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METZGER



(54) NEW PENICILLINS, THEIR PREPARATION AND THEIR USE

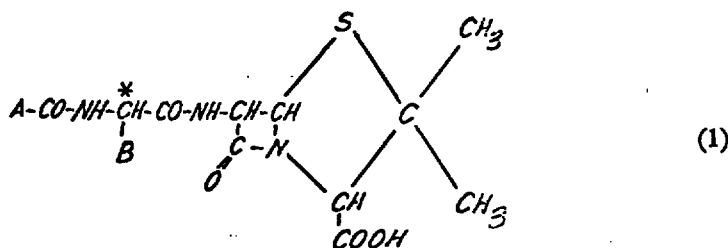
(71) We, BAYER AKTIENGESellschaft formerly known as Farbenfabriken Bayer Aktiengesellschaft, a body corporate organised under the laws of Germany, of 509 Leverkusen-Bayerwerk, Germany, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

The present invention relates to new synthetic compounds which are of value as anti-bacterial agents, foodstuff additives in animal fodder, and therapeutic agents in poultry and animals, as well as in man, in the treatment of illnesses due to infection by Gram-positive and Gram-negative bacteria, and especially by *Klebsiella* bacteria such as *Klebsiella aerobacter*.

Anti-bacterial agents, such as ampicillin (USA Patent Specification 2,985,648) have proved very effective in the therapy of infections by Gram-positive and Gram-negative bacteria. However, they are not capable of effectively combating *Klebsiella* infections. Carbenicillin (USA Patent Specifications 3,142,673 and 3,282,926) is only effective in man in the case of infections by *Klebsiella bacteria* if it is administered in continuing high doses, such as are only achieved by infusion.

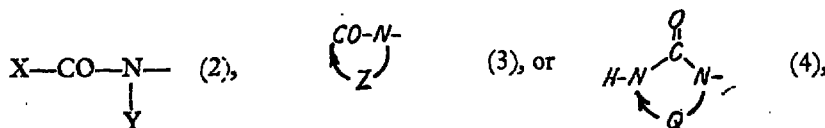
6-(α -3-Acylureidoacetamido)-penicillanic acids are described in Netherlands Patent Application Nos. 6,901,646 and 6,908,909 and in US Patents Nos. 3,479,339, 3,483,188, 3,481,922 and German Offenlegungsschrift 1,959,920 but all 3-acylureidoacetamidopenicillanic acids described and claimed in these patents and applications possess, in contrast to those of the present invention, a hydrogen atom on the nitrogen atom present in the 3-position in the acylureido group. The presence of this hydrogen atom and the absence of another substituent at this position of the acylureido group in part necessarily results from the different way of synthesising these penicillins.

The present invention provides new penicillins of the general formula:—



in which general formula:—

A is a group of the general formula:—



[in which general formulae (2), (3) and (4)

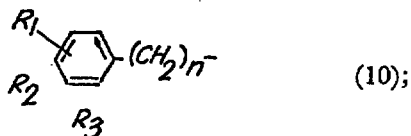
5 X is a hydrogen atom, or an alkyl, alkenyl, cycloalkyl or cycloalkenyl group with up to ten carbon atoms, or a vinyl, arylvinyl, mono-, di-, or tri-halo (lower alkyl), (lower alkyl)-amine, di(lower alkyl)-amino monoarylamino, aryl (lower alkyl) amino or aryloxy group, or an alkoxy or aralkoxy group with up to eight carbon atoms, or a cycloalkoxy group with up to seven carbon atoms, or a group of the general formula:—

10 (lower alkyl) —O—V— (5);
 (lower alkyl) —S—V (6);
 N≡C—V— (7);
 (lower alkyl)-O—CO—V— (8);
 di(lower alkyl)amino-CO—V— (9);

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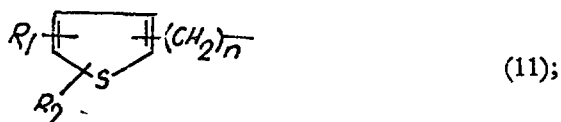
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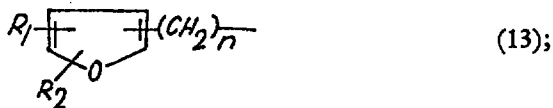


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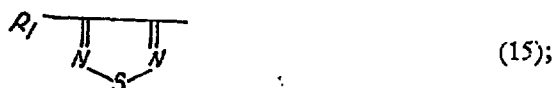
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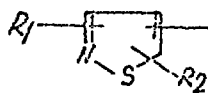


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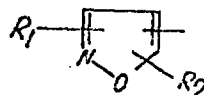


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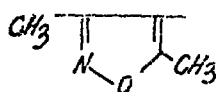
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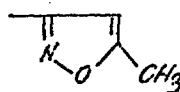
(16);



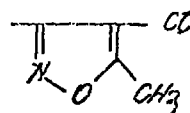
(17);



(18);



(19); or



(20);

[in which general formulae (5) to (20):

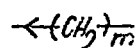
V is a bivalent organic radical with 1 to 3 carbon atoms;

n is 0, 1 or 2; and

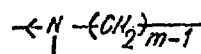
R₁, R₂ and R₃, which may be the same or different, are each a hydrogen, chlorine, bromine, iodine or fluorine atom or a nitro, nitrile, di(lower alkyl)amino, di(lower alkyl)amino-carbonyl, lower alkanoylamino, lower alkoxy-carbonyl, lower alkanoyloxy, lower alkyl, lower alkoxy, sulphonyl, or trifluoromethyl group;

Y is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group with up to ten carbon atoms, or a vinyl, propenyl, mono-, di-, or tri-halo (lower alkyl), aryl, or heterocyclic group, or an aralkyl group with up to eight carbon atoms;

-Z- is a divalent group of the formula: —

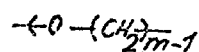


(21);

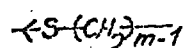


(22);

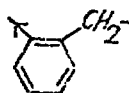
(lower alkyl)



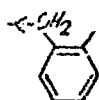
(23);



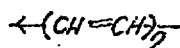
(24);



(25);



(26); or



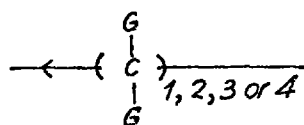
(27);

[in which general formula (21) to (27) m is 3, 4 or 5 and the arrow $\leftarrow$ means that the two free valencies of the group Z are not arbitrarily joined to the N and C atoms of the group

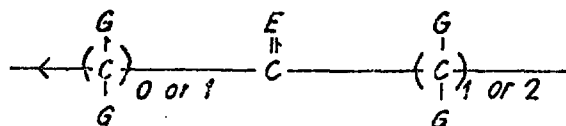


(3)

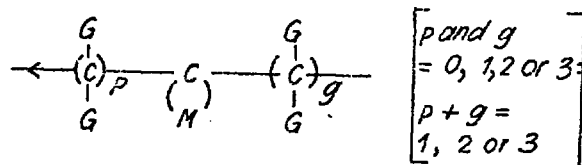
but are oriented as indicated by the arrow;]; Q is a divalent group, and in particular a group of the general formula:—



(32);

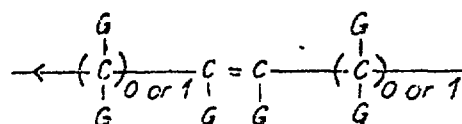


(33);

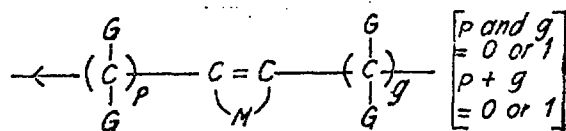


(34);

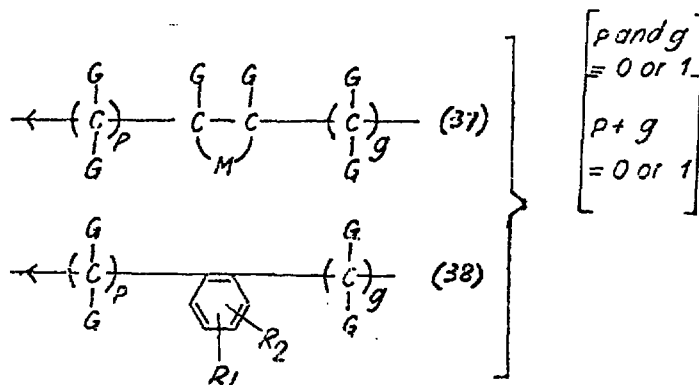
$$\left[\begin{array}{l} p \text{ and } g \\ = 0, 1, 2 \text{ or } 3; \\ p + g = \\ 1, 2 \text{ or } 3 \end{array} \right]$$



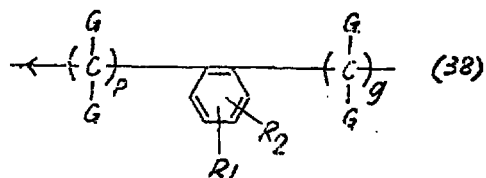
(35);



(36);



(37)



(38)

$$\left[\begin{array}{l} p \text{ and } g \\ = 0 \text{ or } 1; \\ p + g \\ = 0 \text{ or } 1 \end{array} \right]$$

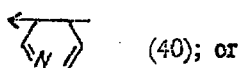
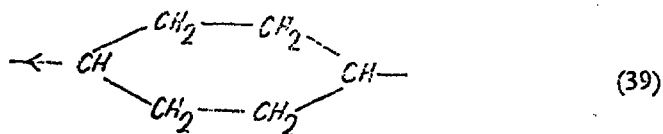
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in which general formulae (32) to (41):

E is a oxygen or sulphur atom;

G is a hydrogen atom or a lower alkyl group;

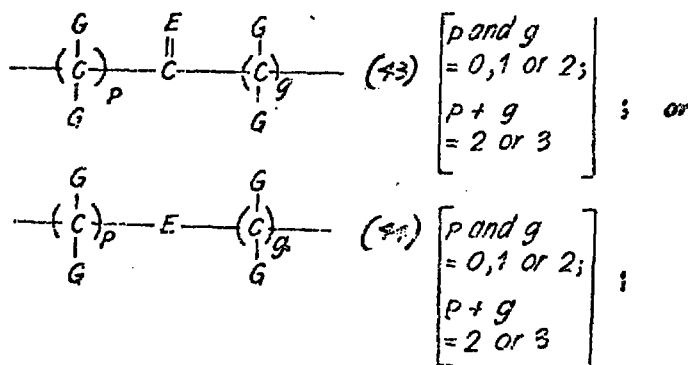
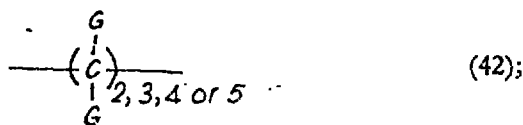
R₁ and R₂ are as defined in claim 1;

the arrow in the divalent group $\leftarrow Q \rightarrow$ means that the two free valencies of the group Q are not arbitrarily joined to the two nitrogen atoms of the group



but are oriented as indicated by the arrow:

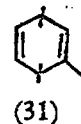
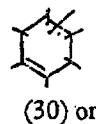
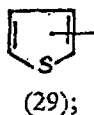
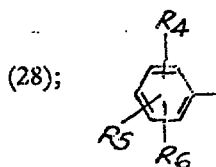
M is a group of the general formula: —



in which general formulae (42), (43) and (44),

E and G have the meanings given above.]

B is a group of the general formula: —



[in which general formulae (28), (29), (30) and (31) R₄, R₅ and R₆, which may be the same or different, are each a hydrogen or halogen atom or a lower alkyl, lower alkoxy, lower alkylthio, lower alkylthionyl, lower alkylsulphonyl, nitro, di(lower alkyl) amino, lower alkanoylamino, hydroxy, or lower alkanoyloxy group], and which, as regards the chirality centre C*, can have either of the two possible R— and S— stereomeric configurations; and the salts of these penicillins.

The invention covers not only pure R— and S—stereoisomers, but also mixtures of these isomers in any proportions.

The salts to which the invention more particularly relates are the non-toxic pharmaceutically tolerated salts, which include salts of the acid carboxyl group.

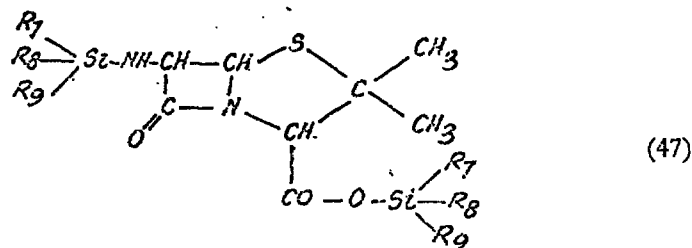
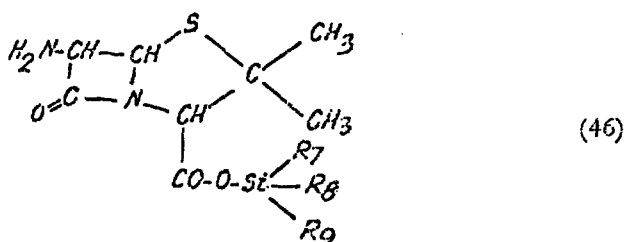
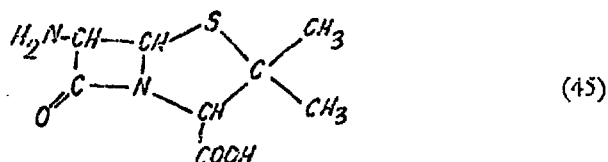
The above mentioned non-toxic, pharmaceutically tolerated salts of the acid carboxyl group, such as sodium, potassium, magnesium, calcium, aluminium and ammonium salts, and non-toxic substituted ammonium salts with amines such as di- and tri-lower alkylamines, procaine, dibenzylamine, N,N'-dibenzylethylenediamine, N-benzyl-2-phenylethylamine, N-methylmorpholine and N-ethylmorpholine, 1-phenamine, dehydroabietylamine, N,N'-bis-dehydroabietylthylenediamine, N-lower alkylpiperidine and other amines which have been used for forming salts of penicillins.

The term "lower alkyl" is to be understood, in the present invention, as meaning both a straight-chain and a branched alkyl group with up to 6 carbon atoms. In conjunction with other groups, such as in "di-lower alkylamino", the term "lower alkyl-" only relates to the alkyl part of the particular group.

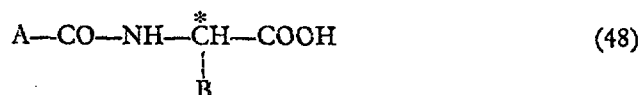
Preferred groups "B" are the phenyl, *p*-methylthiophenyl, *p*-methylphenyl, *p*-methoxyphenyl, *p*-chlorophenyl and thienyl-(2) groups.

The chirality centre C* is preferably in the R-configuration.

The invention further provides a process for the preparation of the above penicillins and salts in which 6-aminopenicillanic acid (45) or a compound of the general formula (46) or (47):—



in which R₇, R₈ and R₉ are the same or different alkyl groups having up to 6 carbon atoms; is reacted at a temperature of -30 to +50° C. with a carboxylic acid of the general formula:—



modified at the carboxyl group, in which general formula (48) A, B and C* are as defined above.

Another process for producing the penicillins and salts according to the invention is disclosed and claimed in our copending application No. 16880/71 (Serial No. 1,301,961).

The reaction in the process according to the present invention is, when 6-aminopenicillanic acid is used, carried out in an anhydrous or aqueous solvent, in the presence of a base. If a compound of the general formula (46) or (47) is used, the reaction is carried out in an anhydrous solvent, free of hydroxyl groups, with or without the addition of a base.

in which U is as defined above, in an anhydrous, inert organic solvent, in the presence of at least one molar equivalent of a tertiary organic base, at a temperature of from -25°C. to $+25^{\circ}\text{C.}$, with one molar equivalent of thionyl chloride, to obtain an intermediate product, with one molar equivalent of base hydrochloride being formed. The intermediate product is then reacted, without isolation and in the presence of a further molar equivalent of a base, with a molar equivalent of the carboxylic acid of the general formula (48) at a temperature of about -25°C. to $+25^{\circ}\text{C.}$, to give the modified carboxylic acid of the general formula (53).

This invention thus not only provides new compounds which, in the treatment of infections by gram-positive and gram-negative bacteria, particularly by strains of *Klebsiella aerobacter*, are able, with low dosage, to give valuable therapeutic help, but also provides a process for the production of these new compounds which is superior for such production to the processes known from the literature for the acylation of 6-aminopenicillanic acid.

In carrying out the process of the invention using 6-amino-penicillanic acid, the modified carboxylic acid of general formula (48), preferably in the form of a solution in an anhydrous, inert organic solvent, is brought together with a solution of 6-amino-penicillanic acid in water or in an aqueous or anhydrous organic solvent, in the presence of a base. Suitable solvents for the carboxylic acids modified at the carboxyl group are, for example, acetone, tetrahydrofuran, dioxane, dimethylformamide, dimethylsulphoxide and hexamethylphosphoric acid triamide for an aqueous reaction medium, and preferably methylene chloride and chloroform for an anhydrous reaction medium.

The 6-aminopenicillanic acid is preferably employed in the reaction according to the invention as a solution of its salt with a base, in water or in a mixture of water and a water-miscible solvent, or in an anhydrous organic solvent. Suitable solvents for the 6-aminopenicillanic acid or its salt, apart from water, are preferably acetone, tetrahydrofuran, dioxane, acetonitrile, dimethylformamide, dimethylsulphoxide, hexamethylphosphoric acid triamide and isopropanol for an aqueous reaction medium and, in addition to the solvents mentioned, preferably methylene chloride and chloroform for an anhydrous reaction medium. In order to convert the 6-aminopenicillanic acid into the salt of a base, the salt being dissolved in a solvent, inorganic bases such as sodium carbonate, sodium hydroxide, sodium bicarbonate, the corresponding potassium and calcium compounds, magnesium oxide or magnesium carbonate or buffer mixtures can for example be used as bases suitable for the purpose in the case of an aqueous or water-containing reaction mixture, whilst triethylamine, pyridine, diethylamine, N-ethylpiperidine or N-ethylmorpholine can preferably be used in the case of an anhydrous reaction medium.

The reaction, according to the invention, of the carboxylic acids of the general formula (48), modified at the carboxyl group, with the silylated 6-aminopenicillanic acids of the general formulae (46) and (47) is carried out in inert organic solvents which are free of hydroxyl groups, for example in carbon tetrachloride, methylene chloride, chloroform, tetrahydrofuran, benzene, diethyl ether and toluene.

The reaction, according to the invention, of the carboxylic acids of the general formula (48), in the form which is modified at the carboxyl group, with the 6-aminopenicillanic acid, in an aqueous or water-containing medium, can be carried out at a pH of, preferably, 6.5 to 8.0, or also at a pH of about 3.

As in the case of most chemical reactions, higher or lower temperatures than those indicated in the Examples can be used. However, if the values indicated in the Examples are substantially exceeded, side-reactions will occur to an increasing extent, and these reduce the yield or disadvantageously affect the purity of the products. On the other hand, excessively lowered reaction temperatures reduce the speed of reaction so much that reductions in yield can occur. Reaction temperatures of -20°C. to $+30^{\circ}\text{C.}$ are therefore preferred in the reaction according to the invention, of the carboxylic acids of the general formula (48), modified at the carboxyl group, with the 6-aminopenicillanic acid or the silylated 6-aminopenicillanic acids of the general formulae (46) and (47). Only in cases where the carboxylic acids modified at the carboxyl group are insufficiently stable, or there is the danger that racemisation may occur at an optionally active centre located near the carboxyl group, can it be advisable preferably to carry out the process at reaction temperatures below -20° . In the reaction, according to the invention, of the carboxylic acids of the general formula (48), modified at the carboxyl group, with the 6-aminopenicillanic acid or the compounds of the general formulae (46) and (47), the reactants can be reacted in equimolar amounts. It may however be advisable to use one of the two reactants in excess in order to facilitate the purification of the desired penicillin, or its preparation in a

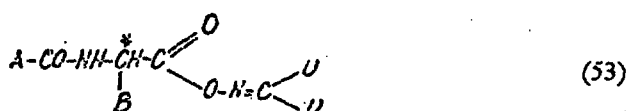
pure form, and to increase the yield. Thus it is, for example, possible to employ the 6-aminopenicillanic acid or the compounds of the general formulae (46) and (47) in an excess of 0.1 to about 0.4 mol equivalent and thereby to achieve better utilisation of the carboxylic acids of the general formula (48). When working up the reaction mixture and isolating the penicillin, 6-aminopenicillanic acid which may be present can be easily removed because of its good solubility in aqueous mineral acids. Any carboxylic acid [see formula (48)] which may be present can, on the other hand, only be separated with much greater difficulty from the penicillin formed.

The amount of bases added in the reaction, according to the invention, of the carboxylic acids of the general formula (48), modified at the carboxyl group, with 6-amino-penicillanic acid or the compounds of the general formulae (46) and (47) is for example determined by the desired maintenance of a particular pH. Where a pH measurement and adjustment is not carried out, or is not possible or sensible because of the absence of sufficient amounts of water in the diluent, about 0.5 to 2.0 mol equivalents of base are added in the case where the compounds of the general formula (46) or (47) are used, and about 1.5 to 2.5 mol equivalents of base are added in the case where 6-aminopenicillanic acid and an anhydrous reaction medium are used.

The working up of the reaction batches for the manufacture of the penicillins according to the invention, and of their salts, in all cases takes place in the manner generally known for penicillins.

The carboxylic acids of the general formula (48) can be modified at the carboxyl group, according to the invention, by reacting them with about one molar equivalent of a compound of one of the general formulae (49), (50), (51) or (52) in an anhydrous, inert organic solvent in the presence of about one molar equivalent of a base, preferably a tertiary organic base, at a temperature of about -60°C. to $+30^{\circ}\text{C.}$, preferably -30°C. to $+5^{\circ}\text{C.}$, most preferably -20°C. to $+5^{\circ}\text{C.}$ The forms of the carboxylic acids, modified at the carboxyl group, which are thereby produced are preferably not isolated, but used, together with the solvent in which they are present, for the reaction with the 6-aminopenicillanic acid or the compounds of the general formulae (46) or (47). If the reaction mixture for the reaction with the aminopenicillanic acid contains water, organic solvents which are miscible with water, for example acetone, tetrahydrofurane, dioxane, dimethylformamide, dimethylsulphoxide or hexamethylphosphoric acid triamide, are preferentially used as solvents for the reaction of the carboxylic acids (48) with the compounds (49), (50), (51) or (52). If the reaction mixture for the reaction with 6-aminopenicillanic acid does not contain any water, or if the reaction mixture for the reaction with compounds of the general formulae (46) or (47) is concerned, solvents such as, preferably, methylene chloride or chloroform are also used, in addition to the solvents mentioned.

According to the invention it is also possible to modify the carboxylic acids of general formula (48) at the carboxyl group by conversion into the derivatives of the general formula:—



in which A, B, C* and U are as defined above.

This is expediently done by first converting a compound of the general formula (54):—



in an anhydrous, inert organic solvent, for example acetone, tetrahydrofurane, methylene chloride, dioxane, chloroform or dimethylformamide, in the presence of at least, and preferably, one mol equivalent of a tertiary base, preferably triethylamine, at temperatures of about -25°C. to $+25^{\circ}\text{C.}$, preferably -10°C. , into an intermediate product by means of one mol equivalent of thionyl chloride, with one mol equivalent of base hydrochloride being formed. This intermediate product, the constitution of which is unknown, is not isolated, but is reacted in the presence of a further molar equivalent of an organic base, also preferably triethylamine, with one molar equivalent of the carboxylic acid of general formula (48) at a temperature of about -25°C. to

+25° C., preferably -10° C. to +10° C. After the base hydrochloride has been removed by filtration, the appropriate compound of the general formula (53) can be isolated by evaporating off the solvent and can optionally be purified by recrystallisation from inert solvents or, if the substance is not crystalline, by brief washing of a solution, for example in ether or benzene, with an aqueous bicarbonate solution at as low a temperature as possible.

The 6-aminopenicillanic acid used as starting material in the process of the invention can be obtained by known methods, for instance by fusion of penicillin-G, either by microbiological or by chemical means.

The carboxylic acids of general formula (48) can be obtained from the amino-acids of the general formula:—



by reaction with the compounds of the general formula:—



in which general formulae (55) and (56) A, B and W are as defined above.

The compounds of the general formula (56) in which W stands for halogen, can be obtained by processes described in German Offenlegungsschrift 1,793,287, in German Patent No. 1,259,871 and in U.S. Patents Nos. 3,275,618 and 3,337,621. Furthermore, some of the compounds of general formula (56) in which W stands for halogen can be obtained from the corresponding amide by metallization at the amide nitrogen atom with methyl lithium, followed by reaction with phosgene.

The compounds of general formula (56) in which W is halogen and A is



can be obtained from the cyclic ureas of general formula:—



in which Q is as defined above, and phosgene. The reaction is illustrated in the Examples.

The production of the reagents of the general formulae (49), (50) and (52) is described in the literature [see J. Med. Chem. 9, (1966), p980; Ber. 96, (1963) p2681; Tetrahedron 17, (1962), p114]. The reagent of general formula (51) can be obtained from N,N'-dimethylethylene diamine after converting it into the N,N'-bis-trimethylsilyl compound, reacting this with phosgene to give the corresponding cyclic urea, and reacting the latter with phosgene.

The penicillins according to the invention can also be obtained from the carboxylic acids of the general formula (48) and 6-aminopenicillanic acid, or the silylated 6-aminopenicillanic acids [see general formulae (46) and (47)] by the known methods of peptide chemistry (see E. Schröder & K. Lübke, "The Peptides", Methods of Peptide Synthesis, Vol. I, pages 76—128). This method of production is however inferior to that of the present invention.

On attempting to obtain some of the penicillins according to the invention via the acid chlorides, prepared in the usual manner from the acids (general formula 48) and thionyl chloride, and 6-aminopenicillanic acid, we obtained a mixture of several penicillins amongst which the desired penicillin, [identified by a preparation via a different, unambiguous route (from ampicillin and the corresponding acid chloride A—CO—Cl; compare general formula (48)] was either not present at all or only present in very small amounts. This was deduced from a comparison of the "in vitro"

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bacterial spectra and of the thin layer chromatogram. In an experiment to obtain the penicillins according to the invention via the mixed anhydrides, prepared in the usual manner from the acids by means of chloroformic acid ethyl ester, and aminopenicillanic acid, it was only possible to isolate ethoxycarbonyl-penicillin in a yield of 20%.

The chemotherapeutic activity of the new penicillins was tested *in vivo* and *in vitro*. The *in vitro* inhibition values (MIC=minimum inhibition concentration (see Table 1) were determined in a liquid medium in the test tube series dilution test, with readings being taken after 24 hours' incubation at 37° C. The MIC is indicated by the non-turbid test tube in the dilution series. A complete medium of the following composition was used as the nutrient medium:

Lab Lemco (OXOID)	10 g
Peptone (DIFCO)	10 g
NaCl	3 g
D-(+)-Dextrose (MERCK)	10 g
Buffer pH 7.4	1000 ml.

(The words OXOID, DIFCO and MERCK are Registered Trade Marks).

The spectrum of action encompasses both Gram-negative and Gram-positive bacteria. The particular advantage of the penicillins according to the invention is that they are effective both *in vitro* (see Table 1) and in animal experiments against ampicillin-resistant and carbenicillin-resistant *Klebsiella* bacteria and against ampicillin-resistant *Proteus* bacteria. Furthermore, ampicillin-resistant varieties of *Pseudomonas* are attacked *in vitro* and *in vivo*. The concentrations required for destruction of the bacteria are reached in the serum after parenteral administration.

The effect, which is generally excellent, is achieved both on a single administration and on repeated administration. The penicillins according to the invention are stable to acid. Some of the new penicillins are very well tolerated, which is made particularly clear through the extremely high dose which in these cases is tolerated, without complication, on intravenous administration into the vein of the tail.

TABLE 1
(MIC in units/ml) Bacterial strains

Peni- cillin No.*	<i>E. Coli</i>				<i>Proteus. vulg.</i>		<i>Klebsiella</i>		<i>P. aerug.</i>		<i>Staph. aureus</i>		<i>Streptoc.</i> <i>fasc.</i> ATCC 9790
	14	A 261	C 165	183/53	1017	3400	K 10	63	Bonn	Walter	1777 E	133	
1	25	>400	100	100	400	200	50	50	400	200		1.6	200
2	3.1	400	12.5	12.5	100	25	50	50	100	100		~0.8	200
4	0.8-4	100-500	4-20	4-20	4-20	4-20	20-100	20-100	20-100	20-100		<0.8	100-500
5		100-500	4-20			20-100	20-100	20-100	20-100	20-100		<0.8	100-500
7	100-500	>500	100-500	100-500	~500	100-500	>500	>500	100-500	>500	100-500	0.8-4	100-500
8	>500	>500	>500	>500	>500	>500	>500	>500	>500	>500	100-500	4-20	>500
9	20-100	>500	100-500	100-500	>500	>100	>500	>500	>500	>500		0.8-4	~500
10 B	12.5	>400	50	50	200	200	50	50	200	200	400	1.6	100
11 C	6.3	>400	50	12.5	100	100	50	100	400	200	400	1.6	200
12	6.3	>400	50	12.5	100	100	50	100	400	200	400	1.6	200
14	4-20	>500	20-100	20-100	100-500	~100	20-100	20-100	100-500	100-500		0.8-4	100-500
15	20-100	>500	100-500	100-500	>500	>500	>500	>500	>500	>500		0.8-4	>500
17	4-20	>500	20-100	20-100	>500	100-500	20-100	20-100	100-500	100-500		<0.8	20-100
18	4-20	>500	20-100	20-100	100-500	100-500	20-100	20-100	100-500	100-500		0.8-4	~100
20		>500	20-100			100-500	20-100	20-100	100-500	100-500		<0.8	20-100
21		>500	20-100			20-100	20-100	20-100	100-500	100-500		<0.8	100-500

* The numbers in this column are the numbers of the Examples in which the penicillin and its production are described.

TABLE 1 (Continued)

Bacterial strains

Penicillin No.	14	<i>E. Coli</i>			<i>Proteus. vulg.</i>	<i>Klebsiella</i>		<i>Psdm. aerug.</i>		<i>Staph. aureus</i>	<i>Streptoc. faec.</i>
		A 261	C 165	183/58	1017	K 10	63	Bonn	Walter	1777 E	ATCC 9790
22		> 500	4-20		4-20		20-100		20-100	< 0.8	~ 20
23		> 500	100-500		> 500		> 500		> 500	0.8-4	100-500
24	6.3	> 400	25	25	100	50	100	100	100	~ 1.6	200
27	100	> 400	200	200	> 400	> 400	> 400	> 400	> 400	< 6.3	> 400
28	100	> 400	200	400	> 400	> 400	> 400	> 400	> 400	12.5	> 400
29	3.1	> 400	6.3	3.1	12.5	200	100	25	50	< 0.8	100
30	4-20	> 500	20-100	20-100	100-500	100-500	100-500	100-500	100-500	0.8-4	20-100
31	20-100	> 500	100-500	20-100	100-500	100-500	100-500	approx. 500	100-500	0.8-4	> 500
32	approx. 20	> 500	20-100	20-100	approx. 100	100-500	approx. 100	100-500	100-500	approx. 0.8	100-500
33		100-500	4-20		4-20		4-20		4-20	< 0.8	20-100
35	approx 4	100-500	20-100	4-20	20-100	20-100	20-100	4-20	approx. 20	< 0.8	20-100
36		> 500	100-500		> 500		> 500		> 500	4-20	100-500
37	< 0.8	> 500	0.8-4	0.8-4	4-20	20-100	4-20	4-20	4-20	< 0.8	20-100
38	0.8-4	> 500	4-20	4-20	20-100	20-100	20-100	20-100	20-100	< 0.8	100-500
44	6.25	400	25	25	50	50	50	50	50	1.6	100

TABLE 1 (Continued)

Bacteria strains

Penicillin No.	14	<i>E. Coli</i>		183/58	<i>Proteus vulg.</i>		<i>Klebsiella</i>		<i>Psdm. aerug.</i>		<i>Staph. aureus</i>		<i>Streptoc. faec.</i>
		A 261	C 165		1017	3400	K 10	63	Bonn	Walter	1777 E	133	ATCC 9790
45	6.25	>400	25	6.25	100	100	100	100	25	12.5	400	<0.78	50
46	6.25	>400	50	12.5	25	50	100	50	25	25	200	1.56	50
47	3.12	>400	25	6.25	50	100	100	50	12.5	12.5	200	<0.78	50
48	3.12	>400	12.5	6.25	25	50	100	50	25	12.5	200	<0.78	25
51	3.12	400	12.5	12.5	25	25	100	50	12.5	12.5	400	<0.78	25
52	3.12	>400	12.5	6.25	—	—	100	—	12.5	12.5	200	<0.78	—
53	3.12	400	6.25	12.5	6.25	12.5	50	25	6.25	12.5	200	<0.78	12.5
54	6.25	>400	25	6.25	200	100	100	100	12.5	25	200	<0.78	50
55	6.25	>400	25	12.5	100	100	100	100	12.5	25	200	<0.78	50

The invention further relates to the pharmaceutical use of the new penicillins and their pharmaceutically acceptable salts.

Accordingly, the present invention provides an antibiotic pharmaceutical composition containing as an active ingredient at least one of the new penicillins of the general formula (1) given above, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable solid or liquid diluent or carrier as herein-after defined.

In the present specification the expression "pharmaceutically acceptable diluent or carrier" means a non-toxic substance that when mixed with the active ingredient or ingredients renders it suitable for administration. The expression preferably excludes water and low-molecular weight organic solvents commonly used in chemical synthesis, except in the presence of other pharmaceutically necessary ingredients such as salts in correct quantities to render the composition isotonic, buffers, surfactants, colouring and flavouring agents, and preservatives. Examples of suitable liquid diluents and carriers are vegetable oils, polyols, buffered aqueous solutions, isotonic saline aqueous solutions, syrups and lotion bases. Examples of suitable solid diluents and carriers are starches, cellulose and its derivatives, sugars, stearates and stearic acid, talc, certain types of alumina, and ointment bases. Examples of pharmaceutical compositions according to the invention are ointments, pastes, creams, sprays, lotions, aqueous

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suspensions, elixirs, syrups, drops, granules and powders, either free-flowing or compressed into tablets.

The penicillins and pharmaceutically acceptable salts of the present invention may be administered perorally.

One group of preferred pharmaceutical compositions of the invention are therefore those adapted for oral administration. The diluents and carriers used are preferably therefore those that adapt the active ingredient or ingredients for oral administration. Examples of such diluents and carriers are solid vehicles, excipients and lubricants such as glucose, lactose and sucrose, corn and potato starch, sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate, powdered gum tragacanth, gelatin, alginic acid, agar, stearic acid, sodium calcium and magnesium stearates, sodium lauryl sulphate, polyvinylpyrrolidone, sodium citrate, calcium carbonate, dicalcium phosphate, and certain types of alumina.

The pharmaceutical compositions of the invention may also contain other non-toxic adjuvants and modifiers such as dyes, surfactants, perfumes, flavouring agents, preservatives and biocides.

The compounds and pharmaceutically acceptable salts of the invention may also be administered parenterally for example by intramuscular, subcutaneous or intravenous injection, or, if necessary, as a continuous drip infusion. A group of preferred pharmaceutical compositions of the invention are therefore those adapted for parenteral injection. The diluents and carriers used are therefore preferably those that adapt the active ingredient for parenteral administration. Examples of such diluents and carriers are solvents and suspending diluents such as water and water-miscible organic solvents, in particular sesame oil, groundnut oil, aqueous propylene glycol, and N,N'-dimethyl formamide. A preferred example of a pharmaceutical composition of the invention adapted for parenteral administration is a sterile isotonic saline aqueous solution of the active ingredient, which may be buffered with a pharmaceutically acceptable buffer. The solution may be rendered isotonic in any known manner, for example by the incorporation of sodium chloride and/or glucose. Such solutions can be administered as a single dose or as a continuous drip infusion, or divided into a series of doses.

In oral and parenteral administration a dose of 25,000 to 1,000,000 units per kg. body weight is appropriate.

The present invention also provides antibiotic medicaments in dosage unit form as hereinafter defined comprising as an active ingredient at least one penicillin of general formula (1) given above or a pharmaceutically acceptable salt thereof, either alone or in admixture with a pharmaceutically acceptable solid or liquid diluent or carrier. In this case the diluent or carrier is preferably as defined above but can also be water or another common solvent.

The expression "medicament in dosage unit form" as used in the present specification means a medicament in the form of discrete portions each containing a unit dose or a multiple or sub-multiple of a unit dose of the active ingredient(s); for example, one, two, three or four unit doses or a half, a third or a quarter of a unit dose. A "unit dose" is the amount of the active ingredient(s) to be administered on one occasion and will usually be a daily dose, or for example a half, a third, or a quarter of a daily dose depending on whether the medicament is to be administered once or, for example, twice, three times, or four times a day.

The discrete portions constituting the medicament in dosage unit form can include a protective envelope. The active ingredient can be undiluted and contained in such an envelope, or can be mixed with a pharmaceutically acceptable solid or liquid diluent or carrier as defined above. Such portions can for example be in monolithic coherent form, such as tablets, lozenges, pills, suppositories, or dragees; in wrapped or concealed form, the active ingredients being within a protective envelope, such as wrapped powders, cachets, sachets, capsules, or ampoules; or in the form of a sterile solution suitable for parenteral injection, such as ampoules of buffered, isotonic, sterile, pyrogen-free aqueous solution; or in any other form known in the art.

As stated above, peroral administration is one preferred form of administration for the new penicillins of general formula (1) and their salts. Preferred medicaments in dosage unit form according to the invention are therefore those adapted for oral administration, such as tablets, pills, dragees, capsules, and cachets, as well as wrapped powders containing the active ingredient in powdered form with a powdered diluent or carrier for suspension in water before being taken.

solutions, syrups and lotion bases. Examples of suitable solid diluents and carriers are starches, cellulose and its derivatives, sugars, stearates and stearic acid, talc, certain types of alumina, and ointment bases. Examples of pharmaceutical compositions according to the invention are ointments, pastes, creams, sprays, lotions, aqueous

As stated above, another preferred mode of administration for the new penicillins and their pharmaceutically acceptable salts is parenteral administration. Preferred medicaments in dosage unit form according to the invention are therefore those adapted for parenteral injection, such as ampoules containing a measured quantity of a sterile isotonic saline injectable aqueous solution of the new active ingredient, which may be buffered with a pharmaceutically acceptable buffer. A particularly preferred medicament in dosage unit form according to the invention is dry ampoules each containing a unit dose or a multiple or sub-multiple of a unit dose of one of the new penicillins and pharmaceutically acceptable salts according to the invention. Such ampoules may be used at the place and time of administration for making up parenterally injectable solutions.

The preferred unit dose for parenteral and peroral administration of the medicaments of the invention is 1,250,000—90,000,000 units per person of active ingredient.

The following Examples illustrate the invention but do not limit it.

The β -lactam content of the penicillins was determined iodometrically in the following Examples. All substances described here showed an IR spectrum corresponding to their structure. The NMR spectra of the penicillins were recorded in CD_3OD solution; the signals indicated in the Examples correspond to the γ -scale; they agree with the particular structure.

The figures quoted in the Examples for the effectiveness against certain bacteria (units/ml) are minimum inhibitory concentrations in the test tube series dilution test after 24 hours' incubation.

In the case of the data: "Effectiveness in Animal Experiments", "A" denotes that the particular penicillin is more effective than ampicillin when used subcutaneously in mice against *Proteus vulgaris* 1017, and "B" denotes that it is more effective than ampicillin and carbenicillin against *Klebsiella aerobacter* 63.

In calculating the analytical data, the water content of the penicillins was taken into account.

Example 1

Sodium D- α -(3-acetyl-3-allylureido)-benzylpenicillin:

5.5 parts by weight of D- α -(3-acetyl-3-allyl-ureido)- α -phenylacetic acid were dissolved in 50 parts by volume of dichloromethane, with exclusion of moisture, and 2.0 parts by weight of triethylamine were added whilst cooling. The mixture was now cooled to between -5° and -10° C., and 3.6 parts by weight of tetramethylchloroformamidinium chloride were added as several portions over the course of a few minutes. Thereafter, the mixture was stirred for 30 minutes at this temperature and any insoluble matter was filtered off without the solution rising to above 0° C. The filtrate was cooled to -10° C. and added all at once to a solution of 4.1 parts by weight of 6-aminopenicillanic acid and 3.4 parts by weight of triethylamine in 50 parts by volume of dichloromethane, cooled to -10° C. [The aminopenicillanic acid was stirred for 1.5 hours at room temperature with the triethylamine and 2 parts by weight of a molecular sieve (Zeolite VS 10—2) which had been ground in a mortar; thereafter, the mixture was filtered whilst excluding moisture, and the filtrate was employed for the reaction]. The combined solutions were left to stand for one hour at 0° C. and subsequently poured into 100 parts by volume of water. The pH value was adjusted to 6.5, the dichloromethane phase was separated off, and the aqueous phase was covered with 200 parts by volume of a 1:1 mixture of ethyl acetate and ether. Sufficient 2 N hydrochloric acid was added, whilst stirring vigorously and cooling with ice, to obtain a pH value of 2.0 in the aqueous layer. The organic phase was separated off, washed with 2×40 parts by volume of water and dried for two hours over $MgSO_4$ in a refrigerator. 20 parts by volume of a 1 M solution of sodium 2-ethylhexanoate in ether containing methanol were now added, the mixture was largely concentrated in vacuo at 0° C., the residue was taken up in just sufficient methanol, and the sodium salt of the penicillin was precipitated by adding excess ether whilst shaking vigorously.

Yield: 67%.

β -Lactam content: 81%.

	C	H	N	S
Calculated:	51.4	5.3	10.9	6.2
Found:	51.5	6.0	10.3	5.5

According to the IR spectrum and thin layer chromatogram, the product was identical with a comparison sample prepared from ampicillin and N-acetyl-N-allyl-carbamic acid chloride.

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Example 2

Sodium D- α -(3- γ -chlorobutyryl-3-methylureido)-benzylpenicillin:

A solution was prepared, as described in Example 1, from 6.25 parts by weight of D- α -(3- γ -chlorobutyryl-3-methylureido)-phenylacetic acid and 3.6 parts by weight of tetramethylchloroformamidine chloride, and was kept for 1.5 hours at -5° to -10° C. Thereafter it was combined with a solution of 4.1 parts by weight of 6-aminopenicillanic acid and 3.4 parts by weight of triethylamine in dichloromethane, which was stored for one hour at room temperature. Thereafter the mixture was worked up as described in Example 1.

Yield: 62%.

 β -Lactam content: 84%.

	C	H	Cl	N	S
Calculated:	48.0	5.1	6.4	10.2	5.8
Found:	48.1	5.2	5.8	9.9	6.4

NMR signals at τ =2.3—2.9 (5 H), 4.45 (1 H), 4.55 (2 H), 5.8 (1 H), 6.4 (2 H), 6.75 (3 H), 7.3 (2 H), 7.9 (2 H) and 8.5 ppm (6 H).

Example 3

If, in the procedure of Example 2, the D- α -(3- γ -chlorobutyryl-3-methylureido)-phenylacetic acid used there is replaced by 0.02 mol of:—

- D- α -(3- β -chloropropionyl-3-methyl-ureido)-phenylacetic acid,
- D- α -(3- γ -trifluorobutyryl-3-methyl-ureido)-phenylacetic acid,
- D- α -(3- γ -trichlorobutyryl-3-methyl-ureido)-phenylacetic acid,
- D- α -(3- γ -trichlorobutyryl-3- β -chloroethyl-ureido)-phenylacetic acid,
- D- α -(3-cinnamoyl-3-methyl-ureido)-phenylacetic acid,
- D- α -(3-[1,2,5,6-tetrahydrobenzoyl]-3-methyl-ureido)-phenylacetic acid or
- D- α -(3-hexahydrobenzoyl-3-methyl-ureido)-phenylacetic acid,

the following penicillins are obtained in the form of their sodium salts:—

- D- α -(3- β -chloropropionyl-3-methylureido)-benzylpenicillin,
- D- α -(3- γ -trifluorobutyryl-3-methyl-ureido)-benzylpenicillin,
- D- α -(3- γ -trichlorobutyryl-3-methyl-ureido)-benzylpenicillin,
- D- α -(3- γ -trichlorobutyryl-3- β -chloroethyl-ureido)-benzylpenicillin,
- D- α -(3-cinnamoyl-3-methyl-ureido)-benzylpenicillin,
- D- α -(3-[1,2,5,6-tetrahydrobenzoyl]-3-methyl-ureido)-benzylpenicillin or
- D- α -(3-hexahydrobenzoyl-3-methyl-ureido)-benzylpenicillin.

Example 4

Sodium D,L- α -(3-benzoyl-3-methyl-ureido)-4-methylbenzylpenicillin:

This penicillin was prepared, as described in Examples 1 and 2, from 5.5 parts by weight of D,L- α -(3-benzoyl-3-methyl-ureido)-*p*-tolyl-acetic acid, 3 parts by weight of tetramethyl-chloroformamidine chloride and 4.55 parts by weight of 6-aminopenicillanic acid.

Yield: 59%.

 β -Lactam content: 84%.

	C	H	N	S
Calculated:	54.5	5.3	9.7	7.9
Found:	54.9	5.9	9.5	(5.6)

NMR signals at τ =2.5 (5 H), 2.5—3.0 (4 H), 4.3—4.65 (3.0 H), 5.8 (1 H), 6.9 (3 H), 7.7 (3 H) and 8.2—8.5 ppm (6 H).

Effectiveness in Animal Experiments: A and B.

Example 5

Sodium D,L-(3- γ -chlorobutyryl-3-methyl-ureido)-(2-thienyl)-methylpenicillin:

This penicillin was prepared, in the manner described in Examples 1 and 2, from 5.9 parts by weight of D,L-(3- γ -chlorobutyryl-3-methyl-ureido)-(2-thienyl)-acetic acid, 3.5 parts by weight of tetramethylchloroformamidine chloride and 4.06 parts by weight of 6-aminopenicillanic acid.

Yield: 64%.

β -Lactam content: 95.5%.

NMR signals at τ =2.5—3.2 (3 H), 4.1 (1 H), 4.4 (2 H), 5.8 (1 H), 6.3 (2 H), 6.7 (3 H), 7.2 (2 H), 7.9 (2 H) and 8.4 ppm (6 H).

Effectiveness in Animal Experiments: B.

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Example 6

If, in the procedure of Example 1, the D- α -(3-acetyl-3-allyl-ureido)-phenylacetic acid used there is replaced by: 0.02 mol of:

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α -(3-acetyl-3-methylureido)-*p*-tolylacetic acid,
 α -(3-acetyl-3-methylureido)-*p*-chlorophenylacetic acid,
 α -(3-acetyl-3-methylureido)-*p*-methylsulphenylphenylacetic acid,
 α -(3-acetyl-3-methylureido)-*p*-methoxyphenylacetic acid,
 α -(3-acetyl-3-methylureido)-*o*-chlorophenylacetic acid,
 α -(3-acetyl-3-methylureido)-*m*-iodo-phenylacetic acid,
 α -(3-acetyl-3-methylureido)-2,6-dichloro-phenylacetic acid,
 α -(3-acetyl-3-methylureido)-2,6-dimethoxy-phenylacetic acid,
 α -(3-acetyl-3-methylureido)-2,4-dibromo-phenylacetic acid,
 α -(3-acetyl-3-methylureido)-*m*-methyl-phenylacetic acid,
 α -(3-acetyl-3-methylureido)-2,6-dimethyl-phenylacetic acid,
 α -(3-acetyl-3-methylureido)-2-chloro-6-fluoro-phenylacetic acid,
 α -(3-acetyl-3-methylureido)-2-thienyl-acetic acid or
 α -(3-acetyl-3-methylureido)-3-thienyl-acetic acid,

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the sodium salts of the following penicillins are obtained:—

α -(3-acetyl-3-methylureido)-*p*-methylbenzylpenicillin,
 α -(3-acetyl-3-methylureido)-*p*-chloro-benzylpenicillin,
 α -(3-acetyl-3-methylureido)-*p*-methylsulphenyl-benzylpenicillin,
 α -(3-acetyl-3-methylureido)-*p*-methoxybenzylpenicillin,
 α -(3-acetyl-3-methylureido)-*o*-chlorobenzylpenicillin,
 α -(3-acetyl-3-methylureido)-*m*-iodobenzylpenicillin,
 α -(3-acetyl-3-methylureido)-2,6-dichlorobenzylpenicillin,
 α -(3-acetyl-3-methylureido)-2,6-dimethoxybenzylpenicillin,
 α -(3-acetyl-3-methylureido)-2,4-dibromobenzylpenicillin,
 α -(3-acetyl-3-methylureido)-*m*-methylbenzylpenicillin,
 α -(3-acetyl-3-methylureido)-2,6-dimethyl-benzylpenicillin,
 α -(3-acetyl-3-methylureido)-2-chloro-6-fluoro-benzylpenicillin,
 α -(3-acetyl-3-methylureido)- α -2-thienylmethylpenicillin or
 α -(3-acetyl-3-methylureido)- α -3-thienylmethylpenicillin.

Example 7—

Sodium D- α -(3-methoxycarbonyl-3-methyl-ureido)-2,6-dichlorobenzylpenicillin:

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1.35 parts by weight of tetramethylchloroformamidinium chloride were dissolved in 15 parts by volume of dichloromethane and cooled to 0° C. whilst excluding moisture. 2.4 parts by weight of D- α -(3-methoxycarbonyl-3-methyl-ureido)-2,6-dichlorophenylacetic acid, in a little methylene chloride, were added to this solution. A solution of 1.04 parts by volume of triethylamine in 5 parts by volume of dichloromethane was now added dropwise at -5° C. over the course of 30 minutes. After a further 40 minutes at -5° C., the mixture was combined with a solution of the triethylamine salt from 2.22 parts by weight of 6-aminopenicillanic acid and 1.6 parts by volume of triethylamine in 25 parts by volume of dichloromethane, cooled to -20° C. The mixture was now stirred for 30 minutes at 0° C., with a further 0.4 part by volume of triethylamine being added after 15 minutes. Thereafter, the mixture was stirred for a further 30 minutes at room temperature and poured into water, the aqueous layer was separated off at pH 6.5, and the sodium salt of the penicillin was isolated as described in Example 1.

Yield: 28%.

β -Lactam content: 94%.

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NMR signals at τ =2.6 (2.1 H), 2.7 (0.9 H), 3.4 (0.7 H), 3.8 (0.3 H), 4.35—4.50 (2 H), 5.8 (1 H), 6.15 (3 H), 6.8 (2.1 H), 6.85 (0.9 H) and 8.45 ppm (6 H).

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Example 8

Sodium L- α -(3-methoxycarbonyl-3-methylureido)-2,6-dichlorobenzyl penicillin:

This penicillin was prepared, in the manner described in Example 7, from 3.1 parts by weight of L- α -(3-methoxycarbonyl-3-methylureido)-2,6-dichlorophenylacetic acid, 1.74 parts by weight of tetramethylchloroformamidinium chloride and 2.87 parts by weight of 6-aminopenicillanic acid.

Yield: 47%.

β -Lactam content: 92%.

NMR signals at τ =2.6 (1.8 H), 2.7 (1.2 H), 3.35 (0.6 H), 3.8 (0.4 H), 4.4 (2 H), 5.75 (1 H), 6.15 (3 H), 6.8 (1.8 H), 6.85 (1.2 H), and 8.4 ppm (6 H).

Example 9

Sodium D,L- α -(3-methoxycarbonyl-3-methylureido)-2,6-dichlorobenzylpenicillin:

A solution of 5.0 parts by weight of D,L- α -(3-methoxycarbonyl-3-methylureido)-2,6-dichlorophenylacetic acid in 10 parts by volume of acetone was added dropwise, at 0° C., to a suspension of 3.0 parts by weight of finely ground tetramethylchloroformamidinium chloride in 20 parts by volume of dry acetone. After 5 minutes, the mixture was cooled to -5° C. and 2.1 parts by volume of triethylamine in 10 parts by volume of acetone were added dropwise, slowly and uniformly, over the course of 30 minutes whilst excluding moisture. The mixture was kept at 0° C. for one hour, whilst stirring, and thereafter the precipitate was filtered off without the solution rising to above 0° C. The filtrate was now added, in several portions, to a solution of 3.23 parts by weight of 6-aminopenicillanic acid in 25 parts by volume of 80% strength aqueous tetrahydrofuran (sufficient 2 N NaOH being added for solution just to occur [pH~8.2]), at 0° C., whilst keeping the pH value at between 7.5 and 8.0 by adding 2 N NaOH. The mixture was allowed to come to room temperature whilst stirring, where it was stirred until no further addition of sodium hydroxide solution was necessary for maintaining the pH value of 7.5 to 8.0 (1 to 2 hours). Thereafter, the pH value was lowered to 6.5 with a little dilute hydrochloric acid, 20 parts by volume of water were added, and the tetrahydrofuran was evaporated off in vacuo at room temperature. The aqueous solution which remained was extracted once with 25 parts by volume of ether and covered with 50 parts by volume of a 1:1 mixture of ethyl acetate and ether. The solution was acidified to pH 2.0 with dilute hydrochloric acid whilst cooling with ice, and the organic phase was separated off. The latter was twice washed with 10 parts by volume of water at a time, dried over MgSO₄ for 4 hours at 0° C., and filtered. The sodium salt of the penicillin was precipitated by adding 15 parts by volume of a 1 molar solution of sodium 2-ethylhexanoate in ether containing methanol. The solvent was almost completely distilled from the mixture in vacuo at 0° C., the residue was taken up in the minimum possible amount of methanol, and the product was precipitated by adding ether. After standing for one hour at 0° C., it was filtered off, washed with ether containing methanol and subsequently dried for several days over P₂O₅ in a vacuum desiccator.

Yield: 71%.

β -Lactam content: 68%.

	C	H	Cl	N	S
Calculated:	41.3	4.2	12.2	9.6	5.5
Found:	41.1	5.0	14.0	9.0	4.9

NMR signals at τ =2.5 (1.95 H), 2.6 (1.05 H), 3.35 and 3.40 (0.65 H), 3.8 (0.35 H), 4.45 (2 H), 5.8 (1 H), 6.2 (3 H), 6.75 (1.95 H), 6.8 (1.05 H) and 8.4 ppm (6 H).

Example 10

A. D- α -(3-Methoxycarbonyl-3-methylureido)-phenylacetic acid:

15.1 parts by weight of D(-)-C-phenylglycine were stirred for 15 minutes with 20.2 parts by weight of triethylamine in 180 parts by volume of a 3:1 mixture of dimethylsulphoxide and water. 15.2 parts by weight of N-methoxycarbonyl-N-methylcarbamic acid chloride in 30 parts by volume of dry acetone were now added dropwise within 30 minutes in such a way that the temperature did not exceed 20° C. The mixture was stirred for a further 2 hours, 200 parts by volume of water were then added and the whole was acidified to pH 2 with dilute hydrochloric acid. Thereafter

the mixture was extracted three times with 120 parts by volume of ethyl acetate at a time, and the organic phase was washed with 50 parts by volume of water and dried over $MgSO_4$. After filtration, the solvent was distilled off in vacuo, and remnants of dimethylsulphoxide were stripped off at $80^\circ C$. and 0.1 mm Hg. The glassy oil, which was left in 73% yield, was pure methoxycarbonyl-methyl-ureido-phenylacetic acid, according to the NMR spectrum.

	C	H	N
Calculated:	54.0	5.3	10.5
Found:	54.9	5.6	9.6

NMR signals at $\tau=0.4$ (1 H), 2.4—2.8 (5 H), 4.65 (1 H), 6.2 (3 H) and 6.9 ppm (3 H).

B. Sodium D- α -(3-methoxycarbonyl-3-methyl-ureido)-benzylpenicillin:

This penicillin was prepared as described in Example 7, from 5.3 parts by weight of D- α -(3-methoxycarbonyl-3-methyl-ureido)-phenylacetic acid, 3.4 parts by weight of tetramethylchloroformamidinium chloride and 4.0 parts by weight of 6-amino-penicillanic acid.

Yield: 63%.

β -Lactam content: 69%.

NMR signals at $\tau=2.3$ —2.9 (5 H), 4.45 (1 H), 4.5 and 4.55 (2 H), 5.8 (1 H), 6.2 (3 H), 6.85 (3 H) and 8.45 ppm (6 H).

The Table which follows compares the anti-bacterial action of this product (A) with that of the penicillin (B) prepared from ampicillin and N-methoxycarbonyl-N-methyl-carbamic acid chloride, and with the product (C) which was prepared according to the instructions of Example 27:

Type of Bacterium	Effectiveness [units/ml]		
	(A)	(B)	(C)
<i>Escherichia coli</i> 14	12.5	6.25	100
<i>Escherichia coli</i> 183/58	50	25	200
<i>Pseudomonas aerug.</i> Bonn	50	25	>400
<i>Pseudomonas aerug.</i> Walter	50	25	>400
<i>Klebsiella</i> K 10	200	200	>400
<i>Klebsiella</i> 63	200	200	>400
<i>Staphylococcus aureus</i> 133	1.56	1.56	6.25

Example 11

A. D- α -(3-Isopropoxycarbonyl-3-methylureido)-phenylacetic acid:

15.1 parts by weight of D(-)-C-phenylglycine were dissolved in 250 parts by volume of 50% strength aqueous dioxane by adding sufficient dilute sodium hydroxide solution. Thereafter the pH value was lowered to 7.8 with 2 N HCl, whereupon a part of the phenylglycine precipitated in a finely divided form. The mixture was cooled to $0^\circ C$. and 18.0 parts by weight of N-isopropoxycarbonyl-N-methylcarbamic acid chloride in 30 parts by volume of anhydrous dioxane were added dropwise over the course of 30 minutes, the pH value of 7.5—8.0 being maintained by simultaneous addition of 2 N sodium hydroxide solution. The mixture was subsequently stirred at room temperature until no further addition of alkali was necessary for keeping the pH constant. 300 parts by volume of water were now added and the solution was extracted once with 150 parts by volume of ether. Thereafter it was acidified to pH=2 with 2 N HCl, and the oil which precipitated was taken up in several portions

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of ethyl acetate. The combined organic solutions were washed once with 100 parts by volume of water and were dried for some hours over $MgSO_4$. After filtration, they were evaporated, and the oily residue was freed of dioxane at 60—80° C. and 0.1 mm Hg. The glassy product was obtained in 48% yield. It was completely pure, according to the NMR spectrum and the thin layer chromatogram.

	C	H	N
Calculated:	57.1	6.1	9.5
Found:	56.9	5.7	9.8

NMR signals at $\tau = -0.3$ (1 H), $+0.4$ (1 H), 2.3—2.8 (5 H), 4.6 (1 H), 5.0 (1 H), 6.9 (3 H) and 8.75 ppm (6 H).

B. The following α -ureido-arylacetic acids were prepared as described in Example 11 A:

1. *D*- α -(3-Acetyl-3-allylureido)-phenylacetic acid from 8.1 parts by weight of N-acetyl-N-allylcarbamic acid chloride and 7.5 parts by weight of D(-)-C-phenylglycine.

Yield: 100%.

	C	H	N
Calculated:	60.8	5.9	10.1
Found:	60.3	6.1	9.8

NMR signals at $\tau = 0.0$ (1 H), 2.6 (5 H), 3.75—4.5 (1 H), 4.6 (1 H), 4.7—5.15 (2 H), 5.5—5.9 (2 H) and 7.7 ppm (3 H).

2. *D*- α -(3- γ -Chlorobutyryl-3-methylureido)-phenylacetic acid from 9.9 parts by weight of N- γ -chlorobutyryl-N-methylcarbamic acid chloride and 7.5 parts by weight of D(-)-C-phenylglycine.

Yield: 99%.

	C	H	Cl	N
Calculated:	53.8	5.5	11.3	9.0
Found:	53.9	5.8	10.8	9.4

NMR signals at $\tau = -0.1$ (1 H), 2.6 (5 H), 4.6 (1 H), 6.3 (2 H), 6.8 (3 H), 7.2 (2 H) and 7.9 ppm (2 H).

3. *D,L*- α -(3-Benzoyl-3-methylureido)-4-tolylacetic acid from 3.2 parts by weight of N-benzoyl-N-methylcarbamic acid chloride and 3.8 parts by weight of D,L-C-(4-tolyl)-glycine.

Yield: 90%.

NMR signals at $\tau = 2.5$ (5 H), 2.6 (2 H), 2.8 (2 H), 4.5 (1 H), 6.85 (3 H) and 7.7 ppm (3 H).

4. *D*- α -(3-methoxycarbonyl-3-methylureido)-2,6-dichlorophenylacetic acid from 1.75 parts by weight of N-acetyl-N-methylcarbamic acid chloride and 3.31 parts by weight of D(-)-C-(2,6-dichlorophenyl)-glycine hydrobromide. [We assume that the acid, which can be obtained from 2,6-dichlorobenzaldehyde via the hydantoin in a manner which is in itself known, and which after acylation of the amino group and splitting of the racemate with optically active bases, followed by removal of the acylating group, is obtained in a laevo-rotatory and a dextro-rotatory form, belongs, by analogy to the known conditions in the case of C-phenylglycine, to the D-series in the laevo-rotatory form, and to the L-series in the dextro-rotatory form].

Yield: 90%. Melting point = 149° C., $[\alpha]_D = 28.1^\circ$.

NMR signals at $\tau = 0.2$ (1 H), 2.5 (3 H), 3.6 (1 H), 6.2 (3 H) and 6.9 ppm (3 H).

5. *L*- α -(3-Methoxycarbonyl-3-methylureido)-2,6-dichlorophenylacetic acid from 1.6 parts by weight of N-methoxycarbonyl-N-methylcarbamic acid chloride and 3.01 parts by weight of L(+)-C-(2,6-dichlorophenyl)-glycine hydrobromide.

Yield: 100%, $[\alpha]_D = +29.3^\circ$.

NMR signals as indicated in Example 9.B.4.

	6. <i>D,L-α-(3-Methoxycarbonyl-3-methylureido)-2,6-dichlorophenylacetic acid</i> from 3.03 parts by weight of N-methoxycarbonyl-N-methyl-carbamic acid chloride and 4.4 parts by weight of D,L-C-(2,6-dichlorophenyl)-glycine. Yield: 78%. Melting point=216° C. NMR signals as indicated in Example 9.B.4.				5	5	N
	7. <i>D-α-(3-n-Butoxycarbonyl-3-methylureido)-phenylacetic acid</i> from 9.7 parts by weight of N-n-butoxycarbonyl-N-methylcarbamic acid chloride and 7.1 parts by weight of D-C-phenylglycine. Yield: 100%.				10	10	N
10		C	H	N			
	Calculated:	58.4	6.5	9.1			
	Found:	58.6	6.9	9.5			
	NMR signals at $\tau=0.5$ (1 H), 2.6 (5 H), 4.65 (1 H), 5.8 (2 H), 6.9 (3 H), 8.0—9.0 (4 H) and 9.05 ppm (3 H).						
15	8. <i>D,L-α-(3-Benzoyl-3-allylureido)-4-methoxyphenyl-glycine</i> from 4.5 parts by weight of N-benzoyl-N-allyl-carbamic acid chloride and 3.6 parts by weight of D,L-C-(4-methoxyphenyl)-glycine. Yield: 70%.				15	15	N
	NMR signals at $\tau=0.6$ (1 H), 2.5 (5 H), 2.7 (2 H), 3.0 (2 H), 3.8—4.5 (1 H), 4.6—5.2 (3 H), 5.6—5.8 (2 H) and 6.2 ppm (3 H).				20	20	N
20	9. <i>D-α-(3-Acetyl-3-benzylureido)-phenylacetic acid</i> from 8.5 parts by weight of N-acetyl-N-benzyl-carbamic acid chloride and 6.0 parts by weight of D-C-phenylglycine. Yield: 92%. Melting point=183—185° C.						
		C	H	N			
	Calculated:	66.3	5.6	8.6			
	Found:	66.3	5.7	8.6			
	NMR signals at $\tau=-0.1$ (1 H), 2.6 (5 H), 2.7 (5 H), 4.55 (1 H), 5.0 (2 H) and 7.8 ppm (3 H).				25	25	N
25	10. <i>D,L-α-(3-Benzoyl-3-allylureido)-2,6-dichlorophenylacetic acid</i> from 4.5 parts by weight of N-benzoyl-N-allyl-carbamic acid chloride and 4.4 parts by weight of D,L-C-(2,6-dichlorophenyl)-glycine. Yield: 97%.				30	30	N
30		C	H	Cl	N		
	Calculated:	56.0	4.0	17.4	6.9		
	Found:	55.6	4.4	16.0	6.5		
35	NMR signals at $\tau=0$ (1 H), 2.3—2.65 (8 H), 3.6 (1 H), 3.9—4.5 (1 H), 4.8—5.3 (2 H) and 5.6—5.9 ppm (2 H).				35	35	N
40	11. <i>D,L-α-(3-Acetyl-3-allylureido)-2-thienylacetic acid</i> from 3.2 parts by weight of N-acetyl-N-allylcarbamic acid chloride and 2.9 parts by weight of D,L-C-(2-thienyl)-glycine. Yield: 99%.				40	40	N
	NMR signals at $\tau=2.5$ —3.1 (3 H), 3.7—4.4 (1 H), 4.3 (1 H), 4.6—5.1 (2 H), 5.5—5.7 (2 H) and 7.7 ppm (3 H).						
45	12. <i>D,L-α-(3-Dimethylaminocarbonyl-3-methylureido)-2,6-dichloro-phenylacetic acid</i> from 3.3 parts by weight of N-dimethylamino-carbonyl-N-methyl-carbamic acid chloride and 4.4 parts by weight of D,L-C-(2,6-dichlorophenyl)-glycine. Yield: 86%. Melting point=205° C.				45	45	N
	NMR signals at $\tau=1.6$ (1 H), 2.5 (3 H), 3.7 (1 H), 7.0 (3 H) and 7.1 ppm (6 H).						

	22	23	1,301,962	23
from d 4.4			13. <i>D,L</i> - α - (3 - Methoxycarbonyl - 3 - methylureido) - 4 - methoxyphenylacetic acid from 3.0 parts by weight of N-methoxycarbonyl-N-methylcarbamic acid chloride and 3.6 parts by weight of D,L-C-(4-methoxyphenyl)-glycine. Yield: 87%.	
5	5	5	NMR signals at $\tau=2.6$ (2 H), 3.05 (2 H), 4.6 (1 H), 6.2 (6 H) and 6.8 ppm (3 H).	5
s by weight			14. <i>D,L</i> - α - (3 - Dimethylaminocarbonyl - 3 - methylureido) - 4 - methoxyphenylacetic acid from 3.3 parts by weight of N-dimethylaminocarbonyl-N-methylcarbamic acid chloride and 3.6 parts by weight of D,L-C-(4-methoxyphenyl)-glycine. Yield: 100%.	
10	10	10	NMR signals at $\tau=2.0$ (1 H), 2.6 (2 H), 3.05 (2 H), 4.6 (1 H), 6.2 (3 H), 6.95 (3 H) and 7.1 ppm (6 H).	10
—9.0			15. <i>D,L</i> - α - (3 - Methoxycarbonyl - 3 - methylureido) - 2 - thienylacetic acid from 3.0 parts by weight of N-methoxycarbonyl-N-methylcarbamic acid hydrochloride and 2.9 parts by weight of D,L-C-(2-thienyl)-glycine. Yield: 100%.	
s by ht of	15	15	NMR signals at $\tau=0.4$ (1 H), 2.5—3.1 (3 H), 4.25 (1 H), 6.2 (3 H) and 6.8 ppm (3 H).	15
1 H),	20	20	16. <i>D,L</i> - α - (3 - Dimethylaminocarbonyl - 3 - methylureido) - phenylacetic acid from 3.3 parts by weight of N-dimethylaminocarbonyl-3-methylcarbamic acid chloride and 2.9 parts by weight of D,L-C-(2-thienyl)-glycine. Yield: 84%.	20
of N- ycine.			NMR signals at $\tau=1.9$ (1 H), 2.5—3.1 (3 H), 4.3 (1 H), 6.9 (3 H) and 7.1 ppm (6 H).	
25	25	25	17. <i>D,L</i> - α - (3 - Benzoyl - 3 - allylureido) - α - 2 - thienylacetic acid from 4.5 parts by weight of N-benzoyl-N-allylcarbamic acid chloride and 2.9 parts by weight of D,L-C-(2-thienyl)-glycine. Yield: 96%.	25
d 7.8			NMR signals at $\tau=2.5$ (5 H), 2.5—3.1 (3 H), 3.8—4.5 (2 H), 4.8—5.3 (2 H) and 5.5—5.8 ppm (2 H).	
ts by D,L-	30	30	18. <i>D,L</i> - α - (3 - γ - Chlorobutyryl - 3 - methylureido) - 2 - thienylacetic acid from 4.0 parts by weight of N- γ -chlorobutyryl-N-methylcarbamic acid chloride and 2.9 parts by weight of D,L- α -(2-thienyl)-glycine. Yield: 99%.	30
			NMR signals at $\tau=2.5$ —3.1 (3 H), 4.2 (1 H), 6.35 (2 H), 6.7 (3 H), 7.2 (2 H) and 7.9 ppm (2 H).	
35	35	35	19. <i>D,L</i> - α - (3 - [2 - Furoyl] - 3 - methyl - ureido) - 2 - thienylacetic acid from 5.6 parts by weight of N-(2-furoyl)-N-methylcarbamic acid chloride and 4.7 parts by weight of D,L-C-(2-thienyl)-glycine. Yield: 100%.	35
—5.3			20. <i>D</i> - α -(3-Allyloxycarbonyl-3-methylureido)-phenylacetic acid from 15.8 parts by weight of N-allyloxycarbonyl-N-methylcarbamic acid chloride and 15.1 parts by weight of D-C-phenylglycine. Yield: 88%.	
ht of enyl)-	40	40	NMR signals at $\tau=-1.8$ (1 H), +0.4 (1 H), 2.6 (5 H), 3.7—4.3 (1 H), 4.4—4.9 (3 H), 5.3 (2 H), and 6.85 ppm (3 H).	40
2 H),			21. <i>D</i> - α - (3 - [3 - Nitro - 4 - methylbenzoyl] - 3 - methyl - ureido) - phenylacetic acid from 8.0 parts by weight of N-(3-nitro-4-methylbenzoyl)-N-methylcarbamic acid chloride and 4.7 parts by weight of D-C-phenylglycine. Yield: 46%.	
acid acid	45	45	NMR signals at $\tau=1.6$ —2.8 (8 H), 4.6 (1 H), 6.8 (3 H) and 7.4 ppm (3 H).	45
D.				

22. *D* - α - (3 - [4 - Methylbenzoyl] - 3 - methylureido) - phenylacetic acid from 13 parts by weight of N-p-methylbenzoyl-N-methylcarbamic acid chloride and 9.2 parts by weight of D-C-phenylglycine.
Yield: 85%.
- 5 NMR signals at $\tau=0.2$ (1 H), 2.4—2.9 (9 H), 6.65 (1 H), 6.9 (3 H) and 7.6 ppm (3 H). 5
23. *D,L* - α - (3 - Benzoyl - 3 - methylureido) - 2,6 - dichlorophenylacetic acid from 7.2 parts by weight of N-benzoyl-N-methylcarbamic acid chloride and 8.0 parts by weight of D,L-C-(2,6-dichlorophenyl)-glycine.
Yield: 100%. Melting point=200° C.
- 10 NMR signals at $\tau=-0.4$ (1 H), 2.2—2.7 (8 H), 3.5 (1 H), and 6.9 (3 H). 10
24. *D,L* - α - (3 - Benzoyl - 3 - methylureido) - 4 - methylsulphenylphenylacetic acid from 10.0 parts by weight of N-benzoyl-N-methylcarbamic acid chloride and 10.0 parts by weight of D,L-C-(4-methylsulphenylphenyl)-glycine.
Yield: 73%.
- 15 NMR signals at $\tau=0.2$ (1 H), 2.3—2.8 (9 H), 4.65 (1 H), 6.9 (3 H) and 7.5 ppm (3 H). 15
25. *D,L* - α - (3 - Ethoxycarbonyl - 3 - methylureido) - 4 - methylsulphenylphenylacetic acid from 16.8 parts by weight of N-ethoxycarbonyl-N-methylcarbamic acid chloride and 20.0 parts by weight of D,L-C-(4-methylsulphenylphenyl)-glycine.
Yield: 85%. Melting point=120—122° C.
- 20 NMR signals at $\tau=0.4$ (1 H), 2.4—2.9 (4 H), 4.65 (1 H), 5.75 (2 H), 6.85 (3 H) and 7.55 ppm (3 H). 20
26. *D,L* - α - (3- β -Chloropropionyl - 3 - methylureido) - (1,2,5,6 - tetrahydrophenylacetic acid from 18.4 parts by weight of N- β -chloropropionyl-N-methylcarbamic acid chloride and 15.5 parts by weight of D,L-C-(1,2,5,6-tetrahydrophenyl)-glycine.
Yield: 73%.
- 25 NMR signals at $\tau=0.6$ (1 H), 4.3 (2 H), 5.7 (1 H), 6.2 (2 H), 6.8 (2 H) and 7.7—8.8 ppm (7 H). 25
27. *D* - α - (3 - [2 - Thienoyl] - 3 - methyl - ureido) - phenylacetic acid from 9.0 parts by weight of N-(2-theonyl)-N-methylcarbamic acid chloride and 6.6 parts by weight of D-C-phenylglycine.
Yield: 50%.
- 30 30
28. *D* - α - (3 - [3,5 - Dimethyl - isoxazol - 4 - oyl] - 3 - methyl - ureido) - phenylacetic acid from 8.5 parts by weight of N-(3,5-dimethyl-isoxazol-4-oyl)-N-methylcarbamic acid chloride and 5.9 parts by weight of D-C-phenylglycine.
Yield: 32%.
- 35 35
- C. Sodium D- α -(3-isopropoxycarbonyl-3-methylureido)-benzylpenicillin:
This penicillin was manufactured as described in Example 9 from 5.9 parts by weight of D- α -(3-isopropoxycarbonyl-3-methyl-ureido)-phenylacetic acid, 3.7 parts by weight of tetramethylchloroformanidium chloride and 4.0 parts by weight of 6-aminopenicillanic acid.
Yield: 45%.
 β -Lactam content: 86%.
- 40 40
- | | C | H | N | S |
|-------------|------|-----|------|-----|
| Calculated: | 48.8 | 5.6 | 10.4 | 5.9 |
| Found: | 48.7 | 5.9 | 10.8 | 5.8 |
- 45 45
- NMR signals at $\tau=2.3$ —2.8 (5 H), 4.4 (1 H), 4.55 (2 H), 5.0 (1 H), 5.8 (1 H), 6.85 (3 H), 8.5 (6 H), and 8.7 ppm (6 H).

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The Table which follows compares the anti-bacterial action of this product (A) with the penicillin (B) prepared from ampicillin and N-*i*-propoxycarbonyl-N-methyl-carbamic acid chloride and with the product (C) which was obtained from D- α -(3-*i*-propoxycarbonyl-3-methylureido)-phenylacetic acid according to the procedure described in Example 28:

Type of Bacterium	Effectiveness [units/ml]		
	(A)	(B)	(C)
<i>Escherichia coli</i> 14	6.25	6.25	100
<i>Escherichia coli</i> C 165	50	25	200
<i>Escherichia coli</i> 183/58	23.5	6.25	400
<i>Pseudomonas aer.</i> Bonn.	59	25	>400
<i>Pseudomonas aer.</i> Walter	100	50	>400

Example 12

Sodium D- α -(3-*n*-butoxycarbonyl-3-methylureido)-benzylpenicillin:

This penicillin was prepared in the manner described in Example 9 from 5.6 parts by weight of D- α -(3-*n*-butoxycarbonyl-3-methylureido)-phenylacetic acid, 3.3 parts by weight of tetramethyl-chloroformamidinium chloride and 3.6 parts by weight of 6-aminopenicillanic acid. The ureidoacetic acid was stirred with the tetramethyl-chloroformamidinium chloride in acetone at -5°C . for only 20 minutes.

Yield: 38%.

β -Lactam content: 61%.

	C	H	N	S
Calculated:	48.1	6.0	9.7	5.6
Found:	48.4	5.5	9.4	5.5

NMR signals at $\tau = 2.3-2.8$ (5 H), 4.45 (1 H), 4.55 (2 H), 5.8 (3 H), 6.85 (3 H) and 8.1-8.9 ppm (13 H).

Example 13

If, in the procedure of Example 10, the D- α -(3-methoxycarbonyl-3-methyl-ureido)-phenylacetic acid used there is replaced by 0.018 mol of:

- D- α -(3-ethoxycarbonyl-3-methyl-ureido)-phenylacetic acid,
- D- α -(3-dimethylaminocarbonyl-3-methyl-ureido)-phenylacetic acid,
- D- α -(3-dimethylaminocarbonyl-3-ethyl-ureido)-phenylacetic acid,
- D- α -(3-dimethylaminocarbonyl-3-propyl-ureido)-phenylacetic acid,
- D- α -(3-dimethylaminocarbonyl-3-*i*-propyl-ureido)-phenylacetic acid,
- D- α -(3-dimethylaminocarbonyl-3-*n*-butyl-ureido)-phenylacetic acid,
- D- α -(3-dimethylaminocarbonyl-3-allyl-ureido)-phenylacetic acid,
- D- α -(3-dimethylaminocarbonyl-3-cyclohexyl-ureido)-phenylacetic acid,
- D- α -(3-dimethylaminocarbonyl-3-phenyl-ureido)-phenylacetic acid,
- D- α -(3-[1-pyrrolidylcarbonyl]-3-methyl-ureido)-phenylacetic acid,
- D- α -(3-[1-piperidylcarbonyl]-3-methyl-ureido)-phenylacetic acid,
- D- α -(3-diethylaminocarbonyl-3-methyl-ureido)-phenylacetic acid,
- D- α -(3-ethylaminocarbonyl-3-methyl-ureido)-phenylacetic acid,
- D- α -(3-methylaminocarbonyl-3-methyl-ureido)-phenylacetic acid,
- D- α -(3-phenylaminocarbonyl-3-methyl-ureido)-phenylacetic acid,
- D- α -(3-[4-morpholinyl]-carbonyl-3-methyl-ureido)-phenylacetic acid,
- D- α -(3-[1-pyrrolidylcarbonyl]-3-ethylureido)-phenylacetic acid,
- D- α -(3-[1-piperidylcarbonyl]-3-ethylureido)-phenylacetic acid,
- D- α -(3-diethylaminocarbonyl-3-ethylureido)-phenylacetic acid,
- D- α -(3-ethylaminocarbonyl-3-ethylureido)-phenylacetic acid,
- D- α -(3-methylaminocarbonyl-3-ethylureido)-phenylacetic acid,
- D- α -(3-phenylaminocarbonyl-3-ethylureido)-phenylacetic acid,

	D- α -(3-phenylaminocarbonyl-3-ethylureido)-phenylacetic acid,				
	D- α -(3-[4-morpholinyl]-carbonyl-3-ethylureido)-phenylacetic acid,				
	D- α -(3-[1-pyrrolidyl]-carbonyl-3- <i>n</i> -propylureido)-phenylacetic acid,				aceti
	D- α -(3-[1-piperidyl]-carbonyl-3- <i>i</i> -propylureido)-phenylacetic acid,				
5	D- α -(3-diethylaminocarbonyl)-3- <i>n</i> -butylureido)-phenylacetic acid or	5		D- α	
	D- α -(3-dimethylaminocarbonyl)-3-cyclohexylureidophenylacetic acid,		5	D- α	
	the sodium salts of the following penicillins are obtained: —			D- α	
	D- α -(3-ethoxycarbonyl-3-methylureido)-benzylpenicillin,			D- α	
	D- α -(3-dimethylaminocarbonyl-3-methylureido)-benzylpenicillin,			D- α	
10	D- α -(3-dimethylaminocarbonyl-3-ethylureido)-benzylpenicillin,	10		D- α	
	D- α -(3-dimethylaminocarbonyl-3-propylureido)-benzylpenicillin,		10	D- α	
	D- α -(3-dimethylaminocarbonyl-3- <i>i</i> -propylureido)-benzylpenicillin,			D- α	
	D- α -(3-dimethylaminocarbonyl-3- <i>n</i> -butylureido)-benzylpenicillin,			D- α	
	D- α -(3-dimethylaminocarbonyl-3-allylureido)-benzylpenicillin,			D- α	
15	D- α -(3-dimethylaminocarbonyl-3-cyclohexylureido)-benzylpenicillin,	15		D- α	
	D- α -(3-dimethylaminocarbonyl-3-phenylureido)-benzylpenicillin,		15	D- α	
	D- α -(3-[1-pyrrolidylcarbonyl]-3-methylureido)-benzylpenicillin,			D- α	
	D- α -(3-[1-piperidylcarbonyl]-3-methylureido)-benzylpenicillin,			D- α	
	D- α -(3-diethylaminocarbonyl-3-methylureido)-benzylpenicillin,			D- α	
20	D- α -(3-ethylaminocarbonyl-3-methylureido)-benzylpenicillin,	20		D- α	
	D- α -(3-methylaminocarbonyl-3-methylureido)-benzylpenicillin,		20	D- α	
	D- α -(3-phenylaminocarbonyl-3-methylureido)-benzylpenicillin,			D- α	
	D- α -(3-[4-morpholinyl]-carbonyl-3-methylureido)-benzylpenicillin,			D- α	
	D- α -(3-[1-pyrrolidylcarbonyl]-3-ethylureido)-benzylpenicillin,			D- α	
25	D- α -(3-[1-piperidylcarbonyl]-3-ethylureido)-benzylpenicillin,	25		D- α	
	D- α -(3-diethylaminocarbonyl-3-ethylureido)-benzylpenicillin,		25	D- α	
	D- α -(3-ethylaminocarbonyl-3-ethylureido)-benzylpenicillin,			D- α	
	D- α -(3-methylaminocarbonyl-3-ethylureido)-benzylpenicillin,			D- α	
	D- α -(3-phenylaminocarbonyl-3-ethylureido)-benzylpenicillin,			D- α	
30	D- α -(3-[4-morpholinyl]-carbonyl-3-ethylureido)-benzylpenicillin,	30		D- α	
	D- α -(3-[1-pyrrolidyl]-carbonyl-3- <i>n</i> -propylureido)-benzylpenicillin,		30	D- α	
	D- α -(3-[1-piperidyl]-carbonyl-3- <i>i</i> -propylureido)-benzylpenicillin,			D- α	
	D- α -(3-diethylaminocarbonyl)-3- <i>n</i> -butylureido)-benzylpenicillin or			D- α	
	D- α -(3-diethylaminocarbonyl)-3-cyclohexylureido)-benzylpenicillin.				
35	Example 14	35			
	Sodium D,L- α -(3-benzoyl-3-allylureido)-4-methoxybenzylpenicillin:			D- α	
	This penicillin was prepared in the manner described in Example 9, from 4.4		35	D- α	
	parts by weight of D,L- α -(3-benzoyl-3-allylureido)-4-methoxyphenylacetic acid, 2.26			D- α	
40	parts by weight of tetramethylchloroformamidinium chloride and 2.6 parts by weight	40		D- α	
	of 6-aminopenicillanic acid.			D- α	
	Yield: 51%.		40	D- α	
	β -Lactam content: 65%.			D- α	
				D- α	
				D- α	
45	Calculated: C 55.4 H 5.2 N 9.2 S 5.3	45		D- α	
	Found: C 55.4 H 4.8 N 8.1 S 4.5		45	D- α	
				D- α	
	NMR signals at τ =2.6 (5 H), 2.7 (2 H), 3.2 (2 H), 3.9—4.5 (1 H), 4.55 (3 H),			D- α	
	4.7—5.2 (2 H), 5.6—5.9 (3 H), 6.25 (3 H) and 8.4 ppm (6 H).			D- α	
	Example 15			D- α	
	Sodium D,L- α -(3-benzoyl-3-allylureido)-2,6-dichlorobenzylpenicillin:			D- α	
50	This penicillin was prepared in the manner described in Example 9 from 7.2	50		D- α	
	parts by weight of D,L- α -(3-benzoyl-3-allylureido)-2,6-dichlorophenylacetic acid,			D- α	
	4.05 parts by weight of tetramethylchloroformamidinium chloride and 3.86 parts by			D- α	
	weight of 6-aminopenicillanic acid.			D- α	
	Yield: 46%.		55	D- α	
55	β -Lactam content: 83%.	55		D- α	
				D- α	
				D- α	
	Calculated: C 49.5 H 4.3 Cl 10.8 N 8.6 S 4.9			D- α	
	Found: C 49.9 H 5.1 Cl 11.3 N 8.2 S 4.4		60	D- α	
				D- α	
60	NMR signals at τ =2.4—2.9 (8 H), 3.4 (1 H), 3.8—4.4 (1 H), 4.4—4.6 (2 H),	60			
	4.8—5.2 (2 H), 5.5—5.8 (2 H), 5.85 (1 H) and 8.5 ppm (6 H).				

Example 16

If, in the procedure of Example 4, the D,L- α -(3-benzoyl-3-methylureido)-*p*-tolyl-acetic acid used there is replaced by 0.015 mol of:

5	5	D- α -(3-benzoyl-3-methylureido)-phenylacetic acid,	5
		D- α -(3-benzoyl-3-ethylureido)-phenylacetic acid,	
		D- α -(3-benzoyl-3-methylureido)-4-chlorophenylacetic acid,	
		D- α -(3-benzoyl-3-methylureido)-4-methoxyphenylacetic acid,	
10	10	D- α -(3-benzoyl-3-methylureido)-2-chlorophenylacetic acid,	10
		D- α -(3-benzoyl-3-methylureido)-3-iodophenylacetic acid,	
		D- α -(3-benzoyl-3-methylureido)-2,6-dimethoxyphenylacetic acid,	
		D- α -(3-benzoyl-3-methylureido)-2,4-dibromophenylacetic acid,	
		D- α -(3-benzoyl-3-methylureido)-3-thienylacetic acid,	
15	15	D- α -(3-benzoyl-3-methylureido)- <i>m</i> -tolylacetic acid,	15
		D- α -(3-benzoyl-3-methylureido)-2,6-dimethylphenylacetic acid,	
		D- α -(3-benzoyl-3-methylureido)-2-chloro-6-fluorophenylacetic acid,	
		D- α -(3-benzoyl-3-methylureido)-2-thienylacetic acid,	
		L- α -(3-benzoyl-3-methylureido)-phenylacetic acid,	
20	20	D- α -(3-[3-nitro-4-methoxyphenyl]-3-methylureido)-phenylacetic acid,	20
		D- α -(3- <i>p</i> -chlorobenzoyl-3-ethylureido)-phenylacetic acid,	
		D- α -(3- <i>o</i> -bromobenzoyl-3- <i>n</i> -propyl-ureido)-phenylacetic acid,	
		D- α -(3- <i>p</i> -methoxybenzoyl-3-methylureido)-phenylacetic acid,	
		D- α -(3- <i>p</i> -methoxycarbonylamino-benzoyl-3-methylureido)-phenylacetic acid,	
25	25	D- α -(3- <i>p</i> -methylsulphenylbenzoyl-3-methyl-ureido)-phenylacetic acid,	25
		D- α -(3-[2-chloro-5-methoxybenzoyl]-3- <i>n</i> -butyl-ureido)-phenylacetic acid,	
		D- α -(3- <i>p</i> -nitrobenzoyl-3-methyl-ureido)-phenylacetic acid,	
		D- α -(3-[2-chloro-4-ethylsulphenylbenzoyl]-3-methyl-ureido)-phenylacetic acid,	
		D- α -(3- <i>m</i> -cyanobenzoyl-3-methyl-ureido)-phenylacetic acid,	
30	30	D- α -(3-[3,5-dimethylbenzoyl]-3-methyl-ureido)-phenylacetic acid,	30
		D- α -(3-benzoyl-3-allyl-ureido)-phenylacetic acid,	
		D- α -(3- <i>m</i> -iodobenzoyl-3-methyl-ureido)-phenylacetic acid,	
		D- α -(3-benzoyl-3-phenyl-ureido)-phenylacetic acid or	
		D- α -(3-naphthoyl(1)-3-methyl-ureido)-phenylacetic acid,	

the sodium salts of the following penicillins are obtained: —

35	35	D- α -(3-benzoyl-3-methylureido)-benzylpenicillin,	35
		D- α -(3-benzoyl-3-ethylureido)-benzylpenicillin,	
		D- α -(3-benzoyl-3-methylureido)-4-chlorobenzylpenicillin,	
		D- α -(3-benzoyl-3-methylureido)-4-methoxybenzylpenicillin,	
40	40	D- α -(3-benzoyl-3-methylureido)-2-chloro-benzylpenicillin,	40
		D- α -(3-benzoyl-3-methylureido)-3-iodo-benzylpenicillin,	
		D- α -(3-benzoyl-3-methylureido)-2,6-dimethoxy-benzylpenicillin,	
		D- α -(3-benzoyl-3-methylureido)-2,4-dibromo-benzylpenicillin,	
		D- α -(3-benzoyl-3-methylureido)-3-thienylmethylpenicillin,	
45	45	D- α -(3-benzoyl-3-methylureido)-3-methylbenzylpenicillin,	45
		D- α -(3-benzoyl-3-methylureido)-2,6-dimethylbenzylpenicillin,	
		D- α -(3-benzoyl-3-methylureido)-2-chloro-6-fluorobenzylpenicillin,	
		D- α -(3-benzoyl-3-methylureido)-2-thienylmethylpenicillin,	
		L- α -(3-benzoyl-3-methylureido)-benzylpenicillin,	
		D- α -(3-[3-nitro-4-methoxyphenyl]-3-methylureido)-benzylpenicillin,	
		D- α -(3- <i>p</i> -methoxybenzoyl-3-methylureido)-benzylpenicillin,	
50	50	D- α -(3- <i>p</i> -methoxycarbonylamino-benzoyl-3-methylureido)-benzylpenicillin,	50
		D- α -(3- <i>p</i> -chlorobenzoyl-3-ethylureido)-benzylpenicillin,	
		D- α -(3- <i>o</i> -bromobenzoyl-3- <i>n</i> -propyl-ureido)-benzylpenicillin,	
		D- α -(3-[2-chloro-5-methoxybenzoyl]-3- <i>n</i> -butyl-ureido)-benzylpenicillin,	
		D- α -(3- <i>p</i> -methylsulphenylbenzoyl-3-methylureido)-benzylpenicillin,	
55	55	D- α -(3- <i>p</i> -nitrobenzoyl-3-methyl-ureido)-benzylpenicillin,	55
		D- α -(3-[2-chloro-4-ethylsulphenyl-benzoyl]-3-methyl-ureido)-benzylpenicillin,	
		D- α -(3- <i>m</i> -cyano-benzoyl-3-methyl-ureido)-benzylpenicillin,	
		D- α -(3-[3,5-dimethyl-benzoyl]-3-methyl-ureido)-benzylpenicillin,	
		D- α -(3-benzoyl-3-allyl-ureido)-benzylpenicillin,	
60	60	D- α -(3- <i>m</i> -iodobenzoyl-3-methyl-ureido)-benzylpenicillin,	60

om 4.4
d, 2.26
weight

(3 H),
(6 H).

om 7.2
acid,
arts by

(2 H),
(6 H).

D- α -(3-benzoyl-3-phenyl-ureido)-benzylpenicillin or
D- α -(3-naphthyl(1)-3-methyl-ureido)-benzylpenicillin.

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Example 17

Sodium D,L- α -(3-acetyl-3-allylureido)- α -thienyl(2)-methylpenicillin:

This penicillin was prepared in the manner described in Example 9 from 5.0 parts by weight of D,L- α -(3-acetyl-3-allyl-ureido)-2-thienyl-acetic acid, 3.6 parts by weight of tetramethylchloroformamidinium chloride and 3.9 parts by weight of 6-aminopenicillanic acid.

Yield: 53%.

β -Lactam content: 72%.

	C	H	N	S
Calculated:	46.2	4.9	10.8	12.3
Found:	46.6	5.3	10.4	12.3

NMR signals at τ =2.5—3.2 (3 H), 3.8—4.4 (1 H), 4.2 (1 H), 4.5 (2 H), 4.6—5.0 (2 H), 5.5—5.7 (2 H), 5.8 (1 H), 7.7 (3 H) and 8.4 ppm (6 H).

Example 18

Sodium D,L- α -(3-methoxycarbonyl-3-methylureido)-4-methoxybenzylpenicillin:

3.04 parts by weight of tetramethylchloroformamidinium chloride in 20 parts by volume of dry dichloromethane were initially taken at 0° C., and a solution of 4.8 parts by weight of D,L- α -(3-methoxycarbonyl-3-methylureido)-4-methoxyphenylacetic acid in 10 parts by volume of methylene chloride was added. 2.24 parts by volume of triethylamine in 10 parts by volume of methylene chloride were now added dropwise over the course of 30 minutes at 0° C., with exclusion of moisture. Thereafter the mixture was stirred for 20 minutes at +5° C., insoluble matter was filtered off without the solution rising to above 5° C., and the filtrate was cooled to -20° C. A solution of 5.0 parts by weight of 6-aminopenicillanic acid and 3.5 parts by volume of triethylamine in 20 parts by volume of methylene chloride, prepared as described in Example 1, and also cooled to -20° C., was added thereto. The mixture was stirred for 30 minutes at 0° C. and subsequently for a further 30 minutes at room temperature and was finally poured into 150 parts by volume of ice water and adjusted to a pH value of 6.5 with 2 N sodium hydroxide solution. After separating off the organic layer and adding 150 parts by volume of a 1:1 mixture of ethyl acetate and ether, the mixture was worked up as described in Example 1 and the sodium salt of the penicillin was isolated.

Yield: 54%.

β -Lactam content: 75%.

NMR signals at τ =2.6 (2 H), 3.1 (2 H), 4.3—4.9 (3 H), 5.8 (1 H), 6.2 (6 H), 6.85 (3 H) and 8.5 ppm (6 H).

Effectiveness in Animal Experiments: B.

Example 19

Sodium D,L- α -(3-dimethylaminocarbonyl-3-methyl-ureido)-4-methoxybenzylpenicillin:

This penicillin was prepared as described in Example 18, from 6.0 parts by weight of D,L- α -(3-dimethyl-aminocarbonyl-3-methylureido)-4-methoxyphenylacetic acid, 3.8 parts by weight of tetramethylchloroformamidinium chloride and 6.2 parts by weight of 6-aminopenicillanic acid.

Yield: 23%.

β -Lactam content: 59%.

NMR signals at τ =2.65 (2 H), 3.1 (2 H), 4.4—4.8 (3 H), 5.65 (1 H), 6.2 (3 H), 6.9 (3 H), 7.05 (6 H) and 8.4 ppm (6 H).

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Example 20

Sodium D,L- α -(3-methoxycarbonyl-3-methyl-ureido)- α -thienyl(2)-methylpenicillin:

This penicillin was prepared as described in Example 18, from 4.5 parts by weight of D,L- α -(3-methoxycarbonyl-3-methyl-ureido)-thienylacetic acid, 3.2 parts by weight of tetramethylchloroformamidinium chloride and 5.2 parts by weight of 6-amino-penicillanic acid.

Yield: 62%.

β -Lactam content: 84%.

NMR signals at τ =2.5—3.2 (3 H), 4.2 (1 H), 4.5 (2 H), 5.8 (1 H), 6.2 (3 H), 6.8 (3 H) and 8.4 ppm (6 H).

Effectiveness in animal experiments: A.

Example 21

Sodium D,L- α -(3-benzoyl-3-allyl-ureido)- α -thienyl(2)-methylpenicillin:

This penicillin was prepared as described in Example 18, from 6.0 parts by weight of D,L- α -(3-benzoyl-3-allylureido)-2-thienylacetic acid, 3.4 parts by weight of tetramethylchloroformamidinium chloride and 5.5 parts by weight of 6-amino-penicillanic acid.

Yield: 45%.

β -Lactam content: 77%.

NMR signals at τ =2.5 (5 H), 2.5—3.1 (3 H), 3.7—4.4 (2 H), 4.5 (2 H), 4.7—5.2 (2 H), 5.5—5.9 (3 H) and 8.4 ppm (6 H).

Effectiveness in Animal Experiments: B.

Example 22

Sodium D,L- α -(3-furoyl(2)-3-methyl-ureido)- α -thienyl(2)-methylpenicillin:

This penicillin was prepared as described in Example 18, from 11.6 parts by weight of D,L- α -(3-[2-furoyl]-3-methylureido)-2-thienylacetic acid, 6.5 parts by weight of tetramethylchloroform-amidinium chloride and 8.2 parts by weight of 6-amino-penicillanic acid.

Yield: 39%.

β -Lactam content: 88%.

NMR signals at τ =2.2 (1 H), 2.5—3.1 (4 H), 3.35 (1 H), 4.1 (1 H), 4.45 (2 H), 5.8 (1 H), 6.55 (3 H) and 8.4 ppm (6 H).

Effectiveness in animal experiments: A and B.

Example 23

Sodium D,L- α -(3-dimethylaminocarbonyl-3-methylureido)- α -thienyl(2)-methylpenicillin:

A suspension of 3.9 parts by weight of tetramethylchloroformamidinium chloride in 30 parts by volume of dry acetone was treated with a solution of D,L- α -(3-dimethylaminocarbonyl-3-methylureido)-2-thienylacetic acid in 10 parts by volume of acetone over the course of 5 minutes at -20° C., and subsequently 2.1 parts by volume of triethylamine in 5 parts by volume of acetone were added dropwise over the course of 30 minutes. After the mixture had been stirred for a further hour at -20° C., it was filtered in such a way that the temperature of the solution did not rise above -10° C. It was again cooled to -20° C. and combined with a vigorously stirred solution of 3.9 parts by weight of 6-aminopenicillanic acid in 50 ml of 60% strength aqueous tetrahydrofuran (solution took place after adding sufficient 2 N NaOH to establish a pH value of 8.2), cooled to -5° C. A pH range of 7.5—8.0 was maintained by adding 2 N sodium hydroxide solution. After 15 minutes, the mixture was allowed to come to room temperature and stirring was continued until no further change in the pH value was observable. The subsequent working-up of the reaction mixture and the isolation of the penicillin was carried out in the manner indicated in Example 9.

Yield: 43%.

β -Lactam content: 54%.

NMR signals at τ =2.5—3.2 (3 H), 4.5 (3 H), 5.8 (1 H), 6.9 (3 H), 7.05 (6 H), and 8.4 ppm (6 H).

Example 24

Sodium D- α -(3- γ -chlorobutyryl-3-methyl-ureido)-benzylpenicillin:

5.1 parts by weight of D- α -(3- γ -chlorobutyryl-3-methyl-ureido)-phenylacetic acid and 3.0 parts by weight of tetramethylchloro-formamidinium chloride were reacted in methylene chloride as described in Example 18. The resulting solution was combined with a solution of 6.5 parts by weight of N-trimethylsilyl-6-aminopenicillanic acid trimethylsilyl ester in 33 parts by volume of dry methylene chloride at 0° C. 1.3 parts by weight of pyridine were added and the mixture was stirred, whilst excluding moisture, for one hour at 0° C. and subsequently for 2.5 hours at room temperature. It was now poured into 120 parts by volume of ice water, a pH value of 7—8 was established and the methylene chloride was stripped off in vacuo. The aqueous phase was shaken with 50 parts by volume of ether, which was then discarded, whilst the aqueous phase was freed of solid constituents by filtration. It was now covered with 200 parts by volume of a 1:1 mixture of ether and ethyl acetate, cooled to 0° C. and acidified to pH=2 with 2 N hydrochloric acid, whilst stirring vigorously. The organic solution was separated off, twice washed with 50 parts by volume of water at a time, dried over MgSO₄ and filtered, and the sodium salt of the penicillin was precipitated by adding 15 ml of a 1 M solution of sodium 2-ethylhexanoate in ether containing methanol. The entire mixture was concentrated almost to dryness at 0° C., rapidly dissolved in as little methanol as possible, and precipitated by adding excess ether. Non-crystalline solid substance.

Yield: 29%.

 β -Lactam content: 49%.

Position of the NMR signals as indicated in Example 2.

The crude product still contained D- α -(3- γ -chlorobutyryl-3-methylureido)-phenylacetic acid which was removable by fractional extraction of the aqueous penicillin salt solution at pH values of 5.5—6.5.

Examples 25

If, in the procedure of Example 1, the D- α -(3-acetyl-3-allyl-ureido)-phenylacetic acid used there is replaced by 0.02 mol of:

D- α -(3-acetyl-3-methylureido)-phenylacetic acid,
 D- α -(3-acetyl-3-ethyl-ureido)-phenylacetic acid,
 D- α -(3-acetyl-3-vinyl-ureido)-phenylacetic acid,
 D- α -(3-acetyl-3-*n*-propyl-ureido)-phenylacetic acid,
 D- α -(3-acetyl-3-propenyl-ureido)-phenylacetic acid,
 D- α -(3-acetyl-3-*i*-propyl-ureido)-phenylacetic acid,
 D- α -(3-acetyl-3-*n*-butyl-ureido)-phenylacetic acid,
 D- α -(3-acetyl-3- β -methoxyethyl-ureido)-phenylacetic acid,
 D- α -(3-acetyl-3- β -dimethylaminoethyl-ureido)-phenylacetic acid,
 D- α -(3-acetyl-3-cyclohexyl-ureido)-phenylacetic acid,
 D- α -(3-acetyl-3-cyclobutyl-ureido)-phenylacetic acid,
 D- α -(3-acetyl-3-benzyl-ureido)-phenylacetic acid,
 D- α -(3-formyl-3-methyl-ureido)-phenylacetic acid,
 D- α -(3-formyl-3-ethyl-ureido)-phenylacetic acid,
 D- α -(3-formyl-3-propyl-ureido)-phenylacetic acid,
 D- α -(3-formyl-3-*i*-propyl-ureido)-phenylacetic acid,
 D- α -(3-acetyl-3-*t*-butyl-ureido)-phenylacetic acid,
 D- α -(3-formyl-3-*n*-butyl-ureido)-phenylacetic acid,
 D- α -(3-formyl-3-allyl-ureido)-phenylacetic acid,
 D- α -(3-formyl-3-benzyl-ureido)-phenylacetic acid,
 D- α -(3-formyl-3-phenyl-ureido)-phenylacetic acid,
 D- α -(3-formyl-3-cyclopropyl-ureido)-phenylacetic acid,
 D- α -(3-formyl-3-cyclobutyl-ureido)-phenylacetic acid,
 D- α -(3-formyl-3-cyclopentyl-ureido)-phenylacetic acid or
 D- α -(3-formyl-3-cyclohexyl-ureido)-phenylacetic acid,

the following penicillins are obtained in the form of their sodium salts:—

D- α -(3-acetyl-3-methyl-ureido)-benzylpenicillin,
 D- α -(3-acetyl-3-ethyl-ureido)-benzylpenicillin,
 D- α -(3-acetyl-3-vinyl-ureido)-benzylpenicillin,
 D- α -(3-acetyl-3-*n*-propyl-ureido)-benzylpenicillin,
 D- α -(3-acetyl-3-prop-1-enyl-ureido)-benzylpenicillin,

		D- α -(3-acetyl-3- <i>i</i> -propyl-ureido)-benzylpenicillin,	
		D- α -(3-acetyl-3- <i>n</i> -butyl-ureido)-benzylpenicillin,	
		D- α -(3-acetyl-3- <i>t</i> -butyl-ureido)-benzylpenicillin,	
5	5	D- α -(3-acetyl-3-2-methoxyethyl-ureido)-benzylpenicillin,	5
		D- α -(3-acetyl-3- β -dimethylaminoethyl-ureido)-benzylpenicillin,	
		D- α -(3-acetyl-3-cyclohexyl-ureido)-benzylpenicillin,	
		D- α -(3-acetyl-3-cyclobutyl-ureido)-benzylpenicillin,	
10	10	D- α -(3-acetyl-3-benzyl-ureido)-benzylpenicillin,	10
		D- α -(3-formyl-3-methyl-ureido)-benzylpenicillin,	
		D- α -(3-formyl-3-ethyl-ureido)-benzylpenicillin,	
		D- α -(3-formyl-3-propyl-ureido)-benzylpenicillin,	
		D- α -(3-formyl-3- <i>i</i> -propyl-ureido)-benzylpenicillin,	
		D- α -(3-formyl-3- <i>n</i> -butyl-ureido)-benzylpenicillin,	
15	15	D- α -(3-formyl-allyl-ureido)-benzylpenicillin,	15
		D- α -(3-formyl-3-benzyl-ureido)-benzylpenicillin,	
		D- α -(3-formyl-3-phenyl-ureido)-benzylpenicillin,	
		D- α -(3-formyl-3-cyclopropyl-ureido)-benzylpenicillin,	
		D- α -(3-formyl-3-cyclobutyl-ureido)-benzylpenicillin,	
20	20	D- α -(3-formyl-3-cyclopentyl-ureido)-benzylpenicillin, or	20
		D- α -(3-formyl-3-cyclohexyl-ureido)-benzylpenicillin.	

Example 26

If, in the procedure of Example 1, the D- α -(3-acetyl-3-allylureido)-phenylacetic acid used there is replaced by 0.02 mol of:

25	25	D- α -(3-methoxyacetyl-3-methyl-ureido)-phenylacetic acid,	25
		D- α -(3-propionyl-3-methyl-ureido)-phenylacetic acid,	
		D- α -(3-methylsulphenylacetyl-3-methyl-ureido)-phenylacetic acid,	
		D- α -(3-propionyl-3-ethyl-ureido)-phenylacetic acid,	
30	30	D- α -(3-propionyl-3-vinyl-ureido)-phenylacetic acid,	30
		D- α -(3- <i>n</i> -butyl-3-methyl-ureido)-phenylacetic acid,	
		D- α -(3-methoxycarbonyl-acetyl-3-methyl-ureido)-phenylacetic acid,	
		D- α -(3- <i>i</i> -butyl-3-methyl-ureido)-phenylacetic acid,	
		D- α -(3-acryloyl-3-methyl-ureido)-phenylacetic acid,	
35	35	D- α -(3-pivaloyl-3-methyl-ureido)-phenylacetic acid,	35
		D- α -(3-cyanomethyl-acetyl-3-methyl-ureido)-phenylacetic acid,	
		D- α -(3-acetyl-3-phenyl-ureido)-phenylacetic acid,	
		D- α -(3-propionyl-3-phenyl-ureido)-phenylacetic acid,	
		D- α -(hexahydroazepin-2-on-1-yl-carbonylamino)-phenylacetic acid, or	
40	40	D- α -(pyrrolid-2-on-1-yl-carbonylamino)-phenylacetic acid,	40
		the following penicillins are obtained:	
		D- α -(3-methoxyacetyl-3-methyl-ureido)-benzylpenicillin,	
		D- α -(3-propionyl-3-methyl-ureido)-benzylpenicillin,	
		D- α -(3-methylsulphenylacetyl-3-methyl-ureido)-benzylpenicillin,	
45	45	D- α -(3-propionyl-3-ethyl-ureido)-benzylpenicillin,	45
		D- α -(3-propionyl-3-vinyl-ureido)-benzylpenicillin,	
		D- α -(3- <i>n</i> -butyl-3-methyl-ureido)-benzylpenicillin,	
		D- α -(3-methoxycarbonyl-acetyl-3-methyl-ureido)-benzylpenicillin,	
		D- α -(3- <i>i</i> -butyl-3-methyl-ureido)-benzylpenicillin,	
50	50	D- α -(3-acryloyl-3-methyl-ureido)-benzylpenicillin,	50
		D- α -(3-pivaloyl-3-methyl-ureido)-benzylpenicillin,	
		D- α -(3-cyanomethyl-acetyl-3-methyl-ureido)-benzylpenicillin,	
		D- α -(3-acetyl-3-phenyl-ureido)-benzylpenicillin,	
		D- α -(3-propionyl-3-phenyl-ureido)-benzylpenicillin,	
55	55	D- α -(hexahydroazepin-2-on-1-yl-carbonylamino)-benzylpenicillin or	55
		D- α -(pyrrolid-2-on-1-yl-carbonylamino)-benzylpenicillin.	

Example 27

In the reaction of D- α -(3-*i*-propoxycarbonyl-3-methyl-ureido)-phenylacetic acid and of D- α -(3-*n*-butoxycarbonyl-3-methylureido)-phenylacetic acid with thionyl chloride and subsequently with 6-aminopenicillanic acid in the manner described in Example 11 C, products were in each case again obtained which proved to be mixtures of several antibiotically active substances, but of which none was identical with the authentic D- α -(3-*i*-propoxycarbonyl-3-methyl-ureido)-benzylpenicillin or D- α -(3-*n*-butoxycarbonyl-3-methyl-ureido)-benzylpenicillin manufactured according to the in-

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struction of Examples 9C and 10. The R_f values of thin layer chromatograms developed on silica gel with a 9:3:1 mixture of *n*-butanol, pentane and glacial acetic acid were 0.080 and 0.35, and 0.078, 0.46 and 0.75, respectively.

Under the same conditions, the authentic products showed R_f values of 0.56 and 0.64 respectively.

Products from the reaction of D-α-(3-i-propoxycarbonyl-3-methylureido)-phenylacetic acid:

For anti-bacterial effectiveness, see the Table accompanying Example 9C.

Products from the reaction of D-α-(3-n-butoxycarbonyl-3-methylureido)-phenylacetic acid:

The Table which follows compares the anti-bacterial action of this product (A) with the penicillins (B) prepared from ampicillin and N-*n*-butoxycarbonyl-N-methylcarbamic acid chloride:

Type of Bacterium	Effectiveness [units/ml]	
	(A)	(B)
<i>Escherichia coli</i> 14	100	3.12
<i>Escherichia coli</i> C 165	200	6.25
<i>Escherichia coli</i> 183/58	400	6.25
<i>Proteus</i> 3400	>400	25
<i>Proteus</i> 1017	>400	12.5
<i>Pseudomonas aerug.</i> Bonn.	>400	12.5
<i>Pseudomonas aerug.</i> Walter	>400	25
<i>Staphylococcus aur.</i> 133	12.5	<0.78

Example 28 -

Sodium D-α-(3-cyclohexyloxycarbonyl-3-methylureido)-benzylpenicillin:

4.5 parts by weight of 6-aminopenicillanic acid were suspended in 60 parts by volume of 50% strength aqueous tetrahydrofuran, the amount of triethylamine just sufficient to dissolve the aminopenicillanic acid was added, the resulting solution, which had a pH of 8.0 (glass electrode) was cooled to 0° C., and a solution of 8.0 parts by weight of O-[D-α-(3-cyclohexyloxycarbonyl-3-methylureido)-phenylacetyl]-C-cyano-C-ethoxy-carbonyl-formaldehydeoxime in 25 parts by volume of tetrahydrofuran was added dropwise, whilst keeping the pH of the solution at 7.5 by appropriate addition of triethylamine. Thereafter the mixture was stirred for 90 minutes at 22° C., 100 parts by volume of water were added, the solution was adjusted to pH 6.5, the tetrahydrofuran was largely removed in vacuo in a rotary evaporator, and the remaining aqueous solution was covered with a 1:1 mixture of ether and ethyl acetate, stirred, cooled to 0—5° C. and acidified to pH 1.5 with 2 N hydrochloric acid.

The organic phase was then separated off, washed with water and dried over sodium sulphate in a refrigerator, and the sodium salt of the penicillin was precipitated by means of a 1 M solution of sodium 2-ethylhexanoate in ether containing methanol. The supernatant solution was decanted from the initially oily precipitate, and the latter was converted into a colourless powder by trituration with dry ether.

β-Lactam content: 82%.

NMR signals at τ=2.4—3.0 (5 H), 4.3—4.7 (3 H), 5.2 (1 H), 5.8 (1 H), 6.8 (3 H) and 7.9—9.0 ppm (16 H).

The biological activity of this penicillin (A) and of the penicillin (B) prepared from ampicillin and N-cyclohexyloxycarbonyl-N-methyl-carbamic acid chloride were identical within the limit of error, as is shown by the Table below.

Minimum inhibitory concentration in units/ml:

	A	B
<i>E. coli</i> 14	3.12	1.56
<i>E. coli</i> A 261	400	400
<i>E. coli</i> C 165	6.25	6.25
<i>E. coli</i> 183/58	3.12	1.56
<i>Proteus</i> 3400	12.5	6.25
<i>Proteus</i> 1017	12.5	5.25
<i>Pseudomonas aerug.</i> Bonn	25	25
<i>Pseudomonas aerug.</i> Walter	50	50
<i>Klebsiella</i> K 10	200	100
<i>Klebsiella</i> 63	100	100
<i>Staphylococcus aureus</i> 1777 E	200	400
<i>Staphylococcus aureus</i> 133	<0.7	<0.7
<i>Enterococcus</i> ATCC 9790	100	100

Example 29

Sodium D- α -(3-allyloxycarbonyl-3-methylurcido)-benzylpenicillin:

7.1 parts by weight of 6-aminopenicillanic acid were dissolved in a mixture of 120 parts by volume of methylene chloride and 10 parts by volume of triethylamine, 12.4 parts by weight of O-[D- α -(3-allyloxycarbonyl-3-methylurcido)-phenylacetyl]-C-cyano-C-ethoxycarbonyl-formaldehydeoxime were added, the solution was left to stand for 24 hours in a refrigerator, diluted with 150 parts by volume of methylene chloride and exhaustively extracted by shaking with sodium bicarbonate solution, the combined bicarbonate extracts were covered with a 1:1 mixture of ether and ethyl acetate, the pH of the aqueous phase was adjusted to 5.0 with 2 N hydrochloric acid, whilst stirring, the organic phase was separated off, the aqueous phase was covered with fresh ether-ethyl acetate mixture, the aqueous phase was then acidified to pH 1.5 with 2 N hydrochloric acid, whilst stirring and cooling with ice, the organic phase was separated off, and the sodium salt of the penicillin was precipitated and isolated in the manner described in Example 29.

Yield: 30%.

β -Lactam content: 74%.

Calculated: C 49.7 H 5.2 N 10.5 S 6.1

Found: C 49.9 H 6.1 N 10.4 S 5.6

NMR signals at τ =2.4—2.8 (5 H), 3.7—4.3 (1 H), 4.4—4.9 (5 H), 5.1—5.4 (2 H), 5.8 (1 H), 6.8 (3 H) and 8.45 ppm (6 H).

The biological effectiveness of this penicillin (A) and of the penicillin (B) prepared from ampicillin and N-allyloxycarbonyl-N-methyl-carbamic acid chloride were identical within the limit of error, as is shown by the Table below.

Minimum inhibitory concentration in units/ml:

	A	B
<i>E. coli</i> 14	0.8 — 4	3.12
<i>E. coli</i> A 261	100 — 500	>400
<i>E. Coli</i> C 165	4 — 20	12.5
<i>E. coli</i> 183/58	4 — 20	6.25
<i>Proteus</i> 3400	20 — 100	25
<i>Proteus</i> 1017	20 — 100	12.5
<i>Pseudomonas aerug.</i> Bonn	4 — 20	12.5
<i>Pseudomonas aerug.</i> Walter	20 — 100	12.5
<i>Klebsiella</i> K 10	20 — 100	50
<i>Klebsiella</i> 63	20 — 100	25
<i>Staphylococcus aureus</i> 133	0.8 — 4	0.78
<i>Enterococcus</i> ATCC 9790	20 — 100	50

Example 30

Sodium α -(3-benzoyl-3-methylureido)-2,6-dichlorobenzylpenicillin:

This penicillin was prepared in the manner described in Example 29 from 2.82 parts by weight of 6-aminopenicillanic acid, 6.0 parts by weight of O[α -(3-benzoyl-3-methylureido)-2,6-dichlorophenylacetyl]-C-cyano - C - ethoxycarbonyl-formaldehyde-oxime, 50 parts by volume of methylene chloride and 4 parts by volume of triethylamine.

Yield: 40%.

 β -Lactam content: 80%.

Calculated: C 47.4 H 4.3 N 3.8 S 5.0

Found: C 47.1 H 4.7 N 3.9 S 5.4

NMR signals at τ =2.4—2.9 (8 H), 3.3 (0.6 H), 3.8 (0.4 H), 4.45 (2 H), 5.8 (1 H), 6.8 (0.6 H), 6.85 (0.4 H) and 8.45 ppm (6 H).

Example 31

Sodium D,L- α -(3-benzoyl-3-methylureido)-2,6-dichlorobenzylpenicillin:

5.6 parts by weight of α -(3-benzoyl-3-methylureido)-2,6-dichlorophenylacetic acid were dissolved in a mixture of 70 parts by volume of dry acetone and 2.5 parts by volume of triethylamine at -5°C . to -10°C ., 2.9 parts by weight of 1-methyl-2-chloro-pyrrolinium chloride were added, the mixture was stirred for 45 minutes, the precipitate thereby formed (triethylamine hydrochloride) was filtered off, the filtrate was combined with a solution of 4.3 parts by weight of 6-aminopenicillanic acid in water which was prepared with the aid of triethylamine, had a pH of 7.5 and was cooled to -10°C ., the mixture was subsequently stirred for 2 hours at -5°C ., and the pH was at the same time kept at 7.5 by appropriate addition of triethylamine. The mixture was then diluted with 130 parts by volume of water, the pH was adjusted to 6.5 by means of 2 N hydrochloric acid, the acetone was stripped off in vacuo, the solution which remained was adjusted to pH 7.5 and extracted by shaking with a 1:1 mixture of ether and ethyl acetate, the aqueous phase was separated off covered with fresh organic phase, and acidified to pH 1.5 with 2 N hydrochloric acid, whilst stirring and cooling in ice, the organic phase was separated off, washed with water and dried for 2 hours in a refrigerator over sodium sulphate.

Thereafter, 17 parts by volume of a 1 M solution of sodium 2-ethylhexanoate in ether containing methanol were added, the mixture was evaporated almost to dryness in vacuo, and the residue was dissolved in the minimum amount of methanol. On adding excess ether, a non-crystalline product precipitated, which, after the supernatant solution had been decanted, was digested with ether, filtered off and dried over P_2O_5 in a vacuum desiccator.

Yield: 33%.

β -Lactam content: 78%.

NMR signals at τ = 2.4—2.75 (8 H), 3.3 (0.7 H), 3.7 (0.3 H), 4.4 (2 H), 5.75 (1 H), 6.8 (3 H) and 8.45 ppm (6 H).

Effectiveness in animal experiments: A and B.

Example 32

Sodium D,L- α -(3-benzoyl-3-methylureido)-4-methylsulphenylbenzylpenicillin:

This penicillin was prepared, as described in Example 31, from 6.0 parts by weight of α -(3-benzoyl-3-methylureido)-4-methylsulphenylphenylacetic acid, dissolved in 70 parts by volume of acetone and 2.35 parts by volume of triethylamine, after reaction with 2.7 parts by weight of 1-methyl-2-chloropyrrolinium chloride; by combination with a solution of 6-aminopenicillanic acid in water, of pH 7.5, prepared by addition of triethylamine.

Yield: 45%.

β -Lactam content: 72%.

NMR signals at τ = 2.4—2.9 (9 H), 4.4 (1 H), 4.5 (2 H), 5.8 (1 H), 6.9 (3 H), 7.6 (3 H) and 8.45 ppm (6 H).

Effectiveness in animal experiments: A and B

Example 33

α -(3-ethoxycarbonyl-3-methylureido)-4-methylsulphenylbenzylpenicillin:

This penicillin was prepared in the manner described in Example 31 from 6.0 parts by weight of α -(3-ethoxycarbonyl-3-methylureido)-4-methylsulphenylphenylacetic acid, 80 parts by volume of acetone, 2.6 parts by volume of triethylamine and 3.0 parts by weight of 1-methyl-2-chloropyrrolinium chloride, by combination with a solution of 4.4 parts by weight of 6-aminopenicillanic acid in 70 parts by volume of 50% strength aqueous acetone, prepared by addition of triethylamine.

Yield: 44%.

β -Lactam content: 78%.

NMR signals at τ = 2.6 (2 H), 2.75 (2 H), 4.5 (1 H), 4.55 (2 H), 5.5—5.9 (3 H), 6.85 (3 H), 7.55 (3 H), 8.4 (6 H) and 8.6 ppm (3 H).

Example 34

Sodium α -(3-ethoxycarbonyl-3-methylureido)-4-methylsulphenylbenzylpenicillin:

To prepare this penicillin, 6.0 parts by weight of α -(3-ethoxycarbonyl-3-methylureido)-4-methylsulphenylphenylacetic acid were dissolved in 80 parts by volume of acetone, with the addition of 2.6 parts by volume of triethylamine, 3.0 parts by weight of 1-methyl-2-chloro-pyrrolinium chloride were added at -5°C . to -10°C ., the mixture was stirred for 45 minutes at the same temperature, a solution of 4.4 parts by weight of 6-aminopenicillanic acid in a mixture of 70 parts by volume of 50% strength aqueous acetone and triethylamine, which had a pH of 7.5, was added, the mixture was subsequently stirred for 2 hours at -5°C . and diluted with 150 parts by volume of water, and the reaction mixture was worked up as in Example 31, to isolate the sodium salt of the penicillin.

Yield: 44%.

β -Lactam content: 78%.

Calculated: C 46.7 H 5.2 N 9.9 S 11.3

Found: C 47.0 H 5.6 N 9.4 S 10.8

NMR signals as indicated in Example 33. The spectra of both substances are identical.

Effectiveness in animal experiments: A

Example 35

Sodium α -(3- β -chloropropionyl-3-methylureido)-cyclohex-3-enylmethylpenicillin:

This penicillin was prepared in the manner described in Example 32, from 5.3 parts by weight of α -(3- β -chloropropionyl-3-methylureido)-cyclohex-3-enyl-acetic acid, after reaction with 3.0 parts by weight of 1-methyl-2-chloro-pyrrolinium chloride in the presence of 2.6 parts by volume of triethylamine, by reaction with 4.4 parts by weight of 6-aminopenicillanic acid which had been dissolved in 50% strength aqueous acetone, at pH 7.5, by means of triethylamine.

Yield: 44%.

 β -Lactam content: 78%.

NMR signals at τ =4.3 (2 H), 4.5 (2 H), 5.8 (1 H), 6.2 (2 H), 6.65 (3 H), 6.8 (2 H) and 7.7—8.8 ppm (13 H).

Example 36

Sodium D- α -[3-(2-thionoyl)-3-methylureido]-benzylpenicillin:

To prepare this penicillin, 3.9 parts by weight of D- α -[3-(2-thionoyl)-3-methylureido]-phenylacetic acid were dissolved in 55 parts by volume of acetone with the addition of 2.0 parts by volume of triethylamine, 2.3 parts by weight of 1-methyl-2-chloropyrrolinium chloride were added at -5° C. to -10° C., the mixture was stirred for 45 minutes at the same temperature, a solution of 3.1 parts by weight of 6-aminopenicillanic acid in a mixture of 60 parts by volume of 90% strength aqueous acetone and triethylamine, which had a pH of 7.5, was added, and the mixture was stirred for 2 hours at -5° C. and worked up—as described in Example 31—to isolate the sodium salt of the penicillin.

Yield: 56%.

 β -Lactam content: 64%.

NMR signals at τ =2.1—3.0 (8 H), 4.35—4.8 (3 H), 5.8 (1 H), 6.55 (3 H) and 8.45 ppm (6 H).

Example 37

Sodium D- α -[3-(3,5-dimethylisoxazolyl(4)-carbonyl)-3-methylureido]benzylpenicillin:

To prepare this penicillin, 3.9 parts by weight of D- α -[3-(3,5-dimethylisoxazolyl(4)-3-methylureido)-phenylacetic acid were dissolved in 60 parts by volume of methylene chloride with the addition of 2.0 parts by volume of triethylamine, the solution was cooled to -10° C., 2.2 parts by weight of 1-methyl-2-chloropyrrolinium chloride were added, and the mixture was left to stand for 90 minutes at -10 to -35° C. (solution A).

Separately: 3.1 parts by weight of 6-aminopenicillanic acid were suspended in 60 parts by volume of methylene chloride, 3.4 parts by volume of triethylamine were added, and the mixture was stirred for 4 hours at 22° C. (solution B). Solution B was then cooled to between 0 and -5° C., and solution A was added in several portions, over the course of 30 minutes, whilst stirring and continuing to cool.

Thereafter the mixture was stirred for a further hour at 0 to 5° C., the solvent was stripped off in vacuo, the residue was taken up in water and a 1:1 mixture of ether and ethyl acetate, the pH was adjusted to 7.5 whilst stirring, the organic phase was separated off, the aqueous phase was covered with fresh ether-ethyl acetate mixture, the pH was brought to 1.5 by means of 2 N hydrochloric acid, whilst stirring and cooling with ice, the organic phase was separated off, washed with water and dried over magnesium sulphate for 2 hours in a refrigerator, and the penicillin was isolated as the sodium salt, as described in Example 31.

Yield: 50%.

 β -Lactam content: 80%.

Calculated: C 50.7 H 5.0 N 12.3 S 5.6

Found: C 51.1 H 5.4 N 11.6 S 5.8

NMR signals at τ =2.35—2.9 (5 H), 4.4 (1 H), 4.5 (2 M), 5.8 (1 H), 6.8 (3 H), 7.6 (3 H), 7.75 (3 H) and 8.45 ppm (6 H).

Example 38

If, in the procedure of Example 36, the D- α -[3-(2-thenoyl)-3-methylureido]-phenylacetic acid used there is replaced by 0.012 mol of:

D- α -[3-(2-furoyl)-3-methylureido]-phenylacetic acid,
 D- α -[3-(2-furoyl)-3-ethylureido]-phenylacetic acid,
 D- α -[3-(2-furoyl)-3-*n*-propylureido]-phenylacetic acid,
 D- α -[3-(2-furoyl)-3-phenylureido]-phenylacetic acid,
 D- α -[3-(2,5-dimethylfuroyl)-3-3-methylureido]-phenylacetic acid,
 D- α -[3-(5-bromofuroyl)-3-3-methylureido]-phenylacetic acid,
 D- α -[3-(5-methoxymethylfuroyl)-2-3-methylureido]-phenylacetic acid,
 D- α -[3-(3,5-dimethylisothiazol-3-yl)-carbonyl-3-methylureido]-phenylacetic acid,
 D- α -[3-(isoxazol-4-yl)-carbonyl-3-methylureido]-phenylacetic acid,
 D- α -[3-(isoxazol-3-yl)-carbonyl-3-methylureido]-phenylacetic acid,
 D- α -[3-(3-methylthiodiazol(1,2,5)-4-yl)-carbonyl-3-methylureido]-phenylacetic acid or
 D- α -[3-(4-methylthiadiazol(1,2,3)-5-yl)-carbonyl-3-methylureido]-phenylacetic acid
 the sodium salts of the following penicillins are obtained:

D- α -[3-(2-furoyl)-3-methylureido]-benzylpenicillin,
 D- α -[3-(2-furoyl)-3-ethylureido]-benzylpenicillin,
 D- α -[3-(2-furoyl)-3-*n*-propylureido]-benzylpenicillin,
 D- α -[3-(2-furoyl)-3-phenylureido]-benzylpenicillin,
 D- α -[3-(2,5-dimethylfuroyl)-3-3-methylureido]-benzylpenicillin,
 D- α -[3-(5-bromofuroyl)-3-3-methylureido]-benzylpenicillin,
 D- α -[3-(5-methoxymethylfuroyl)-2-3-methylureido]-benzylpenicillin,
 D- α -[3-(3,5-dimethylisothiazol-3-yl)-carbonyl-3-methylureido]-benzylpenicillin,
 D- α -[3-(isoxazol-4-yl)-carbonyl-3-methylureido]-benzylpenicillin,
 D- α -[3-(isoxazol-3-yl)-carbonyl-3-methylureido]-benzylpenicillin,
 D- α -[3-(3-methylthiodiazol(1,2,5)-4-yl)-carbonyl-3-methylureido]-benzylpenicillin or
 D- α -[3-(4-methylthiodiazol(1,2,3)-5-yl)-carbonyl-3-methylureido]-benzylpenicillin.

Example 39

A) D- α -(3-Cyclohexyloxycarbonyl-3-methylureido)-phenylacetic acid:
 13.5 parts by weight of bis-(trimethylsilyl)-C-phenylglycine were dissolved in 100 parts by volume of dry carbon tetrachloride, a solution of 10.0 parts by weight of N-cyclohexyloxycarbonyl-N-methyl-carbanic acid chloride in 30 parts by volume of carbon tetrachloride was slowly added dropwise at 0° C. whilst excluding moisture, and the mixture was left to stand overnight in a refrigerator. Thereafter it was washed 3 times with 50 parts by volume of water at a time, and the organic phase was evaporated to dryness in vacuo.
 Yield of oily product: 95%.

NMR signals at τ =0.5 (1 H), 2.5 (5 H), 4.6 (1 H), 5.2 (1 H), 6.8 (3 H) and 7.9—8.9 ppm (10 H).

B) O-[D- α -(3-Cyclohexyloxycarbonyl-3-methylureido)-phenyl-acetyl] - C - cyano-C-ethoxycarbonyl-formaldehydeoxime:

2.92 parts by weight of C-cyano-C-ethoxycarbonyl-formaldehydeoxime were dissolved in 50 parts by volume of tetrahydrofuran, 2.9 parts by volume of triethylamine were added, the mixture was cooled to -10° C., 1.5 parts by volume of thionyl chloride were then slowly added dropwise whilst stirring and continuing to cool, and the mixture was subsequently stirred for 15 minutes at -10° C. A solution, cooled to 0° C., of 6.88 parts by weight of D- α -(3-cyclohexyloxycarbonyl-3-methylureido)-phenylacetic acid in a mixture of 50 parts by volume of tetrahydrofuran and 2.9 parts by volume of triethylamine was then added dropwise over the course of approx. 45 minutes whilst continuing to cool, and the reaction mixture was subsequently stirred for a further hour at 0° C. The triethylamine hydrochloride which had separated out was then filtered off, the filtrate was evaporated in vacuo from a bath at 15—20° C., using a rotary evaporator, the residue was dissolved in methylene chloride, the solution was cooled to 0° C. and once shaken rapidly with ice water, and the organic phase was subsequently dried at 0° C. over sodium sulphate, filtered, and evaporated in vacuo by means of a rotary evaporator, from a bath at 20° C., and finally from a bath at 40° C. A colourless, varnish-like substance is obtained.

Yield: 98%.

Specific rotation: $[\alpha]_{589} -8.1^\circ$ (54.2 mg; methanol).

The substance showed an IR spectrum corresponding to its structure.

NMR signals at $\tau=0.5$ (1 H), 2.6 (5 H), 4.3 (1 H), 5.25 (1 H), 5.7 (2 H), 6.8 (3 H) and 8.0—9.0 ppm (13 H).

Example 40

O-[D- α -(3-Allyloxycarbonyl-3-methylureido)-phenylacetyl]-C-cyano-C-ethoxycarbonyl-formaldehydeoxime:

This substance was prepared in the manner described in Example 39, from 5.86 parts by weight of C-cyano-C-ethoxycarbonyl-formaldehydeoxime, 100 parts by volume of tetrahydrofuran, 57 parts by volume of triethylamine, 3.0 parts by volume of thionyl chloride and a mixture of 12.0 parts by weight of D- α -(3-allyloxycarbonyl-3-methylureido)-phenylacetic acid, 100 parts by volume of tetrahydrofuran and 5.7 parts by volume of triethylamine. A colourless, varnish-like substance is obtained.

Yield: over 80%.

Specific rotation: $[\alpha]_{589} -19.8^\circ$ (50.6 mg; methanol).

The substance showed an IR spectrum corresponding to its structure.

NMR signals at $\tau=0.4$ (1 H), 2.6 (5 H), 3.7—4.2 (1 H), 4.3 (1 H), 4.5—4.9 (2 H), 5.3 (2 H), 5.65 (2 H), 6.8 (3 H) and 8.65 ppm (3 H).

Example 41

O-[D- α -(3-benzoyl-3-methylureido)-2,6-dichlorophenylacetyl]-C-cyano-C-ethoxycarbonyl-formaldehydeoxime:

This substance was prepared in the manner described in Example 39, from 2.85 parts by weight of C-cyano-C-ethoxycarbonyl-formaldehydeoxime, 50 parts by volume of thionyl chloride and a mixture of 7.6 parts by weight of D- α -(3-benzoyl-3-methylureido)-2,6-dichlorophenylacetic acid, 50 parts by volume of tetrahydrofuran and 2.8 parts by volume of triethylamine. A colourless, varnish-like substance was obtained.

Yield: over 80%.

The IR spectrum of the substance showed the bands corresponding to its structure.

NMR signals at $\tau=0.5$ (1 H), 2.45 (5 H), 3.55 (1 H), 5.65 (2 H), 6.9 (3 H) and 8.7 (3 H).

Example 42

Sodium D,L- α -(pyrrolid-2-on-1-yl-carbonylamino)- α -p-tolyl-methylpenicillin:

This penicillin was prepared in the manner described in Example 1, from 14.5 parts by weight of α -pyrrolid-2-on-1-yl-carbonylamino)- α -p-tolylacetic acid, 10.2 parts by weight of tetramethyl-chloroformamidinium chloride and 15 parts by weight of 6-amino-penicillanic acid.

Yield: 29%.

β -Lactam content: 67%.

NMR signals at $\tau=2.5$ —3.05 (4 H), 4.5 (3 H), 5.8 (1 H), 6.1—6.4 (2 H), 7.4 (2 H), 7.7 (3 H), 8.0 (2 H) and 8.3—8.6 ppm (6 H).

Example 43

Sodium D,L- α -(3-o-fluorobenzoyl-3-methyl-ureido)- α -p-tolyl-methylpenicillin:

This penicillin was prepared in the manner indicated in Example 2, from 9 parts by weight of N-o-fluorobenzoyl-N-methyl-ureido-N-p-tolylacetic acid, 4.95 parts by weight of tetramethyl-chloroformamidinium chloride and 8.5 parts by weight of 6-amino-penicillanic acid.

Yield: 59%.

β -Lactam content: 87%.

Calculated: C 53.7 H 4.8 N 9.7 S 5.5
Found: C 53.4 H(6.0) N 9.7 S 5.9

NMR signals at $\tau=2.3$ —3.1 (8 H), 4.5 (3 H), 5.8 (1 H), 6.3 (3 H), 7.7 (3 H) and 8.2—8.5 ppm (6 H).

Effectiveness in animal experiments: A and B.

Example 44

Sodium D,L- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-p-methylbenzylpenicillin:

3.76 parts by weight of tetramethylchloroformamidinium chloride were suspended in 15 parts by volume of dry acetone and stirred for 10 minutes with exclusion of moisture. The product was filtered off, again with exclusion of moisture, and the reagent was suspended in 40 parts by volume of methylene chloride and cooled to 0° C. 5.53 parts by weight of α -[(imidazolidin-2-on-1-yl)-carbonylamino]-p-methylphenylacetic acid in a little methylene chloride were now added and a solution of 2.0 parts by weight of triethylamine in 20 parts by volume of methylene chloride was added dropwise to the mixture over the course of 30 minutes, whilst stirring and excluding moisture. The mixture was stirred for a further 20 minutes at +5° C. and then cooled to -20° C. and treated, all at once, with a solution of the triethylamine salt of 6-aminopenicillanic acid in methylene chloride, also cooled to -20° C. (This solution had been prepared by stirring 5.8 parts by weight of 6-aminopenicillanic acid, 3.4 parts by weight of triethylamine and 8 parts by weight of anhydrous sodium sulphate in 40 parts by volume of methylene chloride for two hours, and subsequent filtering). The mixture was left to reach 0° C. whilst stirring, was treated with a further 0.9 part by weight of triethylamine after a short time, and was further stirred for 30 minutes at 0° C. and 30 minutes at room temperature. It was now poured into ice water, the pH value was adjusted to 5.5 and the methylene chloride was stripped off *in vacuo*. The residue was twice extracted with ether and the ether was eluted with a little water. The combined aqueous solutions were covered with a layer of ethyl acetate and adjusted to a pH value of 1.5 with dilute hydrochloric acid whilst stirring and cooling with ice. The ethyl acetate phase was separated off, the water was again extracted with ethyl acetate, and the combined extracts were washed with water. They were dried for about one hour at 0° C. over MgSO₄, filtered and treated with 20 parts by volume of a 1 molar solution of sodium 2-ethylhexanoate in ether containing methanol, and the mixture was evaporated *in vacuo* at room temperature until it acquired an oily consistency. It was now dissolved in the requisite amount of methanol and this solution was added dropwise to 500 parts by volume of a mixture of about 500 parts by volume of absolute ether and 50 parts by volume of methanol, whilst stirring vigorously. The product which precipitated was filtered off after standing for a short time, suspended in dry ether and again filtered off. It was dried *in vacuo* over P₂O₅ for about 2 days.

Yield: 70%

β -Lactam content: 86%

NMR signals, see Table 2, page 45.

IR bands at 3280, 1760, 1712, 1655, 1600, 1520, 1270 and 765 cm⁻¹ (in Nujol suspension).

Example 45

Sodium α -[(imidazolidin-2-on-1-yl)-carbonylamino]-p-methylbenzylpenicillin:

2.8 parts by weight of α -[(imidazolidin-2-on-1-yl)-carbonylamino]-p-methylphenylacetic acid were reacted, in the manner described in Example 44, with 1.7 parts by weight of 1-methyl-2-chloro- Δ -1-pyrrolinium chloride instead of tetramethylchloroformamidinium chloride, and subsequently with 2.6 parts by weight of 6-aminopenicillanic acid in the form of its triethylamine salt, to give the sodium salt of α -[(imidazolidin-2-on-1-yl)-carbonylamino]-p-methylbenzylpenicillin.

Yield: 54%

β -Lactam content: 39%

NMR signals, see Table 2, page 45.

The position of the IR bands agrees with that of the penicillin of Example 44.

Example 46

Sodium D,L- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-p-chlorobenzylpenicillin:

This penicillin was manufactured in the manner described in Example 1, from 5.95 parts by weight of α -[(imidazolidin-2-on-1-yl)-carbonylamino]-p-chlorophenylacetic acid, 3.76 parts by weight of tetramethylchloroformamidinium chloride and 5.8 parts by weight of 6-aminopenicillanic acid.

Yield: 59%

β -Lactam content: 86%

NMR signals, see Table 2, page 45.

IR bands at 3300, 1775, 1727, 1667, 1608, 1540, 1287 and 780 cm⁻¹.

Example 47A

Sodium α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*p*-chlorobenzylpenicillin:

3.6 parts by weight of α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*p*-chlorophenylacetic acid were reacted in the manner described in Example 1 with 2.22 parts by weight of 1,3-dimethyl-2-chloro- Δ -1-imidazolinium chloride and subsequently with 3.02 parts by weight of 6-aminopenicillanic acid to give the sodium salt of α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*p*-chlorobenzylpenicillin.

Yield: 65%

β -Lactam content: 72%

NMR signals, see Table 2, page 45.

The IR spectrum in Nujol is identical with that of the penicillin of Example 46.

Example 47B

α -[(Imidazolidin-2-on-1-yl)-carbonylamino]-*p*-methylphenylacetic acid:

16.5 parts by weight of α -(4-methylphenyl)-glycine were dissolved in 200 parts by volume of 50% strength aqueous dioxane, with the addition of sufficient 2 N sodium hydroxide solution. Thereafter the mixture was adjusted back to a pH value of 7-8 with 5 N hydrochloric acid, whereupon the amino acid separated out partially as a fine precipitate. A solution of 11.8 parts by weight of 1-chlorocarbonyl-imidazolidin-2-one in 50 parts by volume of warm acetone was now added dropwise, whilst stirring and cooling by means of an ice bath. The pH was at the same time maintained at between 7 and 8 by appropriate addition of 2 N sodium hydroxide solution. After completion of the addition, the mixture was stirred for a further 15 minutes at room temperature until the pH value remained constant. Unreacted amino acid (6 parts by weight) was filtered off, and the filtrate was evaporated to half its volume *in vacuo* and extracted once with 100 parts by volume of ether. The aqueous phase was adjusted to a pH of 1-2 with 2 N hydrochloric acid and the oil which precipitated was taken up in ethyl acetate by extraction with 2X100 parts by volume. The combined ethyl acetate extracts were washed with 50 parts by volume of water, dried over $MgSO_4$ and subsequently evaporated to dryness. A glassy foam was obtained, which through trituration with petroleum ether was converted into a finely granular, non-crystalline powder.

Yield: 48%. NMR signals, see Table 2, page 46.

Example 47C

The following α -[(imidazolidin-2-on-1-yl)-carbonylamino]-phenylacetic acid was produced as described in Example 47B:

α -[(Imidazolidin-2-on-1-yl)-carbonylamino]-*p*-chlorophenylacetic acid from 18.6 parts by weight of α -(4-chlorophenyl)-glycine and 11.8 parts by weight of 1-chlorocarbonylimidazolidin-2-one. Recovered unreacted α -(4-chlorophenyl)-glycine: 6 parts by weight.

Yield of product moist with ether: 33 parts by weight.

The substance was recrystallised from ethyl acetate/petroleum ether.

1st fraction yield: 35%
2nd fraction, yield: 15% } relative to converted starting material.

Melting point = 115-120° C. NMR signals, see Table 2, page 46.

Example 47D

1-Chlorocarbonyl-imidazolidin-2-one:

4 parts by weight of phosgene in 10 parts by volume of absolute tetrahydrofuran were added dropwise, over the course of 15 minutes, to a vigorously stirred solution of 3.5 parts by weight of imidazolid-2-one [manufactured according to Fischer and Koch, Ann. 232, page 224 (1886)] in 50 parts by volume of absolute tetrahydrofuran. Thereafter the reaction mixture was stirred for 3 hours at 10° C. and a stream of dry air was then passed through it to blow out the hydrochloric acid produced, and residues of phosgene. It was now evaporated to dryness *in vacuo* on a rotary evaporator, and the solid residue was dried over concentrated sulphuric acid at about 12 mm Hg. Yield: 93%. Melting point = 150° C. after recrystallisation from acetone-pentane.

Calculated: C 32.3 H 3.4 N 18.8 Cl 23.9
Found: C 32.3 H(4.5) N 18.7 Cl 23.9

NMR signals at $\tau=5.7$ to 6.1 (2 H) and 6.3 to 6.7 (2 H), (acetone- d_6 as the solvent), symmetrical A_2B_2 -system.
IR bands at 3230 , 1790 , 1700 , 1270 and 1150 cm^{-1} .

Example 47E

If, in the procedure of Example 44, the α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*p*-methylphenylacetic acid used therein is replaced by 0.02 mol of one of the following:

- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-thienyl(2)-acetic acid,
- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-thienyl(3)-acetic acid,
- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*p*-hydroxyphenylacetic acid,
- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*m*-hydroxyphenylacetic acid,
- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*o*-chlorophenylacetic acid,
- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*o,o'*-difluorophenylacetic acid,
- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*o,o'*-chlorofluorophenylacetic acid or
- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*p*-acetylaminophenylacetic acid,

the following penicillins are obtained in the form of their sodium salts:

- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-thienyl(2)-methylpenicillin,
- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-thienyl(3)-methylpenicillin,
- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*p*-hydroxybenzylpenicillin,
- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*m*-hydroxybenzylpenicillin,
- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*o*-chlorobenzylpenicillin,
- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*o,o'*-difluorobenzylpenicillin,
- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*o,o'*-chlorofluorobenzylpenicillin or
- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*p*-acetylaminobenzylpenicillin.

Example 48

D- α -[(Imidazolidin-2-on-1-yl)-carbonylamino]-phenylacetic acid:

9.7 parts by weight of D(-)-C-phenylglycine were suspended in 150 parts by volume of 50% strength aqueous dioxane and sufficient 40% strength aqueous sodium hydroxide solution was added dropwise at room temperature, whilst stirring, for the phenylglycine to have just dissolved. Approximately 15% strength hydrochloric acid was then added to this solution, whilst stirring, until the pH of the solution had reached 7.5—8.0. The fine suspension of the phenylglycine which is present at that stage was cooled to about $+5^\circ\text{C}$., 10.6 parts by weight of finely powdered imidazolidin-2-on-1-yl-carbonyl chloride were gradually introduced at this temperature, whilst stirring and at the same time the pH was kept at 7.5—8.0 by appropriate addition of approximately 5 N sodium hydroxide solution. The phenylglycine hereupon dissolved, apart from a small amount of residue. The mixture was stirred for a further 60 minutes at $+5^\circ\text{C}$., during which time a little sodium hydroxide solution still had to be added occasionally in the first 15 minutes only, to maintain the desired pH. Small amounts of insoluble matter were then filtered off. The filtrate was largely freed of dioxane by means of a rotary evaporator, covered with a layer of ethyl acetate, acidified with 2 N hydrochloric acid to pH 1.5—2.0 and thoroughly stirred, and the organic phase was then separated off, twice washed with water, dried over magnesium sulphate and completely evaporated in a rotary evaporator. The residue, a colourless clear foam, was dried for two days over P_2O_5 in a desiccator with an open trap, connected to an oil pump. Yield: 7.9 parts by weight. In the IR spectrum (solvent: dimethylsulphoxide), the substance shows two double bands in the region left open by the solvent, namely at 1720 and 1670 , and at 1525 and 1480 cm^{-1} , respectively. NMR signals, see Table 2, page 46.

Example 49

α -[(Imidazolidin-2-on-1-yl)-carbonylamino]-4-methylthiophenylacetic acid:

a) α -Amino-4-methylthiophenylacetic acid:

This amino acid was obtained according to the usual procedure: starting from 4-methylthiobenzaldehyde, via the cyanohydrin and α -aminonitrile, and its saponification with boiling 20% strength hydrochloric acid. Melting point $>260^\circ$ on the Kofler bench.

The IR spectrum (Nujol) shows a single band in the carbonyl region at 1740 cm^{-1} and a broad absorption between 1570 and 1670 cm^{-1} , with a main peak at 1590 cm^{-1} .

The NMR spectrum ($\text{NaOD}/\text{D}_2\text{O}$) shows signals at $\tau=2.5\text{--}2.8$ (4 H) (AB-system), at 5.6 (1 H) and at 7.6 ppm (3 H).

b) α -[(Imidazolidin-2-on-1-yl)-carbonylamino]-4-methylthiophenylacetic acid:

This compound was manufactured from 13 parts by weight of the aminoacid described above and 10 parts by weight of imidazolidin-2-on-1-yl-carbonyl chloride, in the manner described in Example 5.

Yield: 6.7 parts by weight of a yellowish hard foam.

In the IR spectrum (solvent: dimethylsulphoxide) the substance shows two double bands in the range left open by the solvent, namely at 1710 and 1660 , and at 1520 and 1480 cm^{-1} .

NMR signals, see Table 2, page 46.

Example 50

Sodium D- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin:

3.8 parts by weight of D- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-phenylacetic acid were dissolved in 65 parts by volume of dichloromethane, 2.7 parts by weight of 1-methyl-2-chloro- Δ -1-pyrrolinium chloride were added, and after cooling to -10°C . 2.0 parts by volume of triethylamine were added gradually. This reaction mixture was then stirred for one hour at -5°C . (mixture A). 4.0 parts by weight of 6-aminopenicillanic acid in 80 parts by volume of dichloromethane were treated with 4.4 parts by volume of triethylamine and 4.0 parts by weight of anhydrous sodium sulphate and then stirred for two hours at room temperature. After filtration, the solution was cooled to -20°C . and combined with the mixture A. The reaction mixture was left to reach 0°C . of its own accord, and was then stirred for a further hour at 0°C . The solvent was now removed in a rotary evaporator, the residue was dissolved in water, and the solution was covered with a layer of ethyl acetate and acidified with dilute hydrochloric acid at 0° to 5°C ., whilst stirring, until pH 1.5 was reached. The organic phase was then separated off, washed with water, dried over magnesium sulphate whilst cooling, and filtered, and after dilution with an equal amount of ether the sodium salt of the penicillin was precipitated from the filtrate by adding a solution of sodium 2-ethylcaproate dissolved in ether containing methanol.

Yield: 1.3 parts by weight.

β -Lactam content: 34%.

IR band at 1775 cm^{-1} . NMR signals, see Table 2, page 46.

Example 51

D- α -[(Imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin
(free acid and sodium salt):

Mixture A was prepared in a corresponding manner to Example 50, from 3.8 parts by weight of D- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-phenylacetic acid, 65 parts by volume of dichloromethane, 3.0 parts by weight of 1,3-dimethyl-2-chloro- Δ -1-imidazolinium chloride and 2.0 parts by volume of triethylamine, and reacted with the dried solution prepared from 4.0 parts by weight of 6-aminopenicillanic acid, 80 parts by volume of dichloromethane, 4.4 parts by volume of triethylamine and 4.0 parts by weight of Na_2SO_4 . After removing the solvent and distributing the reaction product between an aqueous phase of pH 1.5 and ethyl acetate, a precipitate which is neither soluble in the acid aqueous phase nor in the organic phase was formed and this was filtered off, washed with water and dried. This product was the free acid of the desired penicillin. Yield 1.5 parts by weight. The ethyl acetate phase which was above the acid aqueous phase was separated off, washed with water, dried over magnesium sulphate and diluted with ether, and the sodium salt of the penicillin was precipitated.

Yield: 1.9 parts by weight.

β -Lactam content (free acid): 92%.

β -Lactam content (sodium salt): 89%.

The two penicillins show an IR spectrum which corresponds to their structure.

NMR signals, see Table 2, page 46.

Example 52

D- α -[(imidazolidin-2-yl)-carbonylamino]-benzylpenicillin
(free acid and sodium salt):

The penicillin was prepared in a manner corresponding to Example 52, from 3.8 parts by weight of D- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-phenylacetic acid, 50 parts by volume of dichloromethane, 1.2 parts by weight of tetramethylchloroformamidinium chloride and 1.0 part by volume of triethylamine, constituting mixture A, and 2.0 parts by weight of 6-aminopenicillanic acid in 50 parts by volume of dichloromethane and 2.2 parts by volume of triethylamine as well as 2.0 parts by weight of sodium sulphate. 0.2 part by weight of penicillin was obtained as the free acid and 1.9 parts by weight as the sodium salt.

B-Lactam content (free acid): 90%.

β -Lactam content (sodium salt): 25%.

The free acid showed an IR spectrum corresponding to its structure.

Example 53

Sodium α -[(imidazolidin-2-on-1-yl)-carbonylamino]-4-methylthiobenzylpenicillin:

This penicillin was prepared in a manner corresponding to Example 50, from 4.5 parts by weight of α -[(imidazolidin-2-on-1-yl)-carbonylamino]-4-methylthio-phenylacetic acid, 80 parts by volume of dichloromethane, 2.7 parts by weight of 1-methyl-2-chloro- Δ -1-pyrrolinium chloride and 2.0 parts by volume of triethylamine, constituting mixture A, and 4.0 parts by weight of 6-aminopenicillanic acid, 80 parts by volume of dichloromethane, 4.4 parts by volume of triethylamine and 4.0 parts by weight of sodium sulphate.

Yield: 4.2 parts by weight of sodium salt.

β -Lactam content: 36%.

NMR signals, see Table 2, page 46.

Example 54

Sodium D,L- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-4-methylthiobenzylpenicillin:

This penicillin was obtained in a manner based on Example 50, from 1.9 parts by weight of α -[(imidazolidin-2-on-1-yl)-carbonylamino]-4-methylthio-phenylacetic acid, 40 parts by volume of dichloromethane, 1.2 parts by weight of tetramethylchloroformamidinium chloride and 0.98 part by volume of triethylamine constituting mixture A, and 1.73 parts by weight of 6-aminopenicillanic acid, 40 parts by volume of dichloromethane, 1.9 parts by volume of triethylamine and 1.5 parts by weight of sodium sulphate constituting mixture B. Yield: 2.0 parts by weight of sodium salt. β -Lactam content: 61%. The penicillin showed an IR spectrum corresponding to its structure.

NMR signals, see Table 2, page 46.

Example 55

1,3-Dimethyl-2-chloro- Δ -1-imidazolinium chloride:a) *N,N'*-Dimethyl-*N,N'*-bis-trimethylsilyl-ethylenediamine:

A mixture of 176 parts by weight of *N,N'*-dimethylethylenediamine, 1000 parts by volume of benzene and 552 parts by volume of triethylamine were stirred at room temperature and at the same time 434 parts by weight of trimethylchlorosilane, diluted with 500 parts by volume of benzene, were added dropwise over the course of 3 hours. The mixture was stirred for a further 3.5 hours and left to stand overnight, and the precipitate present was filtered off and washed with benzene. The combined filtrates were concentrated in a rotary evaporator and the residue was distilled *in vacuo*.

Yield: 364 parts by weight.

Boiling point $n_D^{25} = 55-60^\circ \text{C}$.

The NMR spectrum (CCl_4 as the solvent) showed signals at -160 (4 H) and -148 Hz (6 H), with the signal of the trimethylsilyl radicals (9 H) being at 0 Hz.

Analysis: Calculated: C 51.7 H 12.1 N 12.1

Found: C 51.1 H 11.9 N 12.1

b) *N,N'*-Dimethylimidazolid-2-one.

A solution of 363 parts by weight of *N,N'*-dimethyl-*N,N'*-bis-trimethylsilyl-ethylenediamine in 440 parts by volume of dichloromethane, and a solution of 170 parts by weight of phosgene in 700 parts by volume of dichloromethane, were simultaneously and separately added dropwise, over the course of 4.5 hours, to 800 parts

by volume of dichloromethane at room temperature, whilst stirring. The reaction mixture was then left to stand overnight, the unreacted phosgene was flushed out with dry air, the solvent was removed in a rotary evaporator and the residue was distilled *in vacuo*. Yield 119 parts by weight. Boiling point $10-10.5$ mm Hg = $95-95.5^{\circ}$ C.

5 c) 1,3-Dimethyl-2-chloro- Δ -1-imidazolinium chloride: 5

A solution of 150 parts by weight of 1,3-dimethylimidazolid-2-one in 200 parts by volume of toluene was added to a solution of 156 parts by weight of phosgene in 330 parts by volume of toluene, and the mixture was left to stand overnight at room temperature. The product which had then crystallised out was filtered off, washed with carbon tetrachloride and dried over P_2O_5 in a desiccator.

Yield: 177 parts by weight.

Melting point: about $95-100^{\circ}$ C. (Kofler bench). The product is crystalline and very hygroscopic. The NMR spectrum (solvent: chloroform) shows signals at $\tau=5.6$ (4 H) and 6.65 ppm (6 H).

Example 56 15

If, in the procedure of Example 44, the α -[(imidazolidin-2-on-1-yl)-carbonyl-amino]-*p*-methylphenylacetic acid used therein is replaced by 0.02 mol of:—

D- α -[(1,3-diazacyclohexan-2-on-1-yl)-carbonylamino]-phenylacetic acid, 20

α -[(1,3-diazacyclohexan-2-on-1-yl)-carbonylamino]-*p*-methylphenylacetic acid, 20

α -[(1,3-diazacyclohexan-2-on-1-yl)-carbonylamino]-*p*-chlorophenylacetic acid, 20

α -[(1,3-diazacyclohexan-2-on-1-yl)-carbonylamino]-*p*-methylthiophenylacetic acid, 25

α -[(diazacyclohexan-2-on-1-yl)-carbonylamino]-*p*-hydroxyphenylacetic acid, 25

α -[(1,3-diazacyclohexan-2-on-1-yl)-carbonylamino]-thienyl(2)-acetic acid, 25

α -[(1,3-diazacyclohexan-2-on-1-yl)-carbonylamino]-thienyl(3)-acetic acid, 25

D- α -[(benzimidazol-1-yl)-carbonylamino]-phenylacetic acid, 25

α -[(benzimidazol-1-yl)-carbonylamino]-*p*-methylphenylacetic acid, 25

α -[(benzimidazol-1-yl)-carbonylamino]-*p*-chlorophenylacetic acid, 25

α -[(benzimidazol-1-yl)-carbonylamino]-*p*-methylthio-phenylacetic acid, 25

α -[(benzimidazol-1-yl)-carbonylamino]-*p*-hydroxy-phenylacetic acid, 25

α -[(benzimidazol-1-yl)-carbonylamino]-thienyl(2)-acetic acid, 25

α -[(benzimidazol-1-yl)-carbonylamino]-thienyl(3)-acetic acid, 25

D- α -[(5-methyl-imidazolidin-2-on-1-yl)-carbonylamino]-phenylacetic acid, 25

α -[(4-methylimidazolidin-2-on-1-yl)-carbonylamino]-*p*-methylphenylacetic acid, 25

α -[(5-methylimidazolidin-2-on-1-yl)-carbonylamino]-*p*-chlorophenylacetic acid, 25

α -[(5-methylimidazolidin-2-on-1-yl)-carbonylamino]-*p*-methylthiophenylacetic acid, 25

α -[(5-methylimidazolidin-2-on-1-yl)-carbonylamino]-*p*-hydroxyphenylacetic acid, 25

α -[(5-methylimidazolidin-2-on-1-yl)-carbonylamino]-thienyl(2)-acetic acid, 25

α -[(5-methylimidazolidin-2-on-1-yl)-carbonylamino]-thienyl(3)-acetic acid, 25

D- α -[(5,5-dimethylimidazolidin-2-on-1-yl)-carbonylamino]-phenylacetic acid, 25

α -[(5,5-dimethylimidazolidin-2-on-1-yl)-carbonylamino]-*p*-methylphenylacetic acid, 25

α -[(5,5-dimethylimidazolidin-2-on-1-yl)-carbonylamino]-*p*-chlorophenylacetic acid, 25

α -[(4,5-dimethylimidazolidin-2-on-1-yl)-carbonylamino]-*p*-methylthiophenylacetic acid, 25

α -[(5,5-dimethylimidazolidin-2-on-1-yl)-carbonylamino]-*p*-hydroxyphenylacetic acid, 25

α -[(5,5-dimethylimidazolidin-2-on-1-yl)-carbonylamino]-thienyl(2)-acetic acid or 25

α -[(4,4-dimethylimidazolidin-2-on-1-yl)-carbonylamino]-thienyl(3)-acetic acid, 25

the following penicillins are obtained in the form of their sodium salts:—

D- α -[(1,3-diazacyclohexan-2-on-1-yl)-carbonylamino]-benzylpenicillin, 50

α -[(1,3-diazacyclohexan-2-on-1-yl)-carbonylamino]-*p*-methylbenzylpenicillin, 50

α -[(1,3-diazacyclohexan-2-on-1-yl)-carbonylamino]-*p*-chlorobenzylpenicillin, 50

α -[(1,3-diazacyclohexan-2-on-1-yl)-carbonylamino]-*p*-methylthio-benzylpenicillin, 50

α -[(1,3-diazacyclohexan-2-on-1-yl)-carbonylamino]-*p*-hydroxybenzylpenicillin, 50

α -[(1,3-diazacyclohexan-2-on-1-yl)-carbonylamino]-thienyl(2)-methylpenicillin, 50

α -[(1,3-diazacyclohexan-2-on-1-yl)-carbonylamino]-thienyl(3)-methylpenicillin, 50

D- α -[(benzimidazol-1-yl)-carbonylamino]-benzylpenicillin, 50

α -[(benzimidazol-1-yl)-carbonylamino]-*p*-methyl-benzylpenicillin, 50

α -[(benzimidazol-1-yl)-carbonylamino]-*p*-chlorobenzylpenicillin, 50

α -[(benzimidazol-1-yl)-carbonylamino]-*p*-methylthio-benzylpenicillin, 50

α -[(benzimidazol-1-yl)-carbonylamino]-*p*-hydroxy-benzylpenicillin, 50

α -[(benzimidazol-1-yl)-carbonylamino]-thienyl(2)-methylpenicillin, 50

α -[(benzimidazol-1-yl)-carbonylamino]-thienyl(3)-methylpenicillin, 50

α -[(benzimidazol-1-yl)-carbonylamino]- α -thienyl(3)-methylpenicillin,
D- α -[(5-methylimidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin,
 α -[(4-methylimidazolidin-2-on-1-yl)-carbonylamino]-*p*-methyl-benzylpenicillin,
 α -[(5-methylimidazolidin-2-on-1-yl)-carbonylamino]-*p*-chloro-benzylpenicillin,
5 α -[(5-methylimidazolidin-2-on-1-yl)-carbonylamino]-*p*-methylthio-benzylpenicillin, 5
 α -[(5-methylimidazolidin-2-on-1-yl)-carbonylamino]-*p*-hydroxy-benzylpenicillin,
5 α -[(5-methylimidazolidin-2-on-1-yl)-carbonylamino]- α -thienyl(2)-methylpenicillin,
 α -[(5-methylimidazolidin-2-on-1-yl)-carbonylamino]- α -thienyl(3)-methylpenicillin,
10 D- α -[(5,5-dimethylimidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin,
 α -[(5,5-dimethylimidazolidin-2-on-1-yl)-carbonylamino]-*p*-methyl-benzylpenicillin, 10
 α -[(5,5-dimethylimidazolidin-2-on-1-yl)-carbonylamino]-*p*-chlorobenzylpenicillin,
10 α -[(4,5-dimethylimidazolidin-2-on-1-yl)-carbonylamino]-*p*-methylthio-benzyl-
penicillin,
15 α -[(5,5-dimethylimidazolidin-2-on-1-yl)-carbonylamino]-*p*-hydroxy-benzylpenicillin,
 α -[(5,5-dimethylimidazolidin-2-on-1-yl)-carbonylamino]- α -thienyl(2)-methylpenicillin 15
or
 α -[(4,4-dimethylimidazolidin-2-on-1-yl)-carbonylamino]- α -thienyl(3)-methylpenicillin.

Example 57

If, in the procedure of Example 44, the α -[(imidazolidin-2-on-1-yl)-carbonyl-
20 amino]-*p*-methylphenylacetic acid used therein is replaced by 0.02 mol of:— 20

D- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*p*-methoxyphenylacetic acid,
L- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*p*-methoxyphenylacetic acid,
D,L- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*p*-methoxyphenylacetic acid,
25 D- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*o,o'*-dichlorophenylacetic acid,
L- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*o,o'*-dichlorophenylacetic acid or 25
D,L- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*o,o'*-dichlorophenylacetic acid,

the following penicillins are obtained in the form of their sodium salts:—

D- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*p*-methoxy-benzylpenicillin,
L- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*p*-methoxy-benzylpenicillin, 30
D,L- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-*p*-methoxy-benzylpenicillin,
D- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-2,6-dichloro-benzylpenicillin, 30
L- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-2,6-dichloro-benzylpenicillin or
D,L- α -[(imidazolidin-2-on-1-yl)-carbonylamino]-2,6-dichloro-benzylpenicillin.

Table 2 NMR data of some penicillins of the general formula (1). Position of the
signals is indicated in the τ -scale [ppm]. Solvent: CD₃OD.

Example	NMR signals at [intensity of the signals, deducting the signals of the intermediate acid]	Impurities visible in the spectrum
45	2.4—3.0 (4 H), 4.3—4.6 (3H) 5.8 (1 H), 5.9—6.4 (2 H), 6.4—6.9 (2 H), 7.7 (3 H) and 8.4 (6 H)	15% by weight of α - (imidazolidin-2-on-1-yl- carbonylamino)- <i>p</i> -methyl- phenylacetic acid
46	as Example 45	60% by weight of α - (imidazolidin-2-on-1-yl- carbonylamino)- <i>p</i> -methyl- phenylacetic acid
47	2.6 (4 H), 4.3—4.6 (3 H), 5.8 (1 H), 5.9—6.8 (4 H) and 8.3—8.6 (6 H)	10% by weight of α - (imidazolidin-2-on-1- yl-carbonylamino)- <i>p</i> - chloro-phenylacetic acid

TABLE 2 (Continued)

Example	NMR signals at intensity of the signals, deducting the signals of the intermediate acid]	Impurities visible in the spectrum.
48A	as Example 47	25% by weight of α -(imidazolidin-2-on-1-yl-carbonylamino)- <i>p</i> -chloro-phenylacetic acid
48B acetone- d ₆ as the solvent	0.9 (1 H), 2.6 (2 H), 2.8 (3 H), 4.5 (1 H), 6.2 (2 H), 6.6 (2 H), and 7.7 (3 H)	—
48C acetone- d ₆ as the solvent	0.9 (1 H), 2.55 (4 H), 4.5 (1 H), 6.2 (2 H), and 6.5 (2 H)	—
49	2.4—2.75 (5 H), 4.45—4.6 (1 H), 6.0—6.85 (4 H)	—
50	2.55—2.8 (4 H), 5.55—4.7 (1 H), 5.95—6.8 (4 H), 7.55 (3 H)	—
51	2.35—2.75, 4.35—4.55, 5.75—5.95—6.85, 8.3—8.55	58% by weight of D- α -(imidazolidin-2- on-1-yl-carbonyl- amino)-phenyl-acetic acid
52	(free acid) 2.4—2.7 (5 H), 4.3—4.6 (3 H), 5.55 (1 H), 5.9—6.7 (4 H), 8.25—8.5 6 H) (Na salt) 2.45—2.75 (5 H), 4.3—4.6 (3 H), 5.8 (1 H), 5.95—6.75 (4 H), 8.3—8.6 (6 H)	—
54	2.45—2.9, 4.35—4.6, 5.8, 5.9—6.85, 7.6, 8.3—8.55	60% by weight of α -(imidazolidin-2- on-1-yl-carbonyl- amino)- <i>p</i> -methyl- thio-phenylacetic acid
55	2.4—2.9, 4.35—4.65, 5.8 5.95—6.8, 7.6, 8.3—8.6	40% by weight of α -(imidazolidin-2- on-1-yl-carbonyl- amino)- <i>p</i> -methylthio- phenylacetic acid

5

10

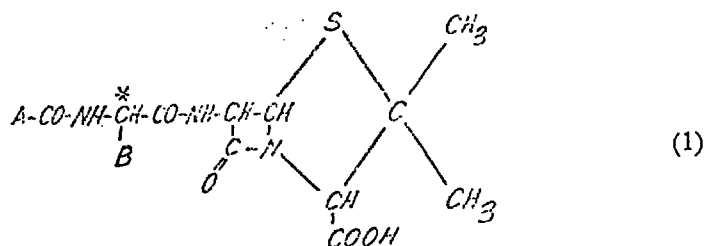
15

20



WHAT WE CLAIM IS:—

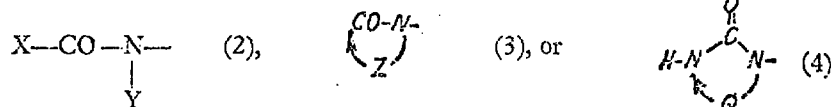
1. Penicillins of the general formula:—



in which general formula:—

5 A is a group of the general formula:—

5



in which general formulac (2), (3) and (4)

X is a hydrogen atom, or an alkyl, alkenyl, cycloalkyl or cycloalkenyl group with up to ten carbon atoms, or a vinyl, arylvinyl, mono-, di-, or tri-halo (lower alkyl), lower alkylamino, di (lower alkyl)amino, monoarylamino, aryl (lower alkyl) amino or aryloxy group, or an alkoxy or aralkoxy group with up to eight carbon atoms, or a cycloalkoxy group with up to seven carbon atoms, or a group of the general formula:—

10

10

(lower alkyl)-O—V— (5);

(lower alkyl)-S—V (6);

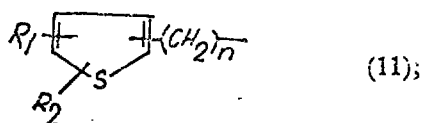
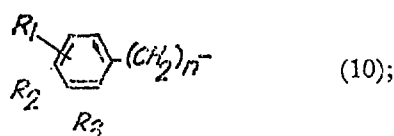
15

15

N≡C—V— (7);

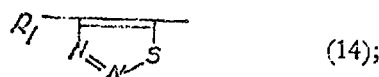
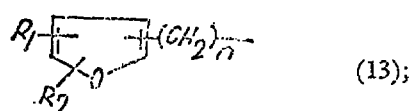
(lower alkyl)-O—CO—V— (8);

di (lower alkyl)amino-CO—V— (9);



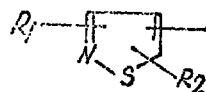
20

20

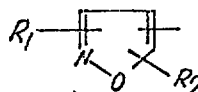




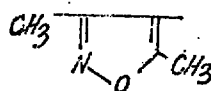
(15);



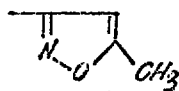
(16);



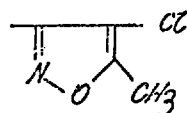
(17);



(18);



(19); or



(20);

[in which general formulae (5) to (20):

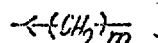
V is a bivalent organic radical with 1 to 3 carbon atoms;

n is 0, 1 or 2; and

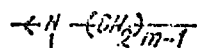
R₁, R₂ and R₃, which may be the same or different, are each a hydrogen, chlorine, bromine, iodine or fluorine atom or a nitro, nitrile, di (lower alkyl)amino, di (lower alkyl)aminocarbonyl, lower alkanoylamino, lower alkoxy-carbonyl, lower alkanoyloxy, lower alkyl, lower alkoxy, sulphonyl, or trifluoromethyl group;]

Y is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group with up to ten carbon atoms, or a vinyl, propenyl, mono-, di-, or tri-halo (lower alkyl), aryl, or heterocyclic group, or an aralkyl group with up to eight carbon atoms;

-<Z-- is a divalent group of the formula: —

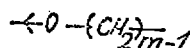


(21);

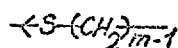


(22);

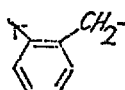
(lower alkyl)



(23);



(24);



(25);



(26); or



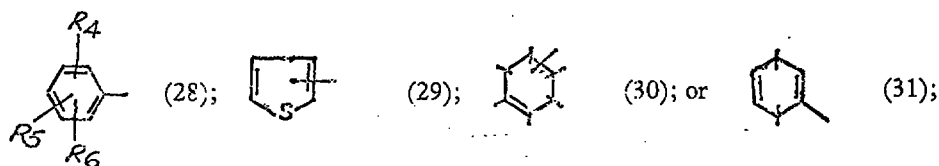
[in which general formula (21) to (27) n is 3, 4 or 5 and the arrow $\leftarrow$ means that the two free valencies of the group Z are not arbitrarily joined to the N and C atoms of the group



but are oriented as indicated by the arrow;]

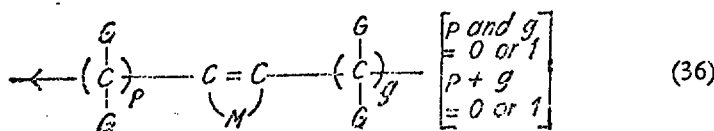
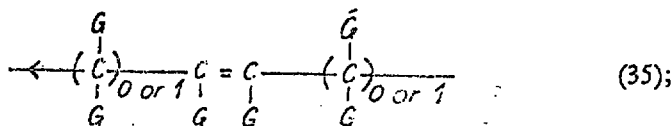
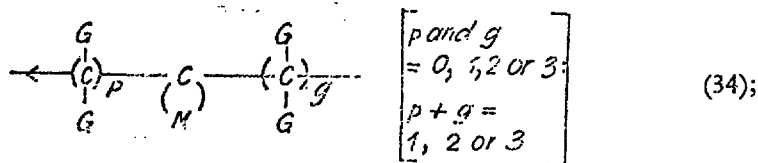
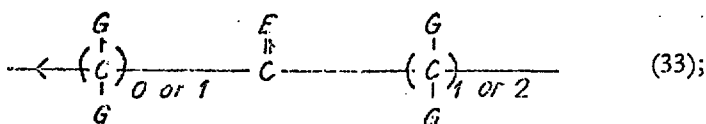
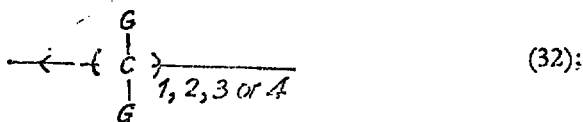
Q is a divalent group;

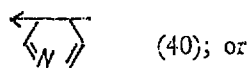
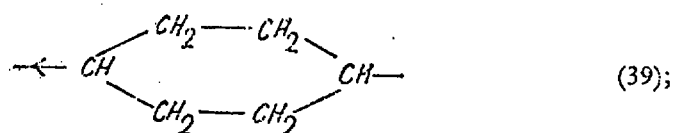
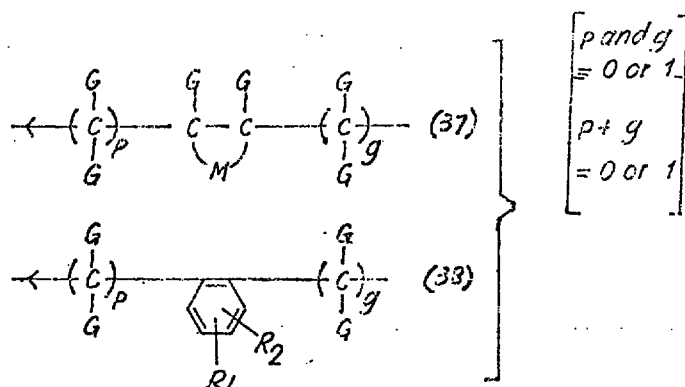
B is a group of the general formula: —



[in which general formulae (28), (29), (30) and (31) R_4 , R_5 and R_6 , which may be the same or different, are each a hydrogen or halogen atom or a lower alkyl, lower alkoxy, lower alkylthio, lower alkylthionyl, lower alkylsulphonyl, nitro, di (lower alkyl) amino, lower alkanoylamino, hydroxy, or lower alkanoyloxy group], and which, as regards the chirality centre C^* can have either of the two possible R— and S— stereoisomeric configurations or can be a mixture of these two diastereomers; and the salts of these penicillins.

2. The penicillins and salts of claim 1 in which Q is a group of the general formula: —





in which general formulae (32) to (41):

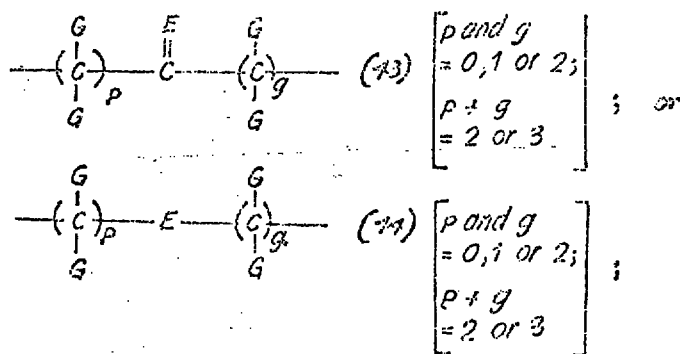
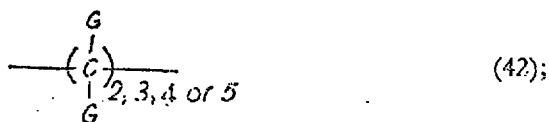
E is a oxygen or sulphur atom;

G is a hydrogen atom or a lower alkyl group;

R₁ and R₂ are as defined in claim 1; the arrow in the divalent group $\leftarrow Q \rightarrow$ means that the two free valencies of the group Q are not arbitrarily joined to the two nitrogen atoms of the group



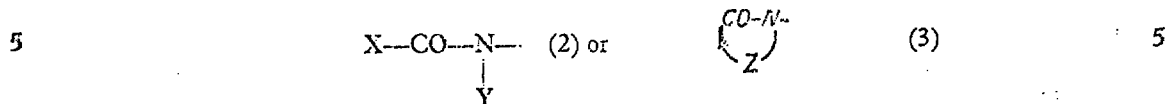
but are oriented as indicated by the arrow;
M is a group of the general formula: --



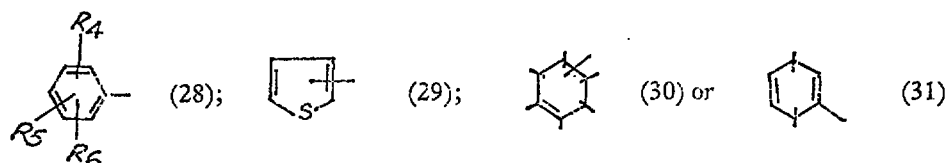


in which general formulae (42), (43) and (44),
E and G have the meanings given above.

3. The penicillins according to claim 1 of general formula (1) in which A is a group of the general formula: —

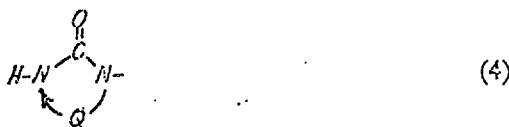


in which X, Y and Z are as defined in claim 1, and B is a group of the general formula: —



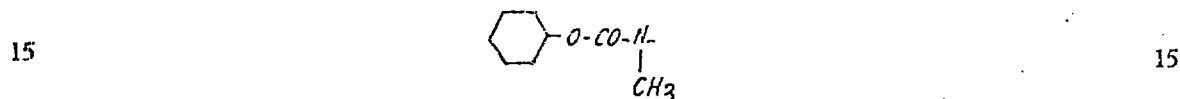
and their pharmaceutically acceptable salts.

10 4. The penicillins according to claim 1 of general formula (1) in which A is a group of the general formula: — 10

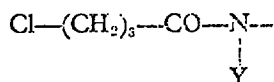


in which Q is as defined in claim 1 or 2, and their pharmaceutically acceptable salts.

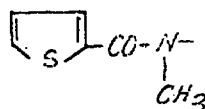
5. The penicillins and salts of claim 1 or 3 in which A is the group:



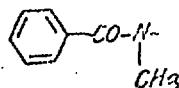
6. The penicillins and salts of claim 1 or 3 in which A is the group:



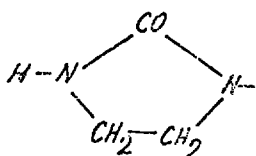
7. The penicillins and salts of claim 1 in which A is the group: —



20 8. The penicillins and salts of claim 1 or 3 in which A is the group: — 20



9. The penicillins and salts of claim 2 or 4 in which A is the group: —





10. The penicillins and salts of any preceding claim in which B is a phenyl group.
11. The penicillins and salts of any preceding claim in which B is a *p*-methylthiophenyl group.
- 5 12. The penicillins and salts of any preceding claim in which B is a *p*-methylphenyl group. 5
13. The penicillins and salts of any preceding claim in which B is a *p*-methoxyphenyl group.
14. The penicillins and salts of any preceding claim in which B is a thienyl-(2) group. 10
- 10 15. The penicillins and salts of any preceding claim in which C* is in the R-configuration. 10
16. D- α -(3-Acetyl-3-allyl-ureido)-benzylpenicillin and its sodium salt.
17. D - α - (3 - γ - Chlorobutyryl - 3 - methyl - ureido) - benzylpenicillin and its sodium salt. 15
- 15 18. D,L- α -(3-Acetyl-3-allyl-ureido)- α -thienyl(2)-methylpenicillin, and its sodium salt. 15
19. α -(3- β -Chloropropionyl-3-methyl-ureido)-cyclohex - 3 - enyl-methylpenicillin, and its sodium salt.
- 20 20. D,L - (3 - γ - Chlorobutyryl - 3 - methyl - ureido) - (2 - thienyl) - methylpenicillin, and its sodium salt. 20
21. D,L - α - (3 - Dimethylaminocarbonyl - 3 - methyl - ureido) - 4 - methoxybenzylpenicillin, and its sodium salt.
22. D,L - α - (3 - Dimethylaminocarbonyl - 3 - methyl - ureido) - α - thienyl(2)-methylpenicillin, and its sodium salt. 25
- 25 23. D,L - α - (Pyrrolid - 2 - on - 1 - yl - carbonyl - amino) - α - *p* - tolylmethylpenicillin, and its sodium salt. 25
24. D - α - (3 - Methoxycarbonyl - 3 - methyl - ureido) - benzylpenicillin, and its sodium salt.
25. D - α - (3 - Isopropoxycarbonyl - 3 - methyl - ureido) - benzylpenicillin and its sodium salt. 30
- 30 26. D - α - (3 - *n* - Butoxycarbonyl - 3 - methyl - ureido) - benzylpenicillin and its sodium salt. 30
27. D - α - (3 - Cyclohexyloxycarbonyl - 3 - methyl - ureido) - benzylpenicillin and its sodium salt.
- 35 28. D - α - (3 - Allyloxycarbonyl - 3 - methyl - ureido) - benzylpenicillin and its sodium salt. 35
29. D - α - (3 - Methoxycarbonyl - 3 - methyl - ureido) - 2,6 - dichlorobenzylpenicillin, and its sodium salt.
30. L - α - (3 - Methoxycarbonyl - 3 - methyl - ureido) - 2,6 - dichlorobenzylpenicillin, and its sodium salt. 40
- 40 31. D,L - α - (3 - Methoxycarbonyl - 3 - methyl - ureido) - 2,6 - dichlorobenzylpenicillin, and its sodium salt.
32. D,L - α - (3 - Methoxycarbonyl - 3 - methyl - ureido) - 4 - methoxybenzylpenicillin, and its sodium salt.
- 45 33. D,L - α - (3 - Methoxycarbonyl - 3 - methyl - ureido) - α - (thienyl(2)-methylpenicillin, and its sodium salt. 45
34. α - (3 - Ethoxycarbonyl - 3 - methyl - ureido) - 4 - methylsulphenylbenzylpenicillin, and its sodium salt.
35. D,L - α - [(Imidazolidin - 2 - on - 1 - yl) - carbonylamino] - *p* - methylbenzylpenicillin, and its sodium salt. 50
- 50 36. D,L - α - [(Imidazolidin - 2 - on - 1 - yl) - carbonylamino] - *p* - chlorobenzylpenicillin, and its sodium salt.
37. D,L - α - [(Imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methylthiobenzylpenicillin, and its sodium salt.
- 55 38. D,L - α - [(Imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 2,6 - dichlorobenzylpenicillin, and its sodium salt. 55
39. D - α - [(Imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 2,6 - dichlorobenzylpenicillin, and its sodium salt.
40. L - α - [(Imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 2,6 - dichlorobenzylpenicillin, and its sodium salt. 60
- 60 41. D,L - α - [(Imidazolidin - 2 - on - 1 - yl) - carbonylamino] - *p* - methoxybenzylpenicillin, and its sodium salt.
42. D - α - [(Imidazolidin - 2 - on - 1 - yl) - carbonylamino] - *p* - methoxybenzylpenicillin, and its sodium salt. 40

43. L - α - [(Imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - methoxybenzylpenicillin, and its sodium salt.

44. D,L - α - (3 - Benzoyl - 3 - methylureido) - 4 - methylsulphenylbenzylpenicillin, and its sodium salt.

45. D,L - α - (3 - Benzoyl - 3 - methyl - ureido) - 4 - methylbenzylpenicillin, and its sodium salt.

46. D,L - α - (3 - Benzoyl - 3 - allyl - ureido) - 4 - methoxybenzylpenicillin, and its sodium salt.

47. D,L - α - (3 - Benzoyl - 3 - allyl - ureido) - 2,6 - dichlorobenzylpenicillin, and its sodium salt.

48. D,L - α - (3 - Benzoyl - 3 - methyl - ureido) - 2,6 - dichlorobenzylpenicillin, and its sodium salt.

49. D,L - α - (3 - o - Fluorobenzoyl - 3 - methyl - ureido) - α - p - tolyl - methylpenicillin, and its sodium salt.

50. D,L - α - (3 - Benzoyl - 3 - allyl - ureido) - α - thienyl(2) - methylpenicillin, and its sodium salt.

51. D,L - α - (3 - Furoyl(2) - 3 - methyl - ureido) - α - thienyl(2) - methylpenicillin, and its sodium salt.

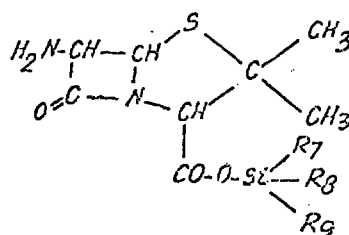
52. D - α - [3 - (2 - Thienoyl) - 3 - methyl - ureido] - benzylpenicillin, and its sodium salt.

53. D - α - [3 - (3,5 - Dimethylisoxazolyl(4) - carbonyl) - 3 - methyl - ureido] - benzylpenicillin, and its sodium salt.

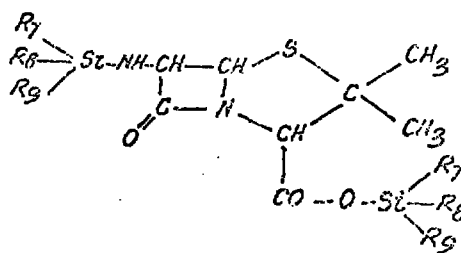
54. The penicillins of claim 1, and the penicillin salts of claim 1 and their corresponding free penicillins, that are hereinbefore specifically mentioned in Examples 3, 5, 6, 12, 13, 16, 24, 25, 26, 27, 34 and 38.

55. The penicillins of claim 1, and the penicillin salts of claim 1 and their corresponding free penicillins, that are hereinbefore specifically mentioned in Examples 45, 47A, 51, 56 and 56.

56. A process for the preparation of the penicillins and salts of claim 1 and 2 in which 6-amino-penicillanic acid or a compound of the general formula:—

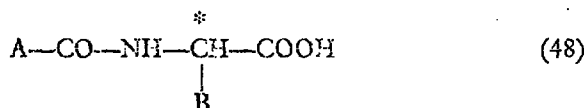


(46) or



(47)

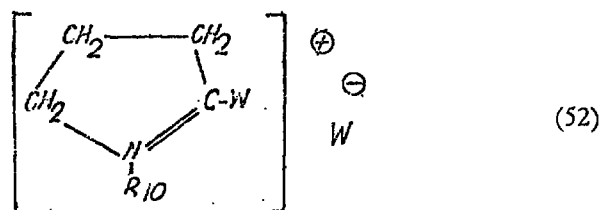
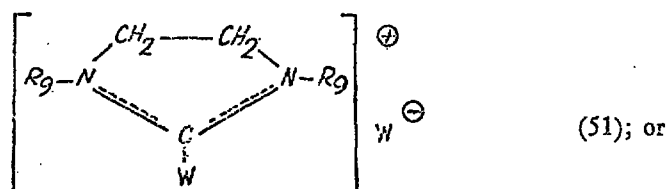
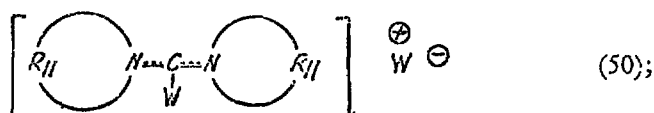
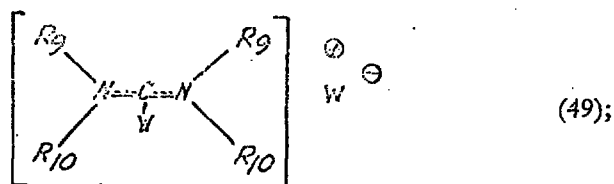
in which R₇, R₈, and R₉ are the same or different alkyl groups having up to six carbon atoms; is reacted at a temperature of -30 to +50° C. with a carboxylic acid of the general formula:—



modified at the carboxyl group, in which general formula (48) A and B have the meanings given in claim 1 or 2; in the case of 6-amino-penicillanic acid, in a solvent in the presence of a base, and in the case of the compounds of general formulae (46) and (47), in a water- and hydroxyl group-free solvent with or without a base.

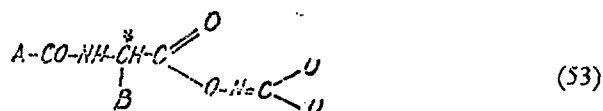


57. The process of claim 56 in which the carboxylic acid of general formula (48) has been modified at the carboxyl group by reaction with about one molar equivalent of a compound of the general formula: —



in which general formula R_9 is as defined in claim 56, R_{10} may have the same meanings as R_9 and may in addition be a phenyl group, R_{11} is a divalent organic radical $-(CH_2)_4-$, $-(CH_2)_5-$, or $-(CH_2)_2-$, $-O-(CH_2)_2-$, and W is a halogen atom; in a water-free inert organic solvent in the presence of about a molar equivalent of a base at a temperature of -60 to $+30^\circ$ C.

58. The process of claim 56 in which the carboxylic acid of general formula (48) has been modified at the carboxyl group by conversion into the derivative of the general formula:—



in which A, B and C* have the meanings given in claim 1 or 2 and U is a —CN and/or a —CO—O (lower alkyl) radical.

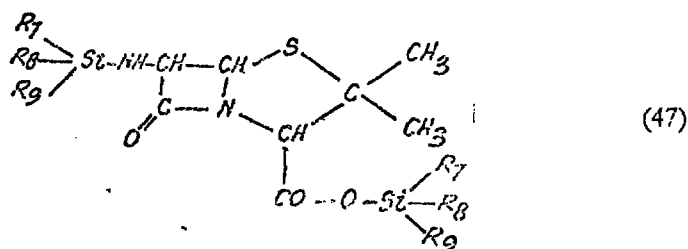
59. The process of claim 58 in which the derivative of general formula (53) has been prepared by reacting a compound of the general formula:—



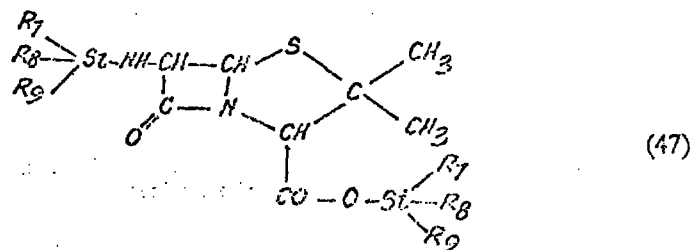
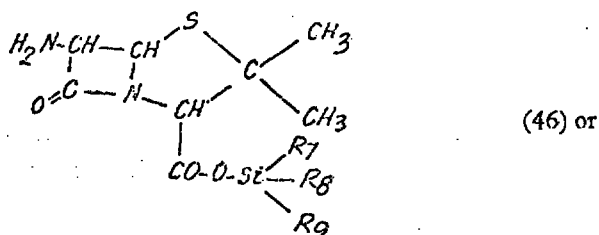
in a water-free inert organic solvent in the presence of at least one molar equivalent of a tertiary organic base, at a temperature of -25 to $+25^{\circ}\text{C}.$, with one molar equivalent of thionyl chloride to obtain with the formation of one molar equivalent



5 60. A process for the production of the penicillins and salts of claim 3 in which 6-amino-penicillanic acid or a compound of the general formula, ---

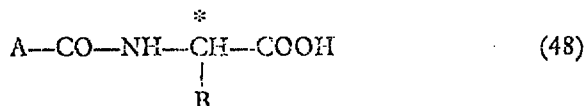

$$\text{A}-\text{CO}-\text{NH}-\overset{*}{\underset{\text{R}}{\text{CH}}}-\text{COOH} \quad (48)$$

61. A process for the production of the penicillins and salts of claim 4 in which 6-amino-penicillanic acid or a compound of the general formula: —





in which R₁, R₂, R₃ are the same or different alkyl groups having up to six carbon atoms; is reacted at a temperature of -20 to +50° C. with a carboxylic acid of the general formula:—



- 5 modified at the carboxyl group, in which general formula (48) A, B and C* have the meanings given in claim 4; in the case of 6-amino-penicillanic acid, in the presence of a base, and in the case of the compounds of general formulae (46) and (47), in a water- and hydroxyl-group-free solvent with or without a base.
- 10 62. The process of claim 56 substantially as hereinbefore specifically described in any of Examples 1 to 41.
63. The process of claim 56 substantially as hereinbefore specifically described in Example 42 and 43.
64. The process of claim 56 substantially as hereinbefore specifically described in any of Examples 44 to 57.
- 15 65. The penicillins and salts of claim 1 whenever produced by the process of any of claims 56 to 59 and 62.
66. The penicillins and salts of claim 3 whenever produced by the process of claim 60 or 62.
- 20 67. The penicillins and salts of claim 23 or 49 whenever produced by the process of claim 63.
68. The penicillins and salts of claim 2 or 4 whenever produced by the process of claim 61 or 64.
- 25 69. An antibiotic pharmaceutical composition containing as an active ingredient at least one penicillin of any of claim 1 to 55 and 65 to 68 or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable solid or liquid diluent or carrier as hereinbefore defined.
70. The composition of claim 69 containing as an active ingredient at least one penicillin of any of claims 3, 16 to 22, 24 to 34, 44, 48, 50 to 54, and 62 or a pharmaceutically acceptable salt thereof.
- 30 71. The composition of claim 69 containing as an active ingredient at least one penicillin of any of claims 23, 49, 63 and 67.
72. The composition of claim 69 containing as an active ingredient at least one penicillin of any of claims 4, 43, 55, 64 and 68.
- 35 73. The composition of any of claims 69 to 72 adapted for peroral administration.
74. The composition of any of claims 69 to 72 adapted for parenteral administration.
75. The composition of claim 74 which is a sterile isotonic saline aqueous solution.
- 40 76. The composition of any of claims 69 to 75 substantially as hereinbefore specifically described.
77. An antibiotic medicament in dosage unit form as hereinbefore defined comprising as an active ingredient at least one penicillin of any of claims 1 to 55 or 65 to 68 or a pharmaceutically acceptable acceptable salt thereof, either alone or in admixture with a solid or liquid diluent or carrier.
- 45 78. The medicament of claim 77 adapted for peroral administration.
79. The medicament of claim 77 adapted for parenteral administration.
80. The medicament of claim 79 which is a dry ampoule containing a measured quantity of the active ingredient.
81. A medicament according to any of claims 78 to 80 substantially as hereinbefore specifically described.

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