1R_2 , in which R_1 and R_2 have the meanings defined in claim 1, is reacted with a reactive derivative of a 6-formamido penicillanic acid ester.

14. A process for the preparation of a compound of the formula defined in claim 1, wherein a compound of formula III as defined in claim 12 is reacted with a 1,1-dihalodimethyl ether in the presence of a tertiary organic base, and wherein the intermediate formed is thereafter treated with an amine of the formula HNR_1R_2 , in which R_1 and R_2 are as defined in claim 1.



15. A process for the preparation of a compound of the formula defined in claim 1, substantially as hereinbefore described in any one of Examples 1 to 58 of the foregoing Examples.

16. A pharmaceutical preparation in dosage unit form for the oral, enteral or parenteral treatment of patients suffering from infectious diseases, which comprises as an active ingredient a compound as claimed in any one of claims 1 to 10 and an atoxic pharmaceutically acceptable carrier, the quantity of the said compound being from 0.05 to 0.5 g. per dosage unit.

17. A pharmaceutical preparation as claimed in claim 16, wherein the compound is 6-[(hexahydro-1H-azepin-1-yl)-methylecamino]-penicillanic acid.

18. A pharmaceutical preparation as claimed in claim 16, wherein the compound is pivaloyloxymethyl 6-[(hexahydro-1H-azepin-1-yl)-methylecamino]-penicillanate, hydrochloride.

19. A preparation as claimed in any one of claims 16 to 18, wherein the dosage unit is in the form of a tablet or a pill.

20. A preparation as claimed in any one of claims 16 to 18, wherein the dosage unit is in the form of a capsule.

21. A pharmaceutical preparation for oral treatment, comprising from 10 to 50 mg. of a compound as claimed in any one of claims 1 to 10 in the form of an ester which is hydrolysable in the human body per ml. of a carrier in which the compound is presented.

22. An injectable preparation as claimed in claim 16 or 17, in the form of the free acid in a sterile aqueous medium.

23. A pharmaceutical preparation in dosage unit form substantially as hereinbefore described in Example 59 or 60 of the foregoing Examples.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1972.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

