

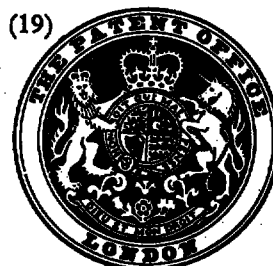
PATENT SPECIFICATION

(11)

1 392 850

392 850

- (21) Application No. 48700/72 (22) Filed 23 Oct. 1972
 (31) Convention Application No. 2 152 968 (32) Filed 23 Oct. 1971
 (31) Convention Application No. 2 152 968 (32) Filed 25 March 1972 in
 (33) Germany (DT)
 (44) Complete Specification published 30 April 1975
 (51) INT CL² C07D 499/68; A61K 31/43
 (52) Index at acceptance
 C2C 1313 1414 1510 214 215 220 226 22Y 246 247 250
 252 254 256 25Y 280 282 28X 292 29Y 30Y 313
 31Y 338 342 34Y 351 352 355 366 367 368 396
 519 575 594 604 615 628 62X 638 63X 658 790
 79Y KE KM RE RF



(72) Inventors HANS-BODO KÖNIG, WILFRIED SCHRÖCK and
 KARL-GEORG METZGER

(54) NEW PENICILLIN COMPOUNDS, THEIR PRODUCTION AND THEIR MEDICINAL USE

(71) We, BAYER AKTIENGESellschaft, a body corporate organised under the laws of Germany, of Leverkusen, 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:—

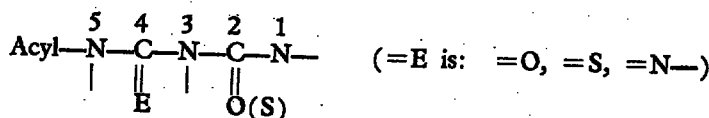
The present invention relates to a process for the production of certain penicillin compounds, to a particular group of these compounds, and to the medicinal use of this group in human and veterinary medicine, as therapeutic agents in poultry and mammals, and as feedstuff additives and as growth-promoting agents in animals.

These penicillin compounds are valuable as therapeutic agents in poultry and mammals, and in man, in the treatment of infectious illnesses caused by Gram-positive and Gram-negative bacteria and especially of those caused by bacteria from the group of the enterobacteria and pseudomonades. They can be used orally and parenterally.

Antibacterial agents, such as ampicillin (British Patent Specification No. 873,049), have proved very effective in the therapy of infections caused by Gram-positive and Gram-negative bacteria. However they are not able to combat infections which are caused, for example, by bacteria of the group of *Klebsiella-Aerobacter* or by indole-positive strains of *Proteus*.

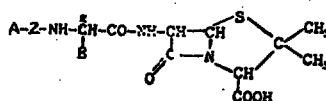
Carbenicillin (U.S. Patent No. 3,142,673 and British Patent Specification No. 1,004,670) is only effective in man in the case of infections of *Klebsiella-Aerobacter* if given in a continuous high dosage, such as is only achieved by infusion.

The penicillin compounds of the present invention may be regarded as methyl-penicillins which are substituted at the methyl group by a radical B and an acylbiureido radical, of which the carbonyl group in the acyl group can be replaced by a —SO₂— group:



6-(α-Biureido)-acetamido-penicillanic acids are described in British Patent Specifications Nos. 1,265,760 and 1,292,969, but none of the 6-(α-biureido)-acetamido-penicillanic acids described and claimed in these patents possess an acyl radical on the nitrogen atom of the biureido radical which is located in the 5-position.

This invention provides penicillin compounds which are compounds of the following general formula I or their salts:—



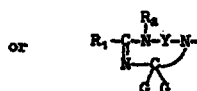
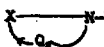
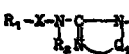
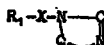
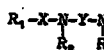
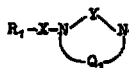
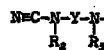
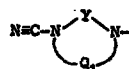
I

in which

C* is a carbon atom constituting a centre of chirality;

A is a radical of one of the general formulae:—

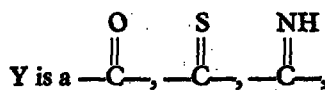
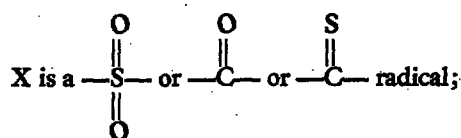
5



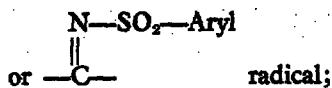
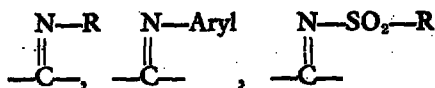
5

[in which general formulae:

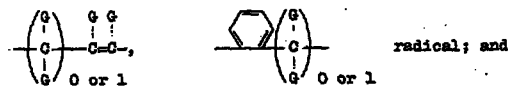
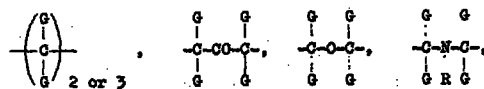
10



10



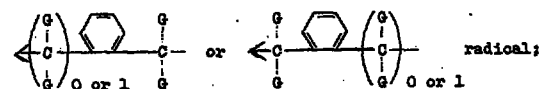
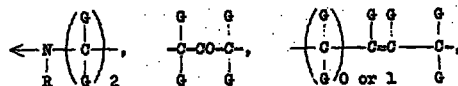
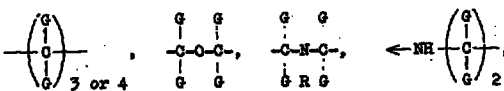
Q₁ is a



15

Q₂ is a

15



20

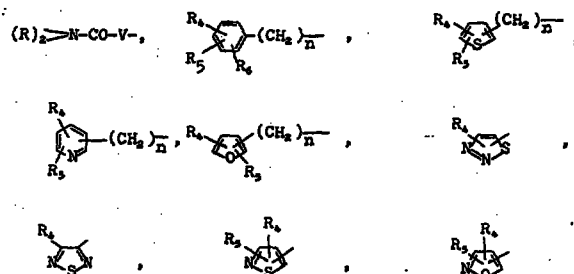
(in which general formulae:—

20

R is a straight-chain or branched alkyl radical with up to 5 carbon atoms,

R₁ is a hydrogen atom or an alkyl, cycloalkyl, alkenyl or cycloalkenyl radical with up to 10 carbon atoms, or a vinyl, arylvinyl, mono-, di- or tri-halo-lower alkyl radical,

or an H_2N- , $R-NH-$, $(R)_2>N-$, aryl- $NH-$, or aryl-lower alkylamino radical, or an alkoxy* or aralkoxy* radical with up to 8 carbon atoms, or a cycloalkoxy* radical with up to 7 carbon atoms, or an aryloxy*, $R-O-V-$, $R-S-V-$, $N\equiv C-V-$, $R-O-CO-V-$, $H_2N-CO-V-$, $R-NH-CO-V-$,



radical;

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

n is 0, 1 or 2;

R_2 and R_3 , which may be the same or different, are each a hydrogen atom or an alkyl or alkenyl radical with up to 8 carbon atoms, or a vinyl, allyl or propenyl radical, or a cycloalkyl or cycloalkenyl radical with up to 6 carbon atoms, or a mono-, di- or tri-halo-lower alkyl or aryl radical;

R_4 , R_5 and R_6 , which may be the same or different, are each a hydrogen, nitro, nitrile, $(R)_2=N-$, $(R)_2=N-CO-$, $R-CO-NH-$, $R-O-CO-$, $R-CO-O-$, $R-$, $R-O-$, H_2N-SO_2- , chlorine, bromine, iodine, fluorine or trifluoromethyl radical; and

G is a hydrogen atom or a radical R;

with the proviso that the meanings marked * are only available if X is not an $-SO_2-$ radical);

Z is a $-CO-$ or $-SO-$ radical; and

B is a radical of the general formula:—



in which R_7 , R_8 and R_9 , which may be the same or different, are each a hydrogen, halogen, $R-$, $R-O-$, $R-S-$, $R-SO-$, $R-SO_2-$, nitro, $(R)_2=N-$, $R-CO-NH$, HO or $R-CO-O-$ radical, R having the meanings given above, provided that when two of R_7 , R_8 , and R_9 are hydrogen, the other cannot be a hydroxyl radical, and that R_7 , R_8 and R_9 cannot all be hydrogen at once.

In the above general formulae, the arrow in the divalent linkage member



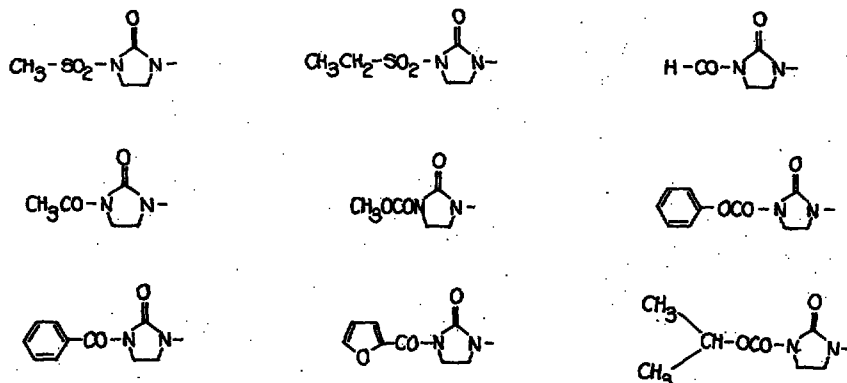
means that the linkage of two atoms by the two free valencies of this linking member is not free to take place in either direction but only in the manner indicated by the arrow.

Our copending Patent Application No. 48699/72 (Serial No. 1 392 849) claims penicillin compounds of the general formula I in which B is unsubstituted phenyl, mono-hydroxyphenyl, or 1,4-cyclohexadienyl.

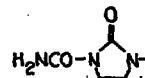
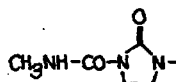
The invention includes within its scope penicillin compounds as defined above in either of the two possible R— and S— configurations resulting from the chirality centre C*, and also mixtures of the diastereomers resulting therefrom.

The term "lower alkyl" in this specification means a straight-chain or branched alkyl radical with up to 6 carbon atoms. In connection with other radicals, such as in "di-lower alkylamino" the term "lower alkyl" only relates to the alkyl part of the radical in question.

Preferred radicals A are the following:—

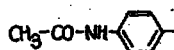


5

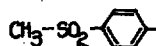


5

Preferred radicals B are the *p*-nitrophenyl, *p*-methylphenyl, *p*-chlorophenyl, thienyl-(2),



and



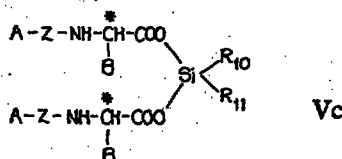
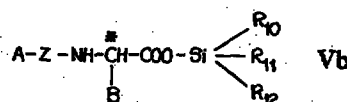
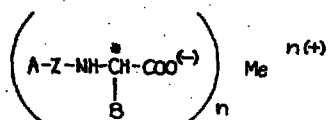
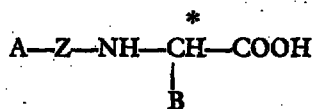
radicals.

Among the penicillin salts of the invention, those that are pharmaceutically acceptable are preferred.

These preferred salts include 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- β -phenylethylamine, *N*-methyl- and *N*-ethylmorpholine, 1-ephedrine, dehydroabietylamine, *N,N'*-bis-dehydroabietyl-ethylenediamine and *N*-lower alkylpiperidine.

This invention further provides a process for the production of a penicillin compound which is a penicillin of the general formula I given above (in which the symbols are as defined below) or a salt thereof, comprising the steps of:—

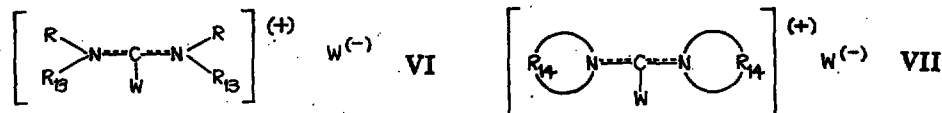
(i) producing a reactive intermediate by reacting a carboxylic acid of the following general formula (V), a carboxylic acid salt of the following general formula Va, or a carboxylic acid silyl or hemisilyl ester of the general formula Vb or Vc:



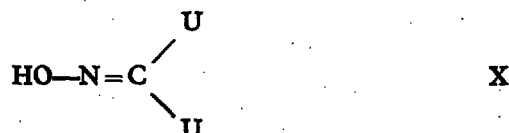
in an aqueous or anhydrous organic solvent when a compound of the general formula V or Va is reacted, or in an anhydrous inert organic solvent free of hydroxyl groups when

a compound of general formula Vb or Vc is reacted, at -70°C to $+30^{\circ}\text{C}$, with either:

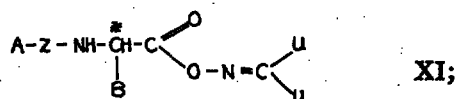
(a) a compound of one of the following general formulae VI to IX:—



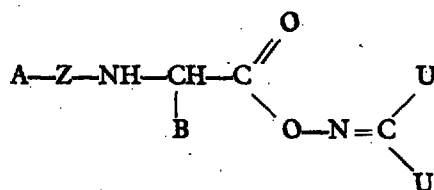
(b) with a reaction product produced by the reaction of a compound of the general formula:—



with about 1 mol equivalent of thionyl chloride in an inert anhydrous organic solvent in the presence of at least one mol equivalent of an organic base acting as an acid-acceptor at a temperature within the range -40°C to $+25^{\circ}\text{C}$; the said reaction product being reacted without prior isolation in the presence of a further mol equivalent of a base, with about 1 mol equivalent of the carboxylic acid of general formula V, or in the presence of 0—1 mol equivalent of a base, with about 1 mol equivalent of a compound of the general formula Va, Vb or Vc, at a temperature of -40°C to $+30^{\circ}\text{C}$, whereby the reactive intermediate produced is of the general formula:—

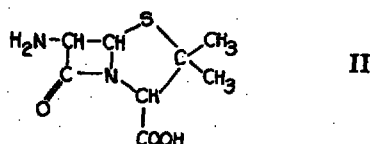


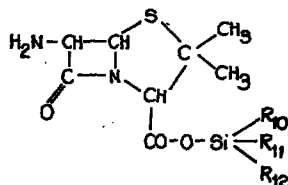
(c) [only available for carboxylic acids of general formula V] with about 1 mol equivalent of a carbodiimide in a diluent and in the presence of about 1 mol equivalent of a compound of the general formula X, whereby the reactive intermediate produced is of the general formula:—



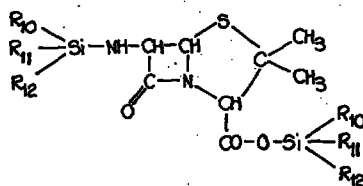
the said diluent being anhydrous and free of hydroxyl groups if a compound of the general formula III or IV is to be used in step (ii);

and (ii) reacting the reactive intermediate with 6-aminopenicillanic acid of the following general formula II or silyl- or di-silyl-6-aminopenicillanic acid of the general formula III or IV:—





III



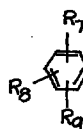
IV

in a solvent in the presence of a base when 6-aminopenicillanic acid is used, or in an anhydrous solvent free of hydroxyl groups when a compound of the general formulae III or IV is used, at a temperature in the range of -70°C to $+50^{\circ}\text{C}$, to produce the desired penicillin compound of the present invention;

[in which general formulae II to XI:

A, C*, R, and Z are as defined above;

B is a radical of the formula:—



or



[in which R_7 , R_8 , and R_9 are identical or different radicals selected from hydrogen, halogen, R—, R—O—, R—SO—, R—SO₂—, nitro, $(R_2)=N$ —, R—CO—NH, HO and R—CO—O radicals, R being as defined above];

$\text{Me}^{n(+)}$ is a cation of an n -valent alkali metal or alkaline earth metal or an aluminium cation;

R_{10} , R_{11} and R_{12} are the same or different lower alkyl radicals;

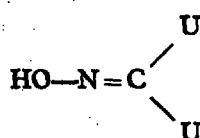
R_{13} can have any of the meanings given for R and can also be a phenyl radical;

R_{14} is a $-(\text{CH}_2)_x-$, $-(\text{CH}_2)_y-$, or $-(\text{CH}_2)_z-\text{O}-(\text{CH}_2)_2-$ radical;

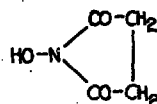
the groups U which can be the same or different are $-\text{C}\equiv\text{N}$ or $-\text{CO}-\text{O}-$ (lower alkyl) radicals; and

W is a halogen atom].

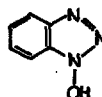
In step (i)(a), the reaction by which the reactive intermediate is produced is preferably carried out at -50°C to 0°C . Here, and for the subsequent reaction with the compounds of the general formulae II, III or IV, it can be of advantage if this reaction is allowed to take place in the presence of about one mol equivalent of an N-hydroxy compound of the formula:



X



Xa



Xb

[in which U is as defined above].

The reaction may be carried out in the presence or absence of a base.

When optical activity is present at the chirality centre C*, a possible racemisation at this position can be prevented by using no organic bases, or only weak organic bases, (i.e. organic bases having pK_a values from 4 to 14), for example N-methylmorpholine, N-ethylmorpholine, N,N-dimethylaniline, pyridine or a weak inorganic base or a buffer, in step (i)(a), (b) and step (ii).

The reactive intermediate produced in step (i) is in all cases, a carboxylic acid of general formula V modified at the carboxyl group.

The reaction in step (ii) is preferably carried out at -50°C to 0°C . It is also preferably carried out in an aqueous solvent at a pH within the range 2—9, more preferably within the range 2—3 or 6.5—8.5, when 6-aminopenicillanic acid is used.

In the production, according to the invention, of the reactive intermediate by step (i)(a), from the carboxylic acid of general formula V or its salt of general formula Va and the compound of the general formulae VI, VII, VIII or IX, anhydrous, inert solvents or mixtures of these solvents, such as tetrahydrofuran, dioxane, dichloromethane, chloroform, ether, benzene, acetone, acetonitrile, dimethylformamide or hexamethylphosphoric acid triamide are preferably used. However, water or alcohols such as isopropanol or tert.-butanol can be present if the amounts are not excessive. However, if in this reaction the starting compounds are the silyl compounds Vb and Vc, preferably only those organic solvents are used which contain neither —NH nor —OH groups, for example dichloromethane, chloroform, tetrahydrofurane, dioxane, diethyl ether, acetonitrile, benzene, acetone and dimethylformamide.

If, in the reaction in step (i)(a) according to the invention between the carboxylic acid of general formula V, the salt of general formula Va or a silyl compound of general formula Vb or Vc with the compound of the general formula VI, VII, VIII or IX, bases are added, practically all bases are suitable for this purpose provided they are sufficiently inert towards acylating agents and provided that when the silyl compounds Vb or Vc are used, they contain no O—H groups, preferably no O—H or N—H groups.

The reactants in the reaction of step (i)(a) are preferably reacted with one another in equimolecular amounts. However, it can have a considerable influence on the purity of the products or on the yield if one of the two reactants is used in a more or less large excess.

When converting the carboxylic acids of the general formula V into the reactive intermediate by any of steps (i)(a), (b) and (c) it is advisable to work at as low a temperature as possible if optical activity present at the chirality centre C* is to be protected against racemisation. Temperatures of —40°C to —70°C are preferred. For the same reasons it is advantageous if the reaction time for converting the carboxylic acids of the general formula V into the forms modified at the carboxyl group is kept as short as possible. It can be advisable to maintain conversion times of only one minute or a few minutes.

The reaction of step (i)(a) when carried out, in the presence of an N-hydroxy compound of general formula X, Xa or Xb, can be carried out in exactly the same way as explained above for step (i)(a) except that about one mol equivalent of the said N-hydroxy compound is added per mol of the compound of general formula V, Va, Vb or Vc.

When the reactive intermediate is produced by the method of step (i)(b), the starting material is an N-hydroxy compound of the general formula X which is converted, in a solvent such as acetone, tetrahydrofuran, dioxane, dichloromethane, chloroform, benzene, ethyl acetate, diethyl ether or dimethylformamide, in the presence of at least one mol equivalent of an organic base, such as triethylamine, pyridine, quinoline, N-methylmorpholine or N,N-dimethylaniline, into a reaction product of (at present) unknown constitution, by reaction with about one mol equivalent of thionyl chloride, at a temperature of —40°C to +25°C. This reaction product is reacted, without isolation, in the presence of a further mol equivalent of a base, which may be one of those just mentioned, and preferably in the same solvent, with one mol equivalent of the carboxylic acid V, or, without further addition of any base or with up to one mol equivalent of the bases, with one mol equivalent of the salt Va or the silyl compound Vb or Vc, at a temperature of —40°C to +30°C. The reactive intermediate of the general formula XI can then, optionally after removal of the hydrochloride of the base which has been produced during the reaction and has separated out, be isolated by evaporation of the solvent. It may also if desired be purified by crystallisation from an inert solvent, or, if not crystalline, by brief washing with a solution, for example in ether or benzene, with an aqueous sodium bicarbonate solution at as low a temperature as possible.

Finally, the reactive intermediate may be produced, according to step (i)(c) of the process of the invention, by reacting the carboxylic acid of the general formula V, in the presence of an N-hydroxy compound of the general formula X, with a carbodiimide. Suitable carbodiimides include for example dicyclohexylcarbodiimide, diisopropylcarbodiimide and N-ethyl-N'-3-dimethylaminopropylcarbodiimide. They are generally used in an aqueous solvent or solvent mixture, which can contain, for example, acetone, tetrahydrofuran, dioxane, acetonitrile, dimethylformamide, hexamethylphosphoric acid triamide, tert.-butanol, isopropanol or formic acid methyl ester, or in an anhydrous solvent or solvent mixture which in addition to the solvent mentioned can also contain dichloromethane, chloroform, ethyl-acetate, ether, benzene, toluene or tetrachloromethane.

In the reaction in step (II), according to the invention, of 6-aminopenicillanic acid (formula II) with the reactive intermediate, the 6-aminopenicillanic acid is preferably employed as a solution of its salt with an acid or a base. Suitable solvents for this purpose are, for example, water or a mixture of water and one or more water-miscible organic solvents, such as tetrahydrofuran, dioxane, acetonitrile, isopropanol, acetone, dimethylformamide, dimethylsulphoxide and hexamethylphosphoric acid triamide. Suitable salt-forming acids are, for example, hydrochloric acid, sulphuric acid and phosphoric acid. In order to convert the 6-aminopenicillanic acid into the salt of a base, dissolved in one of the abovementioned solvents, it is possible to use, as bases suitable for the purpose, for example, inorganic bases such as sodium carbonate, sodium hydroxide and sodium bicarbonate, the corresponding potassium and calcium compounds, calcium oxide, magnesium oxide, magnesium carbonate or buffer mixtures, and organic bases such as N-methylmorpholine, N-ethylpiperidine, N,N-dimethylaniline, pyridine and triethylamine. Chloroform or dichloromethane are particularly suitable as solvents for a solution of 6-aminopenicillanic acid in an anhydrous medium whilst, for example, triethylamine, diethylamine, N-ethylpiperidine, N-ethylmorpholine and pyridine are suitable as the base for salt formation. The salts of 6-aminopenicillanic acid need not be dissolved completely in the reaction, according to the invention, with the reactive intermediate, but can also be present partly dissolved and partly in suspension.

Preferred solvents for the reaction between the silyl compounds of 6-aminopenicillanic acid, of the general formulae III or IV, and the reactive intermediate, are those which are inert towards silanyl radicals located on nitrogen and oxygen. Of these solvents, those preferred are organic solvents which are free of —NH groups as well as hydroxyl groups, for example, tetrahydrofuran, dioxane, diethyl ether, acetonitrile, benzene, tetrachloromethane, chloroform, dichloromethane, dimethylformamide and acetone. If, in this reaction according to the invention between the silyl derivatives III or IV of 6-aminopenicillanic acid and the reactive intermediate, bases are added, these bases are preferably bases containing neither —NH nor —OH groups.

In general, the reaction of step (ii) according to the invention between the reactive intermediate and 6-aminopenicillanic acid or its silyl derivative III or IV is carried out using equimolecular amounts of the reactants. It can, however, be desirable to use one of the two reactants in excess in order to facilitate the purification or pure preparation of the desired penicillin compound and to increase the yield. Thus, for example, 6-aminopenicillanic acid or the compound of the general formula III or IV can be employed in an excess of 0.1 to 0.4 mol equivalent and better utilisation of the carboxylic acids of the general formula V, modified at the carboxyl group, can thereby be achieved. During working up of the reaction mixture and isolation of the penicillin compound, any 6-aminopenicillanic acid present can easily be removed because of its good solubility in aqueous mineral acids. On the other hand, any carboxylic acid of general formula V present is more difficult to separate from the penicillin formed.

The amount of the base added during the reaction of step (ii), according to the invention, of the reactive intermediate, with the 6-aminopenicillanic acid or the compound of the general formula III or IV is determined, for example, by the desired maintenance of a particular pH value. Where a pH measurement and adjustment is not carried out or is not possible or meaningful because of the absence of sufficient amounts of water in the diluent, up to 2.0 mol equivalents of base are generally added when a compound of the general formula III or IV is used, if a base is added at all, whilst 1.5 to 2.5 mol equivalents of base are generally added when 6-aminopenicillanic acid and an anhydrous reaction medium are used. The amount of the acid added during the reaction in step (ii) according to the invention is also determined, for example, by the desired maintenance of a particular pH or pH range. In general it is advantageous to carry out the said reaction between the reactive intermediate and 6-aminopenicillanic acid or its silyl derivative of general formula III or IV at temperatures which are as low as possible. As a result, purer products can be obtained, the yields can be improved and optical activity present at the chirality centre C* can be protected against racemisation. However, limits are here imposed by the possibilities not only of the solubility of the reactants being too low at lower temperatures, and of crystallisation of the solvent beginning. As a result of excessively lowered reaction temperatures, the reaction speed may be so greatly reduced that the yields may even be lowered. As with most chemical reactions, the temperatures used may be lower or higher than those indicated in the examples. However, if the values indicated in the examples are considerably exceeded, side-reactions are to be expected, which reduce the yield and adversely influence the purity of the products.

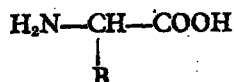
The crude products resulting from the process of the invention can be worked up

to yield the penicillin compounds of the invention in the manner conventional in penicillin chemistry.

The free penicillins of general formula I and their salts can be interconverted in any suitable manner; methods for such interconversion are known in penicillin chemistry.

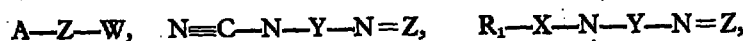
The 6-aminopenicillanic acid used as the starting material in the process of the present invention can be obtained according to known processes by splitting penicillin-G, either by fermentation or by chemical splitting (see Netherlands Patent No. 67/13,809 and German Offenlegungsschrift No. 2,062,925).

The carboxylic acids of the general formula V can be obtained from the amino acids of the general formula:

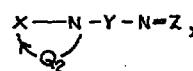
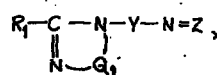


XII

by reaction with compounds of the general formulae XIII, XIV, XV, XVI or XVII:—



XIII



XVI

XVII

[in which A, B, Q₁, Q₂, R₁, R₂, X, Y, Z, C* and W are as defined above].

The production of the compounds of the general formulae XIII, XIV, XV, XVI and XVII is in each case described in the individual Examples which follow.

The production of the compounds of the general formulae VI, VII and IX is described in the literature (see J. med. Chem. 9 (1966) page 980; Ber. 96 (1963) page 2681; Tetrahedron 17 (1962) page 114).

A compound of the general formula VIII was obtained from N,N-dimethylethylenediamine by conversion into the N,N'-bis-trimethylsilyl compound, reaction of the latter with phosgene to give the corresponding cyclic urea, and reacting the cyclic urea with phosgene.

Our copending Application No. 48699/72 (Serial No. 1 392 849) claims another process for the production of penicillin compounds of the general formula I, in which the symbols are as defined above with reference to the process according to the invention.

The penicillin compounds according to the invention can also be obtained from the carboxylic acids of the general formula V, their salts of the general formula Va or their silyl compounds Vb and Vc and 6-aminopenicillanic acid or the silylated 6-aminopenicillanic acids (see the general formulae III and IV) by the customary methods of peptide chemistry (see E. Schröder, and K. Lübke, The Peptides, Methods of Peptide Synthesis, Vol. I, page 76—128). However the process of the invention has certain advantages over these customary methods.

The chemotherapeutic activity of the penicillin compounds was tested *in vivo* and *in vitro*. The determination of the inhibitory values (MIC)* *in vitro* (see Table 1) was carried out in a liquid medium in the test tube series dilution test, the readings being taken after 24 hours incubation at 37°C. The MIC is indicated by the non-turbid test tube in the dilution series. The nutrient medium used was a full medium of the following composition:

Lab Lemco (OXOID)	10 g
Peptone (DIFCO)	10 g
NaCl	3 g
D-(+)-dextrose (MERCK)	10 g
Buffer pH 7.4	1,000 ml

(The word DIFCO is a Registered Trade Mark)

* Minimum inhibitory concentration

Table 1 gives the minimum inhibitory concentrations (MIC values) in units/ml of some penicillins of the present invention against a number of bacterial species. From the table there can also be seen the superiority of many of the penicillins according to the invention as compared with the commercial penicillin ampicillin in their effectiveness against many Gram-negative bacteria. The numbers here assigned to the penicillins correspond with the numbers of the examples in which the manufacture of the respective penicillin is described.

TABLE 1

Peni- cillin- in	BACTERIA TYPE												
	No.	Escherichia coli			Proteus		Pseudomonas aeruginosa		Klebsiella		Staphylococcus aureus		Strept. faec. ATCC
		14	A 261	C 165	183/58	vulg. 1017	morg. 932	F 41	Walter	K 10	63	1756E	
1	0.8	200	3.1	1.6	3.1	-	50	50	6.2	12.5	400	0.8	25
2	1	256	4	4	8	8	128	64	32	128	64	1	64
3	1	256	4	4	4	16	64	64	16	256	128	1	32
4	1.6	200	12.5	6.2	12.5	-	200	200	50	100	200	0.8	100
5	256	>256	>256	256	256	32	>256	>256	>256	>256	>256	4	256
6	8	>512	32	16	32	64	256	128	128	256	128	2	128
7	4	512	16	8	32	16	128	64	32	128	64	1	64
8	2	512	8	8	16	32	128	64	32	128	~64	1	64
9	2	512	8	8	8	8	64	64	32	128	64	2	64
10	128	>512	512	256	256	256	>512	>512	>512	>512	512	16	>512
11	1	512	4	2	4	16	64	64	16	16	128	2	64
13	4	>256	8	4	16	128	128	128	32	64	256	4	128
18	1	>256	8	16	4	<1	256	256	32	32	64	1	32
19	4	>256	8	16	32	4	64	64	32	4	128	1	32
20	4	>256	8	8	8	32	64	32	32	32	64	1	16
Ampi- cillin in	0.8	>400	6	200	400	-	-	200	100-200	100-200	-	1	12.5

The spectrum of activity of the penicillin compounds of the invention encompasses both Gram-negative and Gram-positive bacteria. The particular advantage of the penicillins according to the invention is that both *in vitro* and in animal experiments they are active against ampicillin- and carbenicillin-resistant bacteria of the group *Klebsiella-Aerobacter*, against ampicillin- and carbenicillin-resistant indole-positive *Proteus* and *Providencia* bacteria, ampicillin- and carbenicillin-resistant *Escherichia coli* strains, and against carbenicillin-resistant *Pseudomonas aeruginosa* and *Serratia marcescens* bacteria.

The generally excellent action is achieved both on single and on repeated administration. The penicillins according to the invention are stable to stomach acid. Some of the penicillins show excellent toleration, which is particularly made clear by the extremely high dosage which is tolerated, without complications, in the case of mice when administered intravenously into the vein of the tail.

As stated above, the invention also relates to the use in human and veterinary medicine of the penicillin compounds of the invention.

The present invention provides a pharmaceutical composition containing as active ingredient a compound of the invention in admixture with a solid or liquefied gaseous diluent, or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 (preferably less than 350) except in the presence of a surface active agent.

The invention further provides a pharmaceutical composition containing as active ingredient a compound of the invention in the form of a sterile or isotonic aqueous solution.

The invention also provides a medicament in dosage unit form comprising a compound of the invention either alone or in admixture with a diluent.

The invention also provides a medicament in the form of tablets (including lozenges and granules), dragees, capsules, pills, ampoules or suppositories comprising a compound of the invention either alone or in admixture with the diluent.

"Medicament" as used in this Specification means physically discrete coherent portions suitable for medical administration. "Medicament in dosage unit form" as used in this Specification means physically discrete coherent portions suitable for medical administration each containing a daily dose or a multiple (up to four times) or sub-multiple (down to a fortieth) of a daily dose of the compound of the invention. Whether the medicament contains a daily dose or, for example, a half, a third, or a quarter of a daily dose will depend on whether the medicament is to be administered once or, for example, twice, three times or four times a day respectively.

The pharmaceutical compositions according to the invention may, for example, take the form of ointments, gels, pastes, creams, sprays (including aerosols), lotions, suspensions, solutions and emulsions of the active ingredient in aqueous or non-aqueous diluents, syrups, granules or powders.

The diluents to be used in pharmaceutical compositions (e.g. granulates) adapted to be formed into tablets, dragees, capsules and pills include the following:

(a) fillers and extenders, e.g. starch, sugars, mannitol, and silicic acid; (b) binding agents, e.g. carboxymethyl cellulose and other cellulose derivatives, alginates, gelating and polyvinyl pyrrolidone; (c) moisturizing agents, e.g. glycerol; (d) disintegrating agents, e.g. agar-agar, calcium carbonate and sodium bicarbonate; (e) agents for retarding dissolution e.g. paraffin; (f) resorption accelerators, e.g. quaternary ammonium compounds; (g) surface active agents, e.g. cetyl alcohol, glycerol monostearate; (h) adsorptive carriers, e.g. alumina, kaolin and bentonite; (i) lubricants, e.g. talc, calcium and magnesium stearate and solid polyethylene glycols.

The tablets, dragees, capsules and pills formed from the pharmaceutical compositions of the invention can have the customary coatings, envelopes and protective matrices, which may contain opacifiers. They can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes and protective matrices may be made, for example, of polymeric substances or waxes.

The ingredient can also be made up in microencapsulated form together with one or several of the above-mentioned diluents.

The diluents to be used in pharmaceutical compositions adapted to be formed into suppositories can, for example, be the usual water-soluble or water-insoluble diluents, such as polyethylene glycols and fats (e.g. cocoa oil and high esters [e.g. C₁₄-alcohol with C₁₆-fatty acid]) or mixtures of these diluents.

The pharmaceutical compositions which are ointments, pastes, creams and gels can, for example, contain the usual diluents, e.g. animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silic acid, talc and zinc oxide or mixtures of these substances.

The pharmaceutical compositions which are powders and sprays can, for example,

contain the usual diluents, e.g. lactose, talc, silicic acid, aluminium hydroxide, calcium silicate, and polyamide powder or mixtures of these substances. Aerosol sprays can, for example, contain the usual propellants, e.g. chlorofluorohydrocarbons.

The pharmaceutical composition which are solutions and emulsions can, for example, contain the customary diluents (with, of course, the above-mentioned exclusion of solvents having a molecular weight below 200 except in the presence of a surface-active agent), such as solvents, dissolving agents and emulsifiers; specific examples of such diluents are water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils [for example groundnut oil], glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitol or mixtures thereof.

For parenteral administration, the solutions and emulsions should be sterile, and, if appropriate, blood-isotonic.

The pharmaceutical compositions which are suspensions can contain the usual diluents, such as liquid diluents, e.g. water, ethyl alcohol, propylene glycol, surface-active agents (e.g. ethoxylated isostearyl alcohols, polyoxyethylene sorbite and sorbitan esters), microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth or mixture thereof.

All the pharmaceutical compositions according to the invention can also contain colouring agents and preservatives as well as perfumes and flavouring additions (e.g. peppermint oil and eucalyptus oil) and sweetening agents (e.g. saccharin).

The pharmaceutical compositions according to the invention preferably contain 0.1 to 99.5, more preferably from 0.5 to 95% of the active ingredient by weight of the total composition.

In addition to a compound of the invention, the pharmaceutical compositions and medicaments according to the invention can also contain other pharmaceutically active compounds. They may also contain a plurality of compounds of the invention.

Any diluent in the medicaments of the present invention may be any of those mentioned above in relation to the pharmaceutical compositions of the present invention. Such medicaments may include solvents of molecular weight less than 200 as sole diluent.

The discrete coherent portions constituting the medicament according to the invention (whether in dosage unit form or not) may be, for example, any of the following: tablets, (including lozenges and granules), pills, dragees, capsules, suppositories and ampoules. Some of these forms may be made up for delayed release of the active ingredient. Some, such as capsules, include a protective envelope which renders the portions of the medicament physically discrete and coherent.

The preferred daily dose for administration to human beings of the medicaments of the invention is 1.25×10^6 to 9×10^7 Units of active ingredient. One mole of a penicillin contains 5.9514×10 Units.

The production of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical composition (e.g. a granulate) and then forming the composition into the medicament (e.g. tablets).

This invention further provides a method of combating (including prevention, relief and cure of) the above-mentioned diseases in non-human animals, which comprises administering to the animals a compound of the invention alone or in admixture with a diluent or in the form of a medicament according to the invention.

It is envisaged that these active penicillin compounds will be administered perorally, parenterally (for example intramuscularly, subcutaneously or intravenously, possibly as a continuous drip infusion) or locally.

Finally, the compounds according to the invention may be administered to animals, for prophylactic or curative purposes mixed with the animals' feed. Accordingly this invention also provides an animal feedstuff comprising a nutritious material and a compound of the invention.

In general it has proved advantageous to administer amounts of from 25,000 to 10^6 Units/kg of body weight per day to achieve effective results. Nevertheless, it can at times be necessary to deviate from those dosage rates, and in particular to do so as a function of the nature and body weight of the human or animal subject to be treated, the individual reaction of this subject to the treatment, the type of formulation in which the active ingredient is administered and the mode in which the administration is carried out, and the point in the progress of the disease or interval at which it is to be administered. Thus it may in some case suffice to use less than the above-mentioned minimum dosage rate, whilst other cases the upper limit mentioned must be exceeded to achieve

the desired results. Where larger amounts are administered it can be advisable to divide these into several individual administrations over the course of the day.

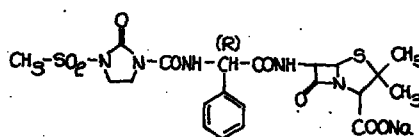
The Examples which follow illustrate the invention without limiting it.

The β -lactam content of the penicillins was determined iodometrically. All the 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 τ -scale; they agree with the particular structure. In calculating the analytical data, the water content of the penicillins was taken into account.

Experimental section

Example 1.

A) Sodium D- α -[(3-methylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin:



6.8 parts by weight of D- α -[(3-methylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-phenylacetic acid were dissolved in 40 parts by volume of methylene chloride with the addition of a little tetrahydrofuran, the solution was cooled to -40°C and 2.0 parts by weight of N-methylmorpholine were added with vigorous stirring. Thereafter, a solution of 3.75 parts by weight of tetramethylchloroformamidinium chloride in 15 parts by volume of methylene chloride, also cooled to -40°C , was added all at once with vigorous stirring and the mixture was stirred for 5 minutes at -40°C and then combined with a solution, cooled to 0°C and kept at pH 2.5, of 4.7 parts by weight of 6-aminopenicillanic acid in 30 parts by volume of 80% (volume/volume) aqueous tetrahydrofuran. The pH value of the mixture was maintained at 2.5 by addition of further N-methylmorpholine. The mixture was stirred for 30 minutes without cooling, whilst the pH was maintained at 2.5. Thereafter, 40 parts by volume of water were added, the pH value was then adjusted to 7, methylene chloride and tetrahydrofuran were stripped off on a rotary evaporator, the solution was extracted once with 50 parts by volume of ethyl acetate and the aqueous phase was covered with fresh ethyl acetate. The mixture was acidified with dilute hydrochloric acid to pH=1.5 under stirring and cooling with ice, the ethyl acetate was separated off, the aqueous phase was extracted twice more with ethyl acetate and the combined organic phases were washed with water and dried over MgSO_4 . Thereafter they were filtered, 20 parts by volume of a molar solution of sodium 2-ethylhexanoate in ether containing methanol were added, the mixture was evaporated practically to dryness *in vacuo*, the residue was dissolved in the minimum possible amount of methanol and the sodium salt of the penicillin was precipitated by adding a 10-fold amount of absolute ether with shaking. It was filtered off, thoroughly washed with absolute ether and dried over P_2O_5 in a vacuum dessicator.

Yield: 84%

β -Lactam content: 74%

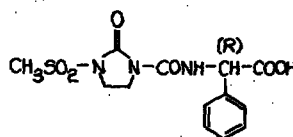
Calculated: C 43.4 H 4.8 N 11.3 S 10.4 %

Found: C 43.4 H 5.4 N 11.3 S 10.3 %

IR-bands at 3325, 3055, 3025, 3002, 2965, 2924, 2865, 1771, 1738, 1679, 1610, 1529, 1398 and 1171 cm^{-1} .

NMR-signals at τ =2.3—2.8 (5H), 4.4 (1H), 4.5 (2H), 5.8 (1H) 6.15 (4H), 8.4 (3H) and 8.5 ppm (3H).

B1) D- α -[(3-methylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-phenylacetic acid:



23

14

1,392,850

14

16.6 parts by weight of (D-)-C-phenylglycine were dissolved in 150 parts by volume of 50% (volume/volume) aqueous dioxane with addition of a sufficient amount of 2N sodium hydroxide solution. The pH of the solution was now reduced to 7.5 by adding 2 N hydrochloric acid, whereupon the aminoacid partially separated out again in a finely divided form. 1-Chlorocarbonyl-3-methylsulphonyl-imidazolid-2-one was now added in portions under cooling with ice and the pH of 7.5 was maintained by simultaneously adding 2 N sodium hydroxide solution. The mixture was further stirred, without cooling until the pH-value remained constant at 7.5 even without addition of sodium hydroxide solution (about 10 minutes). Thereafter, 50 parts by volume of water were added, the mixture was evaporated on a rotary evaporator to half the original volume and the residue was extracted once with 50 parts by volume of ethyl acetate, after unreacted C-phenylglycine had been filtered off. Thereafter the mixture was acidified to pH=2 and repeatedly extracted with ethyl acetate. The combined ethyl acetate phases were washed with water, dried over $MgSO_4$, filtered, evaporated to dryness and recrystallised from acetone/nitromethane. Melting point = 250°C.

Melting point = 250°C.

Yield: 56%.

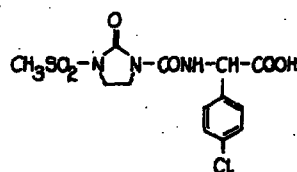
Calculated: C 45.7 H 4.4 N 12.3 S 9.4 %

Found: C 45.7 H 4.5 N 12.3 S 9.2 %

IR-bands at 3345, 3600, 2300, 1731, 1652, 1538, 1210 and 1168 cm^{-1} (in Nujol).

NMR-signals at τ = 1.2 (1H), 2.55 (5H), 4.6 (1H), 6.2 (4H) and 6.6 ppm (3H).

2) D, L - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chloro - phenylacetic acid:



This carboxylic acid was produced as described in Example 1B 1 from 5.8 parts by weight of 4-chloro-C-phenylglycine and 6.8 parts by weight of 1-chlorocarbonyl-3-methylsulphonyl-imidazolid-2-one.

6.8 parts by weight of 1-chlorocarbonyl-3-methylsulphonyl-imidazolid-2-one.

Melting point $\times$ 190°C.

Yield: 88%

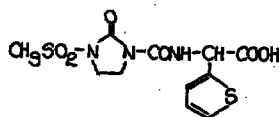
Calculated: C 41.6 H 3.7 Cl 9.4 N 11.2 S 8.5 %

Found: C 40.8 H 3.7 Cl 9.2 N 11.1 S 8.9 %

IR-bands at 3700—2200, 3310, 1730, 1654, 1540 and 1168 cm^{-1} (in Nujol).

NMR-signals at τ = 1.1 (1H), 2.55 (4H), 4.5 (1H), 6.1 (4H) and 6.65 ppm (3H).

3) D,L - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl - (2) - acetic acid:



This carboxylic acid was produced as described in Example 1 B.1 from 5.5 parts by weight of α -thienyl-(2)-glycine and 6.8 parts by weight of 1-chloro-carbonyl-3-methylsulphonyl-imidazolid-2-one.

Yield: 88%

Melting point approx: 110°C, crude product

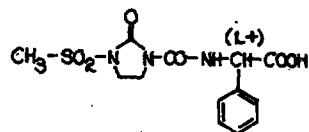
Calculated: C 38.0 H 3.8 N 12.1 S 18.4 %

Found: C 38.2 H 4.8 N 10.8 S 17.0 %

IR-bands at 3600—2200, 3315, 1740, 1725, 1664, 1525 and 1170 cm^{-1} (in Nujol).

NMR-signals at τ = 1.2 (1H), 2.4—3.1 (3H), 4.2 (1H), 6.07 (4H) and 6.67 ppm (3H).

- 4) L - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid:



This carboxylic acid was produced as described in Example 1 B.1 from 5.3 parts by weight of (L+)-C-phenylglycine and 6.8 parts by weight of 1-chlorocarbonyl-3-methylsulphonyl-imidazolid-2-one.

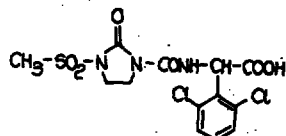
Melting point + 245°C

Calculated: C 45.7 H 4.4 N 12.3 S 9.4 %

Found: C 44.9 H 4.5 N 11.9 S 9.4 %

The IR- and NMR-spectra are identical with those of the product from Example 1, B.1.

- 5) D,L - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 2,6 - dichlorophenylacetic acid:



This carboxylic acid was produced as described in Example 1 B.1 from 7.7 parts by weight of 2,6-dichloro-C-phenylglycine and 6.8 parts by weight of 1-chlorocarbonyl-3-methylsulphonyl-imidazolid-2-one.

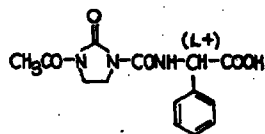
Melting point > 260°C

Yield: 69%

IR-bands at 3400—2200, 3290, 1742, 1714, 1646, 1580, 1522, 1260, 1170, 1130, 783 and 763 cm⁻¹ (in Nujol).

NMR-signals at τ = 0.9 (1H), 2.4—2.65 (3H), 3.4 (1H), 5.8—6.2 (4H) and 6.65 ppm (3H).

- 6) L - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid:



This carboxylic acid was produced as described in Example 1, B.1 from 5.0 parts by weight of (L+)-C-phenylglycine and 5.7 parts by weight of 1-chlorocarbonyl-3-acetyl-imidazolid-2-one.

Melting point = 214°C

Yield: 69%

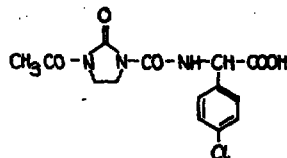
Calculated: C 55.0 H 4.9 N 13.8 %

Found: C (53.5) H 5.2 N 13.7 %

IR-bands at 3650—2250, 3300, 1735, 1665 and 1252 cm⁻¹ (in Nujol).

NMR-signals at τ = 1.0 (1H), 2.3—2.8 (5H), 4.5 (1H), 6.2 (4H) and 7.6 ppm (3H).

- 7) D,L - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4-chloro - phenylacetic acid:



This carboxylic acid was produced as described in Example 1 B.1 from 6.2 parts by weight of D,L-4-chloro-C-phenylglycine and 5.7 parts by weight of 1-chlorocarbonyl-3-acetyl-imidazolid-2-one.

Melting point 194°C

Yield: 53%

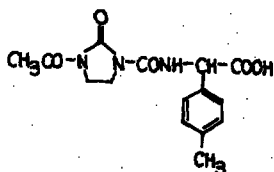
Calculated: C 49.5 H 4.1 Cl 10.4 N 12.4 %

Found: C 49.6 H 4.6 Cl 9.4 N 12.2 %

IR-bands at 3700—2300, 3290, 1725, 1685, 1648 and 1252 cm⁻¹ (in Nujol).

NMR signals at τ =0.9 (1H), 2.55 (4H), 4.45 (1H), 6.2 (4H) and 7.55 ppm (3H).

8) D,L - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4-methylphenylacetic acid:



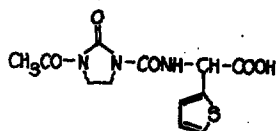
This carboxylic acid was produced as described in Example 1 B.1 from 5.4 parts by weight of 4-methyl-C-phenylglycine and 5.7 parts by weight of 1-chlorocarbonyl-3-acetyl-imidazolid-2-one.

Yield: 42%

IR-bands at 3600—2200, 3310, 1738, 1712, 1678, 1666 and 1256 cm⁻¹ (in Nujol).

NMR-signals at τ =1.0 (1H), 2.6 (2H), 2.8 (2H), 4.5 (1H), 6.2 (4H), 7.6 (3H) and 7.7 ppm (3H) (in acetone-d₆).

9) D,L - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α -thienyl - (2) - acetic acid:



This carboxylic acid was produced as described in Example 1 B.1 from 8.6 parts by weight of thienyl-(2)-acetic acid and 9.5 parts by weight of 1-chlorocarbonyl-3-acetyl-imidazolid-2-one.

Melting point 197°C

Yield: 62%

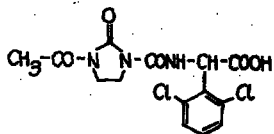
Calculated: C 46.3 H 4.2 N 13.5 S 10.3 %

Found: C 47.1 H 4.4 N 13.8 S 9.7 %

IR-bands at 3280, 3080, 3450—2300, 1728, 1680, 1652, 1522, 1260 and 705 cm⁻¹ (in Nujol).

NMR-signals at τ =1.1 (1H), 2.5—3.2 (3H), 4.2 (1H), 6.2 (4H) and 7.6 ppm (3H).

10) D,L - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 2,6-dichloro - phenylacetic acid:



This carboxylic acid was produced as described in Example 1 B.1 from 6.7 parts by weight of 2,6-dichloro-C-phenylglycine and 5.3 parts by weight of 1-chlorocarbonyl-3-acetyl-imidazolid-2-one.

Melting point: = 250°C

Yield: 74%

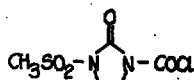
Calculated: C 44.9 H 3.5 Cl 19.0 N 11.2 %

Found: C 45.2 H 3.7 Cl 18.5 N 11.4 %

IR-bands at 3600—2200, 3302, 1735, 1682, 1625, 1520 and 1255 cm⁻¹ (in Nujol).

NMR-signals at τ = 0.7 (1H), 2.3—2.7 (3H), 3.4 (1H), 6.2 (4H) and 7.6 ppm (3H).

C) 1-Chlorocarbonyl-3-methylsulphonyl-imidazolidone-(2):



16.4 parts by weight of 1-methylsulphonyl-imidazolidone-(2) in dioxane were boiled for 3 days with 27 parts by weight of trimethylchlorosilane and 20 parts by weight of triethylamine. The triethylamine hydrochloride which had precipitated was filtered off, 11 parts by weight of phosgene were added and the mixture was left to stand overnight at room temperature. Thereafter it was evaporated to dryness and the product was recrystallised from boiling acetone.

Yield 70%.

Melting point = 178°C

Calculated: C 26.5 H 3.1 Cl 15.7 N 12.4 S 14.1 %

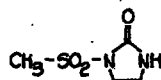
Found: C 27.2 H 3.4 Cl 15.3 N 12.0 S 14.1 %

NMR-signals at τ = 5.6—6.2 (4H), and 6.6 ppm (3H).

IR-bands at 3010, 1807, 1721, 1360, 1165, 984 and 742 cm⁻¹.

The same product can also be advantageously produced from 1-methylsulphonyl-imidazolid-2-one and excess phosgene in methylene chloride in the presence of pyridine.

D) N-methylsulphonyl-imidazolid-2-one:



Instructions 1.

63 parts by weight of methanesulphochloride were added dropwise at room temperature to a suspension of 43 parts by weight of imidazolid-2-one in 400 parts by volume of dry tetrahydrofuran and the mixture was stirred for 1 hour at 30—40°C and then heated for 1 hour under reflux. Thereafter the solvent was distilled off *in vacuo* and the residue was kept for 1 hour at 60°C, under an oil pump. The residue was recrystallised from warm acetone.

Yield: 25%

Melting point = 193°C.

Calculated: C 29.3 H 4.9 N 17.1 S 19.5 %

Found: C 29.0 H 5.0 N 17.2 S 19.6 %

IR-bands at 3250, 3115, 1715, 1350 and 1160 cm⁻¹

NMR-signals at τ = 2.4 (1H), 6.2 (2H), 6.5 (2H), and 6.8 ppm (3H).

Instructions 2.

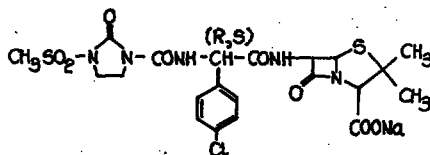
80 parts by weight of methanesulphochloride, followed by 56 parts by weight of triethylamine, were added dropwise over the course of 30 minutes to a suspension of 43 parts by weight of imidazolid-2-one in 300 parts by volume of dry tetrahydrofuran, in such a way that the internal temperature was 35—40°C. The mixture was stirred for a further 2 hours at 45°C, the solvent was then stripped off *in vacuo*, the residue which remained was twice extracted with 150 parts by volume of chloroform at a time and the crystals which remained were recrystallised from methanol.

Yield: 49%.

According to the melting point and IR-spectrum the product agrees with the N-methylsulphonyl-imidazolid-2-one described above.

Example 2.

Sodium D,L - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chloro - benzylpenicillin:



This penicillin was produced as described in Example 1 A from 7.5 parts by weight of D,L - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chlorophenyl acetic acid, 3.75 parts by weight of tetramethylchloroformamidine chloride and 4.7 parts by weight of 6-aminopenicillanic acid. Instead of N-methylmorpholine, 2.02 parts by weight of triethylamine were used.

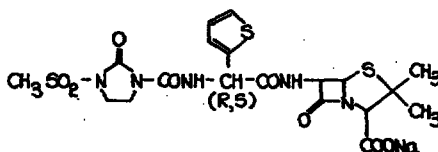
Yield: 65%

β -Lactam content: 62%

According to the NMR-spectrum, the product still contained 24% of methylsulphonylimidazolidonyl-carbonylaminochlorophenyl-acetic acid which was, however, removable by fractional acidification of the aqueous solution of the penicillin sodium salt. IR-bands at 3310, 1760, 1722, 1670, 1605 and 1170 cm^{-1} (in Nujol). NMR-signals at τ = 2.53 (2H), 2.67 (2H), 4.4 (1H), 4.5 (2H), 5.8 (H), 6.1 (4H), 6.65 (3H) and 8.3—8.5 ppm (6H), (in methanol d_4).

Example 3.

Sodium D,L - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl - (2) - methylpenicillin:



This penicillin was produced as described in Example 1 A from 7.0 parts by weight of D,L - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl - (2) - acetic acid, 3.75 parts by weight of tetramethylchloroformamidine chloride and 4.8 parts by weight of 6-aminopenicillanic acid.

Yield: 38%

β -Lactam content: 68%

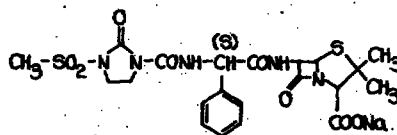
IR-bands at 3310, 1758, 1722, 1650, 1605 and 1170 cm^{-1} .

NMR-signals at τ = 2.5—3.1 (3H), 4.1—4.6 (3H), 5.8 (1H), 6.1 (4H), 6.7 (3H) and 8.25—8.5 ppm (6H).

The crude product still contained about 30% of sodium D,L- α - [(3-methylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]- α -thienyl-(2)-acetate, which was, however, removable by fractional acidification of the aqueous solution.

Example 4.

Sodium L - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:



This penicillin was produced as described in Example 1 A from 6.8 parts by weight of L - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid, 3.75 parts by weight of tetramethylchloroformamidine chloride and 4.7 parts by weight of 6-aminopenicillanic acid.

Yield: 72%

β -Lactam content: 66%

Calculated: C 44.1 H 4.7 N 11.5 S 10.6 %

Found: C 43.5 H 5.5 N 11.5 S 10.1 %

In calculating the analytical values, a water content of 3% and a sodium 2-ethylhexanoate content of 2% were taken into account.

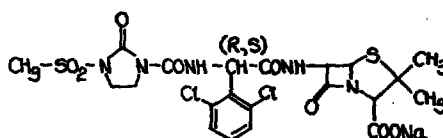
IR-bands at 3310, 1760, 1722, 1665, 1602 and 1168 cm^{-1}

NMR-signals at τ =2.6 (5H), 4.35—4.8 (3H), 5.8 (1H), 6.2 (4H), 6.7 (3H) and 8.4 ppm (6H).

10

Example 5.

Sodium D,L - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 2,6 - dichloro - benzylpenicillin:



15

This penicillin was produced as described in Example 1 A from 7.0 parts by weight of D,L - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 2,6 - dichlorophenyl acetic acid, 3.2 parts by weight of tetramethylchloroformamidinium chloride and 4.3 parts by weight of 6-amino-penicillanic acid.

20

However, the reaction of the substituted phenylacetic acid with the tetramethylchloroformamidinium chloride was not carried out at -40°C , as in Example 1 A, but at -20°C .

Yield: 77%

β -Lactam content: 61.5%

Calculated: C 38.5 H 4.0 Cl 12.2 N 10.0 S 8.7 %

Found: C 36.0 H 4.0 Cl 12.6 N 10.5 S 9.3 %

IR-bands at 3310, 1764, 1720, 1678, 1607, 1512, 1255 and 1167 cm^{-1} (in Nujol)

NMR-signals at τ =2.5—2.9 (3H), 3.8 (1H), 4.45 (2H), 5.8 (1H), 6.15 (4H), 6.7 (3H) and 8.3—8.6 ppm (6H).

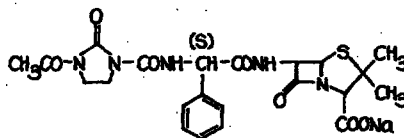
In calculating the analytical values, a content of 62% of penicillin, 30% of sodium α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 2,6 - dichloro - phenylacetate, 4.0% of sodium 2-ethylhexanoate and 3.6% of water was used as the basis. These contents follow from the NMR-spectrum of the crude product. The penicillin can be obtained in the pure form by fractional acidification of the aqueous solution of the crude product.

30

35

Example 6.

A) Sodium L - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:



40

This penicillin was produced as described in Example 1 A from 5.0 parts by weight of L - α - (3-acetyl-1-imidazolidin-2-on-1-yl)-carbonylamino]-phenylacetic acid, 3.1 parts by weight of tetramethylchloroformamidinium chloride and 4.3 parts by weight of 6-aminopenicillanic acid.

Yield: 74%

β -Lactam content: 75%

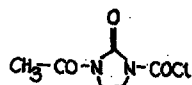
IR-bands at 3305, 1765, 1730, 1675, 1605, 1520 and 1258 cm^{-1} (in Nujol).

NMR-signals at τ =2.4—2.8 (5H), 4.5—4.8 (3H), 5.8 (1H), 6.22 (4), 7.5 (3H) and 8.4 ppm (6H).

45

45

B) 3-Acetyl-imidazolidin-2-on-1-carboxyl chloride:



20 parts by weight of N-acetyl-imidazolidone-2 mixed with 25 parts by weight of triethylamine and 150 parts by volume of dry benzene were initially taken and 27 parts by weight of trimethylchlorosilane in 40 parts by volume of benzene were added dropwise over the course of 30 minutes at room temperature, with stirring. Thereafter, the mixture was boiled for 18 hours under reflux with exclusion of moisture, and after cooling the triethylamine hydrochloride which had precipitated (22 parts by weight = 100%) was filtered off and carefully eluted with dry benzene. The benzene solution thus obtained was treated, at 5°C, with a solution of 17 parts by weight of phosgene in 50 parts by volume of benzene and left to stand overnight at 5°C. Thereafter the solvent was stripped of *in vacuo* and the residue was dried under an oil pump. It was recrystallised from an acetone/pentane mixture.

Yield: 81%

Melting point = 104°C

Calculated: C 37.7 H 3.7 Cl 18.6 N 14.7 %

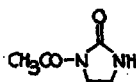
Found: C 39.3 H 4.3 Cl 17.7 N 14.7 %

IR-bands at 1798, 1740, 1690, and 1660 cm⁻¹.

NMR-signals at τ = 5.65—6.3 (4H) and 7.45 ppm (3H)

According to the NMR-spectrum, the product still contained 5—10% of N-acetyl-imidazolone, which however does not interfere in the reaction with C-phenylglycine and other amino-acids (as in Example 1, B6).

C) N-acetyl-imidazolid-2-one:



23.6 parts by weight of acetyl chloride in 100 parts by volume of tetrahydrofuran were added dropwise over the course of 60 minutes, at 0°C, to a suspension of 25.8 parts by weight of imidazolone-2 in 350 parts by volume of dry tetrahydrofuran. The mixture was stirred for 3 hours at room temperature and dry air was subsequently blown through the solution for some time; the solvent was then removed *in vacuo* and the residue was recrystallised from boiling nitromethane.

Yield: 52%

Melting point 188°C.

Calculated: C 46.9 H 6.9 N 21.9 %

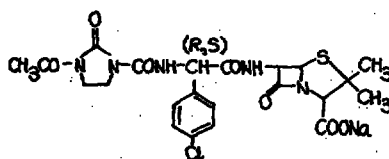
Found: C 47.0 H 6.2 N 22.5 %

IR-bands at 3230, 1730 and 1640 cm⁻¹.

NMR-signals at τ = 6.2 (2H), 6.5 (2H), and 7.6 ppm (3H)

Example 7.

Sodium D,L - α - [(3 - acetyl-imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4-chlorobenzylpenicillin:



This penicillin was produced as described in Example 1 A from 4.0 parts by weight of D,L- α - [(3-acetyl-imidazolidin-2-on-1-yl)-carbonylamino]-4-chlorophenyl-acetic acid, 2.2 parts by weight of tetramethylchloroformamidinium chloride and 3.25 parts by weight of 6-aminopenicillanic acid.

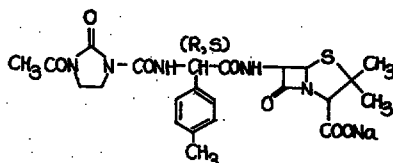
Yield: 76%
 β -Lactam content: 89%
 IR-bands at 3310, 1760, 1730, 1670, 1600, 1518 and 1259 cm^{-1} (in Nujol)
 NMR-signals at $\tau=2.4-2.9$ (4H), 4.4 (1H), 4.5 (2H), 5.8 (1H), 6.2 (4H), 7.5 (3H), and 8.3-8.5 ppm (6H)

5

5

Example 8.

Sodium D,L - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4-methyl - benzylpenicillin:



10

This penicillin was produced as described in Example 1 A from 3.2 parts by weight of D,L - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4-methylphenylacetic acid, 1.9 parts by weight of tetramethylchloroformamidinium chloride and 2.6 parts by weight of 6-aminopenicillanic acid.

10

Yield: 45%
 β -Lactam content: 83%
 IR-bands at 3305, 1760, 1725, 1672, 1600, 1515 and 1255 cm^{-1} (in Nujol)
 NMR-signals at $\tau=2.6-2.8$ (4H), 4.4-4.8 (2H), 5.8 (1H), 6.2 (4H), 7.5 (3H), 7.7 (3H) and 8.3-8.6 ppm (6H)

15

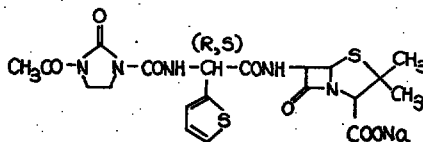
15

Example 9.

Sodium D,L - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α -thienyl - (2) - methylpenicillin:

20

20



25

This penicillin was produced as described in Example 1 A from 8 parts by weight of D,L - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - thienyl-(2) - acetic acid, 4.9 parts by weight of tetramethylchloroformamidinium chloride and 6.5 parts by weight of 6-aminopenicillanic acid.

25

Yield: 88%
 β -Lactam content: 87%
 IR-bands at 3302, 1760, 1732, 1678, 1605, 1520, 1315 and 1261 cm^{-1} (in Nujol)
 NMR-signals at $\tau=2.5-3.2$ (3H), 4.0-4.5 (3H), 5.8 (1H), 6.2 (4H), 7.5 (3H) and 8.2-8.6 ppm (6H)

30

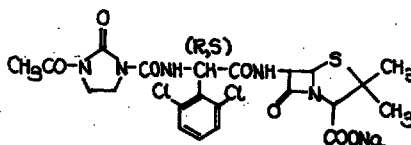
30

Example 10.

Sodium D,L - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 2,6-dichloro - benzylpenicillin:

35

35



40

40

This penicillin was produced as described in Example 1 A from 6.5 parts by weight of D,L - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 2,6 - dichlorophenylacetic acid, 3.2 parts by weight of tetramethylchloroformamidinium chloride and 4.3 parts by weight of 6-aminopenicillanic acid. The reaction of the substituted phenylacetic acid with the tetramethylchloroformamidinium chloride was carried out at -10°C .

Yield: 29%

β -Lactam content: 66%

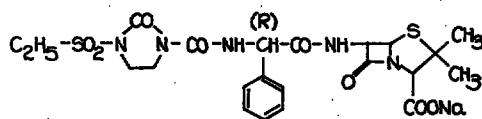
IR-bands at 3310, 1765, 1735, 1685, 1615, 1520, 1265, 1100, 1028 and 805 cm^{-1} (in Nujol)

NMR-signals at $\tau=2.7$ (3H), 3.8 (1H), 4.3—4.6 (2H), 5.8 (1H), 6.2 (4H), 7.5 (3H) and 8.2—8.6 ppm (6H).

According to the NMR-spectrum, the crude product contained 27% of sodium D,L - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 2,6 - dichlorophenylacetate, which is removable from the product by fractional acidification of the aqueous solution.

Example 11.

Sodium D - α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:



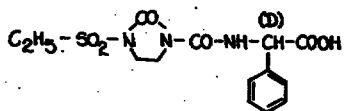
2.9 parts by weight of D- α - [(3-ethylsulphonyl-imidazolidin-2-on-1-yl) carbonylamino] - phenylacetic acid (the substance contained 1 mol of isopropanol and 1 mol of H_2O in the crystal) were dissolved in 30 parts by volume of tetrahydrofuran. The solution was then cooled to -30°C and combined with a solution, cooled to -40°C , of 1.6 parts by weight of tetramethylchloroformamidinium chloride in 30 parts by volume of dichloromethane. Thereafter the mixture was brought to -25°C , and 0.9 part by weight of N-methylmorpholine were added followed, after 3 minutes, by a mixture, cooled to -5°C , of 2.3 parts by weight of 6-aminopenicillanic acid and 25 parts by volume of 90% strength aqueous tetrahydrofuran, which was adjusted to pH 2.5 with approx. 10% strength hydrochloric acid. Thereafter the temperature was allowed to rise to 0°C and the pH of the mixture was kept at 2.5 by appropriate addition of N-methylmorpholine or dilute sodium hydroxide solution. After 1 hour, no further addition of base was necessary to maintain the pH of 2.5. The mixture was now adjusted to pH 7.0, the bulk of the tetrahydrofuran was removed *in vacuo* and the remaining aqueous phase was extracted once by shaking with ether (the ether phase being discarded), covered with an ether-ethylacetate mixture and acidified to pH 1.5. The organic phase was separated off, washed with water and dried for 1 hour over MgSO_4 at 0°C . The drying agent was then removed and the sodium salt of the penicillin was precipitated with a solution of sodium 2-ethylhexanoate in ether containing methanol.

Yield: 3.2 parts by weight

β -Lactam content: 81.9%

NMR-signals at $\tau=2.4$ —2.85 (5H), 4.4—4.8 (3H), 5.8 (1H), 6.15 (4H), 6.3—6.7 (2H) and 8.3—8.8 ppm (9H).

D - α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid:



4.5 parts by weight of 3-ethylsulphonyl-imidazolidin-2-one-1-carbonyl chloride were added at about 0°C to a solution of 5.5 parts by weight of D-bis-trimethylsilyl- α -aminophenyl-acetic acid in 40 parts by volume of tetrachloromethane. The mixture was then left to stand for 4 hours at 20°C ; the solvent was then stripped off and the residue was thoroughly worked with 1 N HCl in a mortar. The solid product was filtered off, washed with water, dried and recrystallised from isopropanol.

Yield: 6.0 parts by weight.

Melting point = 102°C . (re-solidifies, and then:) melting point = 211° (heating bench).

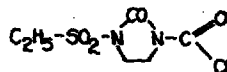
The content of 1 mol of isopropanol and 1 mol of H_2O was taken into account in the calculated analytical data.

Calculated: C 47.1 H 6.3 N 9.7 S 7.4 %
 Found: C 47.1 H 5.7 N 9.7 S 7.6 %
 NMR-signals at τ = 2.6 (5H), 4.6 (1H), 6.1 (4H), 6.3—6.7 (2H) and 8.5—8.7 ppm (3H).

5

3-Ethylsulphonyl-imidazolidin-2-one-1-carbonyl chloride:

5



This product was produced from 3-ethylsulphonyl-imidazolidin-2-one and phosgene in dichloromethane and in the presence of pyridine, at 20°C.

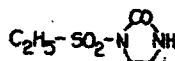
10

Melting point = 174°C.

Calculated: C 29.9 H 3.8 Cl 14.8 N 11.6 S 13.3 %
 Found: C 30.1 H 3.8 Cl 14.7 N 11.8 S 13.3 %
 NMR-signals at τ = 5.5—6.1 (4H), 6.2—6.65 (2H) and 8.4—8.75 ppm (3H).

10

1-Ethylsulphonyl-imidazolidin-2-one:



15

This substance was obtained by heating molar amounts of imidazolidin-2-one and ethylsulphonyl chloride at 150°C. to 180°C. (until the evolution of HCl had ceased). The pure substance was isolated by extraction with hot benzene, acetone and ethyl acetate from the crude product, and recrystallisation from acetone (with addition of active charcoal).

15

20

Melting point = 114°C.

Calculated: C 33.7 H 5.7 N 15.7 S 18.0 %
 Found: C 33.1 H 5.7 N 16.3 S 17.7 %
 NMR-signals at τ = 5.9—6.7 (6H) and 8.5—8.8 ppm (3H).

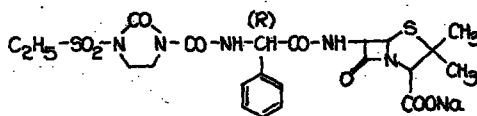
20

Example 12.

25

Sodium D - α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:

25



30

A solution of 8.6 parts by weight of D-bis-trimethylsilyl- α -aminophenylacetic acid in dichloromethane was cooled to 0°C, a solution of 7.0 parts by weight of 3-ethylsulphonyl-imidazolidin-2-one-1-carbonyl chloride in 15 parts by volume of dichloromethane was then added dropwise with further cooling, and the mixture was subsequently left to stand overnight at 0°C. A solution of 5.0 parts by weight of tetramethylchloroformamidinium chloride in 15 parts by volume of dichloromethane was then added and the mixture was left to stand for 1 hour at 0°C. This reaction mixture was then introduced dropwise into a suspension, cooled to 0°C and adjusted to pH 2.5 with dilute hydrochloric acid, of 8.2 parts by weight of 6-aminopenicillanic acid in 85 parts by volume of 80% (volume/volume) aqueous tetrahydrofuran and at the same time the pH was kept at 2.5 by appropriate addition of dilute NaOH. The mixture was then stirred for a further hour at 0°C and during stirring the pH was kept at 2.5 by further addition of dilute sodium hydroxide solution where necessary. The pH was now adjusted to 7.0, the volatile organic solvents were removed *in vacuo* and the sodium salt of the penicillin was isolated in the manner described in the preceding example.

30

35

35

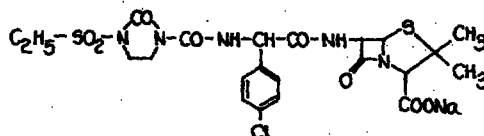
40

40

Yield: 8.0 parts by weight
 β -Lactam content: 58%.

Example 13.

Sodium α [(3-ethylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-p-chlorobenzylpenicillin:

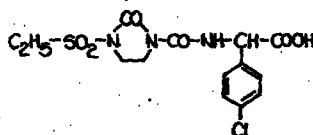


This penicillin was produced as described in Example 11 from 4.5 parts by weight of α [(3-ethylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-p-chlorophenylacetic acid, 2.3 parts by weight of tetramethylchloroformamidinium chloride, 1.3 parts by weight of N-methylmorpholine and 3.2 parts by weight of 6-aminopenicillanic acid. However, the coupling with 6-aminopenicillanic acid was effected not after 3 minutes but after 6 minutes.

Yield: 4.4 parts by weight

IR-bands at 3300, 1765, 1725, 1670, 1600, 1500—1520, 1260, 1165, 1130 cm^{-1} (Nujol).

α [(3-Ethylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-p-chlorophenylacetic acid:



Sufficient concentrated sodium hydroxide solution just to dissolve the acid was added to a suspension of 11.0 parts by weight of p-chloro- α -aminophenylacetic acid in 110 parts by volume of 50% (volume/volume) aqueous dioxane. Dilute hydrochloric acid was then added with stirring until a pH of 7.5—8.0 was reached. 13.0 parts by weight of 3-ethylsulphonyl-imidazolidin-2-one-1-carbonyl chloride were then added in portions at about 0°C and the pH of the mixture was maintained at 7.5—8.0 by means of dilute sodium hydroxide solution. Thereafter the mixture was stirred further for as long as an occasional addition of sodium hydroxide solution was still necessary to maintain the pH of 7.5—8.0. The bulk of the dioxane was then removed *in vacuo* at pH 6.5, about 200 parts by volume of water were added, the mixture was extracted once with ether at pH 9.0 (the ether extract being discarded) and covered with fresh ether, and the pH was brought to 0.5 with stirring. The organic phase was then separated off, washed, dried and completely evaporated *in vacuo*. The residue was dissolved in hot ethyl acetate; thereafter the same amount of benzene and petroleum ether was added until there is turbidity which (only just) disappears again, and the mixture was left to crystallise.

Yield: 4.9 parts by weight.

Melting point = 168°C

NMR-signals at τ = 2.6 (4H), 4.6 (1H), 6.1 (4H), 6.3—6.7 (2H) and 8.4—8.8 ppm (3H).

IR-bands at 3300, 1720, 1650, 1540, 1350 and 1160 cm^{-1} (Nujol).

Example 14.

If, in the manner described in Example 1A, 0.02 mol of:

D - α - [(3-methylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-4-chlorophenylacetic acid,

D - α - [(3-methylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-4-methylphenylacetic acid,

D - α - [(3-methylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-4-nitrophenylacetic acid,

D - α - [(3-methylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-4-hydroxyphenylacetic acid,

D - α - [(3-methylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-thienyl-(2)-acetic acid,

25	D,L - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methylsulphonyl - phenylacetic acid,	
	D - α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chlorophenylacetic acid,	5
5	D - α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methyl-phenylacetic acid,	
	D - α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - nitrophenylacetic acid,	10
10	D - α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl - (2) - acetic acid,	
	D - α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methylsulphonyl - phenylacetic acid,	15
15	D - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chloro-phenylacetic acid,	
	D - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methyl-phenylacetic acid,	20
20	D - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - hydroxy-phenylacetic acid,	
	D - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - thienyl-(2) - acetic acid,	25
25	D,L - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methylsulphonyl - phenylacetic acid,	
	D - α - [(3 - formyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chloro-phenylacetic acid,	30
30	D - α - [(3 - formyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methyl-phenylacetic acid,	
	D - α - [(3 - formyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - nitro-phenylacetic acid,	35
35	D - α - [(3 - formyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl-(2) - acetic acid,	
	D,L - α - [(3 - formyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methylsulphonyl - phenylacetic acid,	40
40	D - α - [(3 - furoyl - (2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chlorophenylacetic acid,	
	D - α - [(3 - furoyl - (2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methylphenylacetic acid,	45
45	D - α - [(3 - furoyl - (2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - nitro-phenylacetic acid,	
	D - α - [(3 - furoyl - (2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - hydroxyphenylacetic acid,	50
50	D - α - [(3 - furoyl - (2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl - (2) - acetic acid,	
	D,L - α - [(3 - furoyl - (2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methylsulphonyl - phenylacetic acid,	55
55	D - α - [(3 - benzoyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chloro-phenylacetic acid,	
	D - α - [(3 - 3 - benzoyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methyl-phenylacetic acid,	60
60	D - α - [(3 - benzoyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - nitro-phenylacetic acid,	
	D - α - [(3 - benzoyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl-(2) - acetic acid, or	65
65	D,L - α - [(3 - benzoyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methylsulphonyl - phenylacetic acid	

is reacted with 0.02 mol of tetramethylchloroformamidinium chloride and 0.022 mol of 6-aminopenicillanic acid, the following penicillins are obtained in the form of their sodium salts:

	D - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4-chloro - benzylpenicillin,	
	D - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4-methyl - benzylpenicillin,	
5	D - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4-nitro - benzylpenicillin,	5
	D - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4-hydroxy - benzylpenicillin,	
10	D - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α -thienyl - (2) - methylpenicillin,	10
	D,L - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4-methylsulphonyl - benzylpenicillin,	
	D - α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4-chloro - benzylpenicillin,	
15	D - α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4-methyl - benzylpenicillin,	15
	D - α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4-nitro - benzylpenicillin,	
20	D - α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4-hydroxy - benzylpenicillin,	20
	D - α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α -thienyl - (2) - methylpenicillin,	
	D,L - α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4-methylsulphonyl - benzylpenicillin,	
25	D - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chloro-benzylpenicillin,	25
	D - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methyl-benzylpenicillin,	
30	D - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - nitro-benzylpenicillin,	30
	D - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - hydroxy-benzylpenicillin,	
	D - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl - (2) - methylpenicillin,	
35	D,L - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methyl-sulphonyl - benzylpenicillin,	35
	D - α - [(3 - formyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chloro-benzylpenicillin,	
40	D - α - [(3 - formyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methyl-benzylpenicillin,	40
	D - α - [(3 - formyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - nitro-benzylpenicillin,	
	D - α - [(3 - formyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - hydroxy-benzylpenicillin,	
45	D - α - [(3 - formyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl - (2) - methylpenicillin,	45
	D,L - α - [(3 - formyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methyl-sulphonyl - benzylpenicillin,	
50	D - α - [(3 - furoyl(2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chloro-benzylpenicillin,	50
	D - α - [(3 - furoyl(2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methyl-benzylpenicillin,	
	D - α - [(3 - furoyl(2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - nitro-benzylpenicillin,	
55	D - α - [(3 - furoyl(2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - hydroxy-benzylpenicillin,	55
	D - α - [(3 - furoyl(2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl - (2) - methylpenicillin,	
60	D,L - α - [(3 - furoyl(2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4-methylsulphonyl - benzylpenicillin,	60
	D - α - [(3 - benzoyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chloro-benzylpenicillin,	
	D - α - [(3 - benzoyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methyl-benzylpenicillin,	

25

- 5 D - α - [(3 - benzoyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - nitro-benzylpenicillin,
D - α - [(3 - benzoyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - hydroxy-benzylpenicillin,
D - α - [(3 - benzoyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl-(2) - methylpenicillin, or
D - α - [(3 - benzoyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methylsulphonyl - benzylpenicillin.

Example 15.

- 10 If, as described in Example 1A, 0.02 mol of
D - α - [(3 - methylaminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino]-phenylacetic acid,
D - α - [(3 - aminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino]-phenylacetic acid,
15 D - α - [(3 - dimethylaminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino]-phenylacetic acid,
D - α - [(3 - i - propyloxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino]-phenylacetic acid,
D - α - [(3 - pyrrolid - 1 - yl - carbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,
20 D - α - [(3 - piperid - 1 - yl - carbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,
D - α - [(3 - phenylaminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino]-phenylacetic acid,
25 D - α - [(3 - phenoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino]-phenylacetic acid,
D - α - [(3 - benzoyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,
D - α - [(3 - furoyl (2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,
D - α - [(3 - n-butyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,
30 D - α - [(2 - methylsulphonylamino - 4,5 - dihydro - imidazol - 1 - yl) - carbonylamino] - phenylacetic acid,
D - α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,
D - α - [(3 - formyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,
D - α - [(3 - pivaloyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,
35 D - α - [(3 - ethoxycarbonylamino - sulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,
D - α - [(3 - cyclohexyloxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino]-phenylacetic acid,
D - α - [(3 - methylsulphonyl - 4 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid or
40 D - α - [(3 - methylsulphonyl - 5 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid
is reacted with 0.02 mol of tetramethylchloroformamidinium chloride and subsequently with 0.022 mol of 6-aminopenicillanic acid, the following penicillins are obtained in the form of their sodium salts:
45 D - α - [(3 - methylaminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino]-benzylpenicillin,
D - α - [(3 - aminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin,
D - α - [(3 - dimethylaminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino]-benzylpenicillin,
50 D - α - [(3 - i - propyloxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino]-benzylpenicillin,
D - α - [(3 - pyrrolid - 1 - yl - carbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin,
D - α - [(3 - piperidid - 1 - yl - carbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin,
55 D - α - [(3 - phenylaminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino]-benzylpenicillin,
D - α - [(3 - phenoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin,
60 D - α - [(3 - benzoyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin,
D - α - [(3 - furoyl (2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin,
D - α - [(3 - butyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin,
D - α - [(2 - methylsulphonylamino - 4,5 - dihydro - imidazol - 1 - yl) - carbonylamino] - benzylpenicillin,

- D- α -[(3-ethylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin,
 D- α -[(3-formyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin,
 D- α -[(3-pivaloyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin,
 5 D- α -[(3-ethoxycarbonylamino-sulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin,
 D- α -[(3-cyclohexyloxycarbonyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin,
 D- α -(3-methylsulphonyl-4-methyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin or
 10 D- α -(3-methylsulphonyl-5-methyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin.

Example 16.

If, as described in Example 1A, 0.02 mol of

- 15 D- α -(5-benzoyl-5-methyl-biureido)-phenylacetic acid,
 D- α -(5-benzoyl-5-methyl-2-thio-biureido)-phenylacetic acid,
 D- α -(5-acetyl-5-methyl-biureido)-phenylacetic acid,
 D- α -(5-acetyl-5-methyl-2-thio-biureido)-phenylacetic acid,
 D- α -[3-(imidazolidin-2-on-1-yl-carbonyl)-ureido]-phenylacetic acid,
 20 D- α -[3-(imidazolidin-2-on-1-yl-carbonyl)-thioureido]-phenylacetic acid,
 D- α -(5-dimethylaminocarbonyl-5-methyl-biureido)-phenylacetic acid,
 D- α -(5-dimethylaminocarbonyl-5-methyl-2-thio-biureido)-phenylacetic acid,
 D- α -(5-methylsulphonyl-5-methyl-biureido)-phenylacetic acid,
 D- α -(5-methylsulphonyl-5-methyl-2-thio-biureido)-phenylacetic acid,
 25 D- α -(5-methylaminocarbonyl-5-methyl-biureido)-phenylacetic acid,
 D- α -(5-methylaminocarbonyl-5-methyl-2-thio-biureido)-phenylacetic acid,
 D- α -(5-furoyl(2)-5-methyl-biureido)-phenylacetic acid,
 D- α -(5-furoyl(2)-5-methyl-2-thio-biureido)-phenylacetic acid,
 D- α -[3-(isothiazolidine-1,1-dioxide-2-yl-carbonyl)-ureido]-phenylacetic acid,
 30 D- α -[3-(isothiazolidine-1,1-dioxide-2-yl-carbonyl)-thioureido]-phenylacetic acid,
 D- α -[3-(pyrrolidin-2-on-1-yl-carbonyl)-ureido]-phenylacetic acid or
 D- α -[3-(pyrrolidin-2-on-1-yl-carbonyl)-thioureido]-phenylacetic acid
 is reacted with 0.02 mol of tetramethylchloroformamidinium chloride and 0.022 mol of
 6-aminopenicillanic acid, the following penicillins are obtained in the form of their
 sodium salts:
- 35 D- α -(5-benzoyl-5-methyl-biureido)-benzylpenicillin,
 D- α -(5-benzoyl-5-methyl-2-thio-biureido)-benzylpenicillin,
 D- α -(5-acetyl-5-methyl-biureido)-benzylpenicillin,
 D- α -(5-acetyl-5-methyl-2-thio-biureido)-benzylpenicillin,
 40 D- α -[3-(imidazolidin-2-on-1-yl-carbonyl)-ureido]-benzylpenicillin,
 D- α -[3-(imidazolidin-2-on-1-yl-carbonyl)-thioureido]-benzylpenicillin,
 D- α -(5-dimethylaminocarbonyl-5-methyl-biureido)-benzylpenicillin,
 D- α -(5-dimethylaminocarbonyl-5-methyl-2-thio-biureido)-benzylpenicillin,
 D- α -(5-methylsulphonyl-5-methyl-biureido)-benzylpenicillin,
 D- α -(5-methylsulphonyl-5-methyl-2-thio-biureido)-benzylpenicillin,
 45 D- α -(5-methylaminocarbonyl-5-methyl-biureido)-benzylpenicillin,
 D- α -(5-methylaminocarbonyl-5-methyl-2-thio-biureido)-benzylpenicillin,
 D- α -(5-furoyl(2)-5-methyl-biureido)-benzylpenicillin,
 D- α -(5-furoyl(2)-5-methyl-2-thio-biureido)-benzylpenicillin,
 50 D- α -[3-(isothiazolidine-1,1-dioxide-2-yl-carbonyl)-ureido]-benzylpenicillin,
 D- α -[3-(isothiazolidine-1,1-dioxide-2-yl-carbonyl)-thioureido]-benzylpenicillin,
 D- α -[3-(pyrrolidin-2-on-1-yl-carbonyl)-ureido]-benzylpenicillin or
 D- α -[3-(pyrrolidin-2-on-1-yl-carbonyl)-thioureido]-benzylpenicillin.

Example 17.

If, as described in Example 1A, 0.02 mol of

- 55 D- α -(3-propionyl-imidazolidin-2-on-1-yl)-carbonylamino]-phenylacetic acid,
 D- α -[(3-acetyl-4-methyl-imidazolidin-2-on-1-yl)-carbonylamino]-phenylacetic acid,
 D- α -[(3-acetyl-5-methyl-imidazolidin-2-on-1-yl)-carbonylamino]-phenylacetic acid,
 60 D- α -[(3-acetyl-1,3-diaza-cyclohexan-2-on-1-yl)-carbonylamino]-phenylacetic acid,
 D- α -[(3-n-propylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-phenylacetic acid,
 D- α -(3-ethylsulphonyl-4-methyl-imidazolidin-2-on-1-yl)-carbonylamino]-phenylacetic acid,

38

	D - α - [(3 - ethylsulphonyl - 5 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
	D - α - (3 - ethylsulphonyl - 1,3 - diazacyclohexan - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
5	D - α - [(3 - methylsulphonyl - 1,3 - diazacyclohexan - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	5
	D - α - [(3 - n - propylsulphonyl - 1,3 - diazacyclohexan - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
10	D - α - [(3 - i - propylsulphonyl - 1,3 - diazacyclohexan - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	10
	D - α - [(3 - i - propylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
	D - α - [(3 - i - propylsulphonyl - 4 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
15	D - α - [(3 - i - propylsulphonyl - 5 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	15
	D - α - [(3 - n - propylsulphonyl - 4 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
20	D - α - [(3 - n - propylsulphonyl - 5 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	20
	D - α - [(3 - phenylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
	D - α - [(3 - p - methylphenylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
25	D - α - [(3 - cyclohexylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	25
	D - α - [(3 - thienyl(2) - sulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
30	D - α - [(3 - formyl - 4 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	30
	D - α - [(3 - formyl - 5 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
	D - α - [(3 - formyl - 1,3 - diazacyclohexan - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
35	D - α - [(3 - methylaminocarbonyl - 4 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	35
	D - α - [(3 - methylaminocarbonyl - 5 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
40	D - α - [(3 - methylaminocarbonyl - 1,3 - diazacyclohexan - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	40
	D - α - [(3 - methoxycarbonyl - 4 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
	D - α - [(3 - methoxycarbonyl - 5 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
45	D - α - [(3 - methoxycarbonyl - 1,3 - diazacyclohexan - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	45
	D - α - [(3 - i - propyloxycarbonyl - 4 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
50	D - α - [(3 - i - propyloxycarbonyl - 5 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	50
	D - α - [(3 - i - propyloxycarbonyl - 1,3 - diazacyclohexan - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
	D - α - [(3 - methylsulphonyl - 4,5 - dimethyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
55	D - α - [(3 - methylsulphonyl - 4,4 - dimethyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	55
	D - α - [(3 - methylsulphonyl - 5,5 - dimethyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	
60	D - α - [(3 - formyl - 4,5 - dimethyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	60
	D - α - [(3 - formyl - 4,4 - dimethyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid or	
65	D - α - [(3 - formyl - 5,5 - dimethyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - phenylacetic acid,	65
	is reacted with 0.02 mol of tetramethylchloroformamidinium chloride and 0.022 mol of	

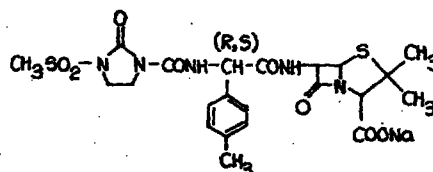
6-aminopenicillanic acid, the following penicillins are obtained in the form of their sodium salts:

- D- α -[(3-propionyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin,
 D- α -[(3-acetyl-4-methyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin,
 5 D- α -[(3-acetyl-5-methyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin,
 D- α -[(3-acetyl-1,3-diazacyclohexan-2-on-1-yl)-carbonylamino]-benzylpenicillin,
 D- α -[(3-n-propylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin,
 D- α -[(3-ethylsulphonyl-4-methyl-imidazolidin-2-on-1-yl)-carbonyl-
 amino]-benzylpenicillin,
 10 D- α -[(3-ethylsulphonyl-5-methyl-imidazolidin-2-on-1-yl)-carbonyl-
 amino]-benzylpenicillin,
 D- α -[(3-ethylsulphonyl-1,3-diazacyclohexan-2-on-1-yl)-carbonyl-
 amino]-benzylpenicillin,
 D- α -[(3-methylsulphonyl-1,3-diazacyclohexan-2-on-1-yl)-carbonyl-
 amino]-benzylpenicillin,
 15 D- α -[(3-n-propylsulphonyl-1,3-diazacyclohexan-2-on-1-yl)-carbonyl-
 amino]-benzylpenicillin,
 D- α -[(3-i-propylsulphonyl-1,3-diazacyclohexan-2-on-1-yl)-carbonyl-
 amino]-benzylpenicillin,
 20 D- α -[(3-i-propylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-
 benzylpenicillin,
 D- α -[(3-i-propylsulphonyl-4-methyl-imidazolidin-2-on-1-yl)-carb-
 onylamino]-benzylpenicillin,
 D- α -[(3-i-propylsulphonyl-5-methyl-imidazolidin-2-on-1-yl)-carb-
 onylamino]-benzylpenicillin,
 25 D- α -[(3-n-propylsulphonyl-4-methyl-imidazolidin-2-on-1-yl)-carb-
 onylamino]-benzylpenicillin,
 D- α -[(3-n-propylsulphonyl-5-methyl-imidazolidin-2-on-1-yl)-carb-
 onylamino]-benzylpenicillin,
 30 D- α -[(3-phenylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-
 benzylpenicillin,
 D- α -[(3-p-methylphenylsulphonyl-imidazolidin-2-on-1-yl)-carbonyl-
 amino]-benzylpenicillin,
 D- α -[(3-cyclohexylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-
 benzylpenicillin,
 35 D- α -[(3-thienyl(2)-sulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-
 benzylpenicillin,
 D- α -[(3-formyl-4-methyl-imidazolidin-2-on-1-yl)-carbonylamino]-
 benzylpenicillin,
 40 D- α -[(3-formyl-5-methyl-imidazolidin-2-on-1-yl)-carbonylamino]-
 benzylpenicillin,
 D- α -[(3-formyl-1,3-diazacyclohexan-2-on-1-yl)-carbonylamino]-
 benzylpenicillin,
 D- α -[(3-methylaminocarbonyl-4-methyl-imidazolidin-2-on-1-yl)-
 carbonylamino]-benzylpenicillin,
 45 D- α -[(3-methylaminocarbonyl-5-methyl-imidazolidin-2-on-1-yl)-
 carbonylamino]-benzylpenicillin,
 D- α -[(3-methylaminocarbonyl-1,3-diazacyclohexan-2-on-1-yl)-carbonyl-
 amino]-benzylpenicillin,
 50 D- α -[(3-i-propyloxycarbonyl-4-methyl-imidazolidin-2-on-1-yl)-
 carbonylamino]-benzylpenicillin,
 D- α -[(3-i-propyloxycarbonyl-5-methyl-imidazolidin-2-on-1-yl)-
 carbonylamino]-benzylpenicillin,
 D- α -[(3-i-propyloxycarbonyl-1,3-diazacyclohexan-2-on-1-yl)-carbonyl-
 amino]-benzylpenicillin,
 55 D- α -[(3-methylsulphonyl-4,5-dimethyl-imidazolidin-2-on-1-yl)-carb-
 onylamino]-benzylpenicillin,
 D- α -[(3-methylsulphonyl-4,4-dimethyl-imidazolidin-2-on-1-yl)-carb-
 onylamino]-benzylpenicillin,
 60 D- α -[(3-methylsulphonyl-5,5-dimethyl-imidazolidin-2-on-1-yl)-carb-
 onylamino]-benzylpenicillin,
 D- α -[(3-formyl-4,5-dimethyl-imidazolidin-2-on-1-yl)-carbonylamino]-
 benzylpenicillin,
 65 D- α -[(3-formyl-4,4-dimethyl-imidazolidin-2-on-1-yl)-carbonylamino]-
 benzylpenicillin or

- D - α - [(3 - formyl - 5,5 - dimethyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin,
 D - α - [(3 - methoxycarbonyl - 4 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin,
 5 D - α - [(3 - methoxycarbonyl - 5 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin and
 D - α - [(3 - methoxycarbonyl - 1,3 - diazacyclohexan - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin.

Example 18.

- 10 A. Sodium D,L - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methyl - benzylpenicillin: 10



This penicillin was produced as described in Example 1A from 7.0 parts by weight of D,L - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methyl - phenylacetic acid, 3.8 parts by weight of tetramethylchloroformamidinium chloride and 5.0 parts by weight of 6-aminopenicillanic acid.

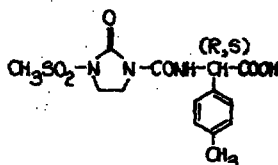
Yield: 57%.

β -Lactam content: 83%.

IR-bands at 3320, 1765, 1727, 1674, 1605, 1515, 1255 and 1170 cm^{-1} (in Nujol)

20 NMR-signals at τ = 2.65 (2H), 2.83 (2H), 4.3—4.6 (3H), 5.8 (1H), 6.15 (4H), 6.7 (3H), 7.7 (3H) and 8.3—8.6 ppm (6H). 20

- B. D,L - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methyl - phenylacetic acid:



25 This carboxylic acid was produced as described in Example 1B.1 from 11.3 parts by weight of 1-chlorocarbonyl-3-methylsulphonyl-imidazolid-2-one and 9.1 parts by weight of D,L- α -4-(methylphenyl)-glycine. 25

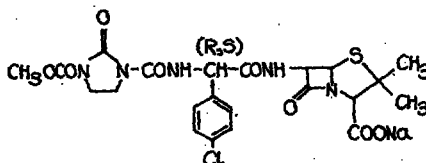
Yield: 42%.

IR-bands at 3700—2200, 3300, 1740—1660, 1540—1500, 1255 and 970 cm^{-1} (in Nujol).

30 NMR-signals at τ = 1.3 (1H), 2.7 (4H), 4.7 (1H), 6.2 (4H), 6.6 (3H) and 7.7 ppm (3H). 30

Example 19.

- 35 A. Sodium D,L - α - [(3 - methoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chloro - benzylpenicillin: 35



This penicillin was produced as described in Example 1A from 9 parts by weight of D,L - α - [(3 - methoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] -

4-chloro-phenylacetic acid, 4.85 parts by weight of tetramethylchloroformamidinium chloride and 6.5 parts by weight of 6-aminopenicillanic acid.

Yield: 80%

β -Lactam content: 85%

IR-bands at 3300, 3050, 1770, 1742, 1730, 1670, 1605, 1520, 1320 and 1260 cm^{-1} (in Nujol).

NMR-signals at τ = 2.57 (2H), 2.65 (2H), 4.35—4.65 (3H), 6.14 (4H), 6.16 (3H) and 8.3—8.6 ppm (6H).

B. D,L- α - [(3-methoxycarbonyl-imidazolidin-2-on-1-yl)-carbonylamino] - 4-chloro-phenylacetic acid:

This carboxylic acid was produced as described in Example 1B.1 from 10.4 parts by weight of 1-chlorocarbonyl-3-methoxycarbonyl-imidazolid-2-one and 10.2 parts by weight of D,L- α -(4-chlorophenyl)-glycine.

Yield: 61%

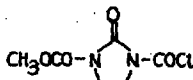
Calculated: C 47.2 H 4.0 Cl 10.0 N 11.8 %

Found: C 47.4 H 4.5 Cl 9.2 N 11.2 %

IR-bands at 3700—2250, 3280, 3060 and 1780—1630 cm^{-1} (in Nujol)

NMR-signals at τ = 1.0 (1H), 2.5 (4H), 4.5 (1H), 6.15 (4H) and 6.20 ppm (3H)

C. 1-Chlorocarbonyl-3-methoxycarbonyl-imidazolid-2-one:



This carbamic acid chloride was produced as described in Example 6B from 8 parts by weight of N-methoxycarbonyl-imidazolid-2-one, 9.7 parts by weight of trimethylchlorosilane, 9 parts by weight of triethylamine and 6.2 parts by weight of phosgene.

Yield: 72%

Melting point = 129°C

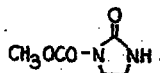
Calculated: C 34.8 H 3.4 Cl 17.2 N 13.6 %

Found: C 34.8 H 3.4 Cl 17.1 N 13.6 %

IR-bands at 1820, 1737, 1690 and 1260 cm^{-1} .

NMR-signals at τ = 5.7—6.3 (4H) and 6.1 ppm (3H)

D. N-methoxycarbonyl-imidazolid-2-one:



14.9 parts by weight of N-chlorocarbonyl-imidazolid-2-one were introduced into 70 parts by volume of ice-cold methanol and the mixture was stirred for 1 hour at room temperature and subsequently for 1 hour at 40—50°C. After stripping off the excess methanol, the product was recrystallised from acetone.

Yield: 55%

Melting point = 185°C

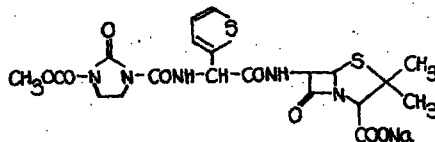
Calculated: C 41.6 H 5.5 N 19.4 %

Found: C 41.8 H 4.8 N 19.2 %

IR-bands at 3320, 1745 and 1670 cm^{-1} .

Example 20.

A. Sodium D,L- α - [(3-methoxycarbonyl-imidazolidin-2-on-1-yl)-carbonylamino] - α - thienyl(2) - methylpenicillin:



This penicillin was produced as described in Example 1A from 8.5 parts by weight of D,L- α -[(3-methoxycarbonyl-imidazolidin-2-on-1-yl)-carbonylamino]- α -thienyl(2)-acetic acid, 5.1 parts by weight of tetramethylchloroformamidinium chloride and 6.9 parts by weight of 6-aminopenicillanic acid.

Yield: 72%

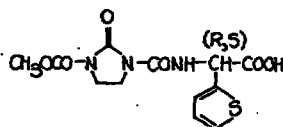
β -Lactam content: 67%

IR-bands at 3310, 1773, 1750, 1730, 1670, 1610, 1520, 1320 and 1265 cm^{-1} (in Nujol)

NMR-signals at τ =2.5—3.2 (3H), 4.1 (1H), 4.4—4.6 (2H), 5.8 (1H), 6.15 (7H) and 8.3—8.55 ppm (6H)

According to the NMR-spectrum, the crude product still contained 23% of D,L- α -[(3-methoxycarbonyl-imidazolidin-2-on-1-yl)-carbonylamino]- α -thienyl(2)-acetic acid, which is however removable by fractional acidification of the aqueous solution.

B. D,L- α -[(3-methoxycarbonyl-imidazolidin-2-on-1-yl)-carbonylamino]- α -thienyl(2)-acetic acid:



This carboxylic acid was produced as described in Example 1B.1 from 8.8 parts by weight of 1-chlorocarbonyl-3-methoxycarbonyl-imidazolid-2-one and 7.3 parts by weight of D,L- α -thienyl(2)-glycine.

Yield: 73%

Calculated: C 44.0 H 4.0 N 12.8 S 9.8 %

Found: C 44.1 H 4.0 N 12.0 S 9.9 %

IR-bands at 3700—2200, 3280, 1775, 1740—1640, 1515 and 1015 cm^{-1} (in Nujol)

NMR-signals at τ =0.9 (1H), 2.5—3.1 (3H), 4.2 (1H), 6.15 (4H) and 6.20 ppm (3H).

Example 21.

Sodium D- α -[(3-ethylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin:

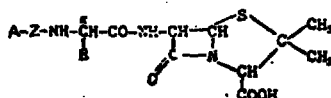
2.9 parts by weight of D- α -[(3-ethylsulphonyl-imidazolidin-2-on-1-yl)-carbonylamino]-phenylacetic acid were dissolved in 30 parts by volume of tetrahydrofuran, the solution was cooled to -30°C and a solution of 1.0 part by weight of tetramethylchloroformamidinium chloride in 30 parts by volume of dichloromethane, pre-cooled to -30°C , was then added all at once. Hereupon, some material precipitated. After the temperature had been allowed to rise to -25°C to -20°C , a clear solution formed. This solution was left to stand for 15 minutes at -25°C . Then this solution was added all at once to a solution or suspension, maintained at 0°C to 5°C , of 2.3 parts by weight of 6-aminopenicillanic acid in 25 parts by volume of 90% strength aqueous tetrahydrofuran which had been adjusted to pH 2.5 by adding 10% wt % aqueous hydrochloric acid. Thereafter, the pH was kept at 2.5 by appropriate addition of 2 N aqueous sodium hydroxide solution and the mixture was cooled with an ice-water mixture, as a result of which the temperature was brought to 0°C , and kept there. After one hour the mixture was worked up, though in order to maintain the pH of 2.5 it was still necessary to add sodium hydroxide solution, if only a little. Working up took place as described in Example 11.

Yield: 2.3 parts by weight

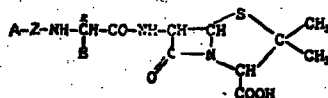
The IR-spectrum of this penicillin was identical to that of the penicillin of Example 11.

WHAT WE CLAIM IS:—

1. Compounds which are penicillins of the following general formula or their salts:—



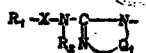
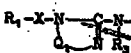
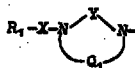
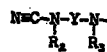
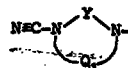
I



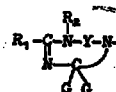
in which

C* is a carbon atom constituting a centre of chirality;
A is a radical of one of the general formulae:—

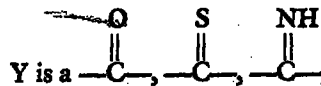
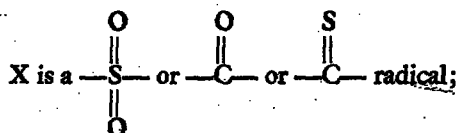
5



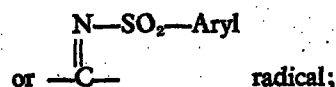
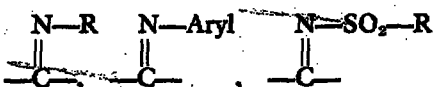
or



[in which general formulae:—

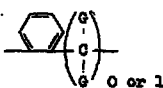
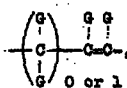
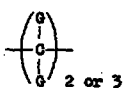


10



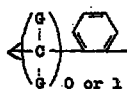
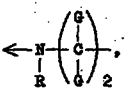
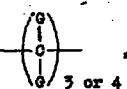
10

Q₁ is a



radical; and

Q₂ is a



radical;

(in which general formulae:—

R is a straight-chain or branched alkyl radical with up to 5 carbon atoms;

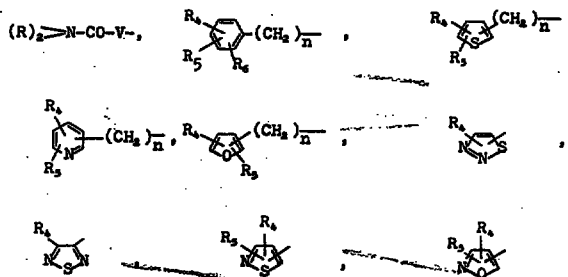
R₁ is a hydrogen atom or an alkyl, cycloalkyl, alkenyl or cycloalkenyl radical with up to 10 carbon atoms, or a vinyl, aryl-vinyl, mono-, di- or tri-halo- lower alkyl radical, or an H₂N—, R—NH—, (R)₂=N—, aryl-NH—, or aryl- lower alkylamino radical or an alkoxy*, or aralkoxy* radical with up to 8 carbon atoms, or a cycloalkoxy* radical with up to 7 carbon atoms, or an aryloxy*, R—O—V—, R—S—V—, N≡C—V—, R—O—CO—V—, H₂N—CO—V—, R—NH—CO—V—, (R)₂=N—CO—V—,

20

20

25

25



radical;

5

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

n is 0, 1, or 2;

R_2 and R_3 which may be the same or different are each a hydrogen atom or an alkyl or alkenyl radical having up to 8 carbon atoms, or a vinyl, allyl or propenyl radical, or a cycloalkyl or cycloalkenyl radical having up to 6 carbon atoms, or a mono-, di- or tri-halogeno-lower alkyl or aryl radical;

10

R_4 , R_5 and R_6 which may be the same or different are each a hydrogen, nitro, nitrile, $(R)_2=N-$, $(R)_2=N-CO-$, $R-CO-NH-$, $R-O-CO-$, $R-CO-O-$, $R, R-O, H_2N-SO_2-$, chlorine, bromine, iodine, fluorine or trifluoromethyl radical; and

15

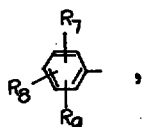
G is a hydrogen atom or a radical R;

with the proviso that the meanings marked * are only available if X is not an $-SO_2-$ radical];

Z is a $-CO-$ or $-SO-$ radical; and

B is a radical of the general formula

20



or



20

[in which R_7 , R_8 and R_9 which may be the same or different, are each a hydrogen, halogen, $R-$, $R-O-$, $R-S-$, $R-SO-$, $R-SO_2-$, nitro, $(R)_2=N$, $R-CO-NH$, HO or $R-CO-O-$ radical, R having the meaning given above, provided that when two of R_7 , R_8 and R_9 are hydrogen, the other cannot be hydroxyl, and that all three of R_7 , R_8 and R_9 cannot at once be hydrogen]; and in which above general formulae the arrow in the divalent linkage member

25

25

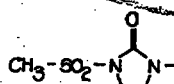


means that the linkage of two atoms by the two free valencies of this linking member is not free to take place in either direction but only in the manner indicate by the arrow.

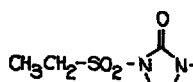
30

2. Compounds according to Claim 1 in which A is

30



3. Compounds according to Claim 1 in which A is



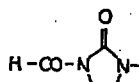
36
45

1,392,850

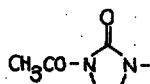


36

4. Compounds according to Claim 1 in which A is

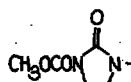


5. Compounds according to Claim 1 in which A is



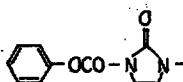
5

6. Compounds according to claim 1 in which A is

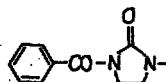


5

7. Compounds according to Claim 1 in which A is



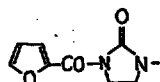
8. Compounds according to Claim 1 in which A is



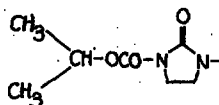
10

10

9. Compounds according to Claim 1 in which A is

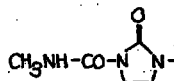


10. Compounds according to Claim 1 in which A is



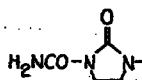
15

11. Compounds according to Claim 1 in which A is



15

12. Compounds according to Claim 1 in which A is



20

13. Compounds according to any of Claims 1 to 12 in which B is *p*-nitrophenyl.
 14. Compounds according to any of Claims 1 to 12 in which B is *p*-methylphenyl.
 15. Compounds according to any of Claims 1 to 12 in which B is *p*-chlorophenyl.

20



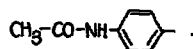
37

* C L M S *

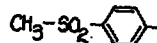
1,392,850

37

16. Compounds according to any of Claims 1 to 12 in which B is



17. Compounds according to any of Claims 1 to 12 in which B is



5

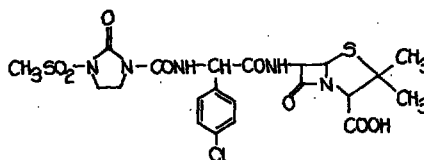
18. Compounds according to any of Claims 1 to 12 in which B is thienyl-(2).

5

19. Compounds according to any preceding claim, in which C* is the R-configuration.

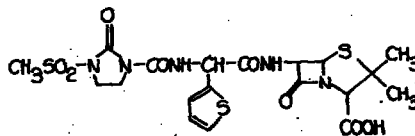
20. α - [(3 - Methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chloro - benzylpenicillin of the formula:—

10



10

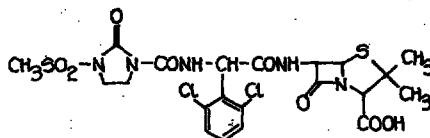
21. α - [(3 - Methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl (2) - methylpenicillin of the formula:—



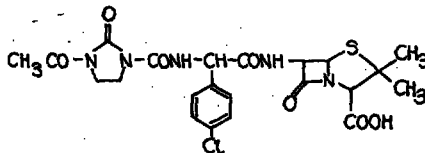
15

22. α - [(3 - Methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 2,6 - dichloro - benzylpenicillin of the formula:—

15



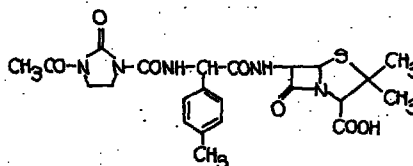
23. α - [(3 - Acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chloro - benzylpenicillin of the formula:—



20

24. α - [(3 - Acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methyl - benzylpenicillin of the formula:—

20



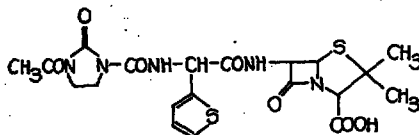


* C L H S *

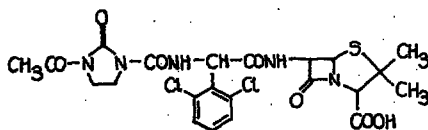
1,392,850

38

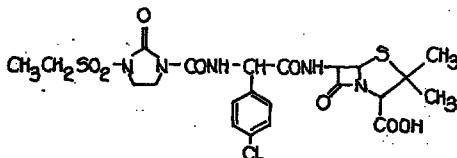
25. α - [(3 - Acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl (2) - methylpenicillin of the formula:—



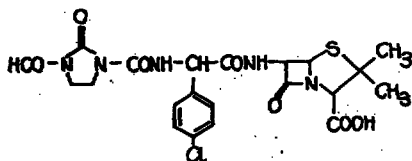
26. α - [(3 - Acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 2,6 - dichloro - benzylpenicillin of the formula:—



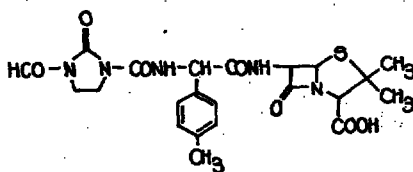
27. α - [(3 - Ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chloro - benzylpenicillin of the formula:—



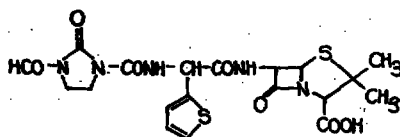
28. α - [(3 - Formyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chloro - benzylpenicillin of the formula:—



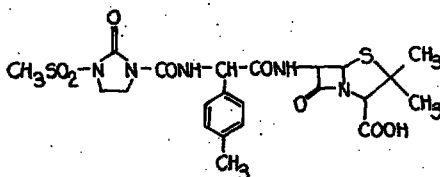
29. α - [(3 - Formyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methyl - benzylpenicillin of the formula:—



30. α - [(3 - Formyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl (2) - methylpenicillin of the formula:—



31. α - [(3 - Methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - methyl - benzylpenicillin of the formula:—



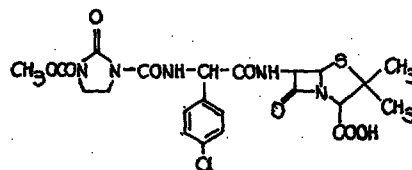


39

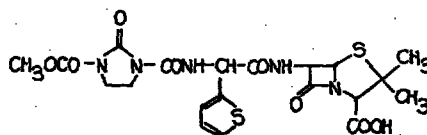
1,392,850

39

32. α - [(3 - Methoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4 - chloro - benzylpenicillin of the formula:—



33. α - [(3 - Methoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl (2) - methylpenicillin of the formula:—

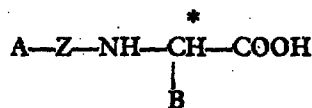


34. Compounds according to any preceding claim which are salts of the acid carboxyl group of a compound of the general formula I with sodium, potassium, magnesium, calcium, aluminium, or unsubstituted or substituted ammonium.

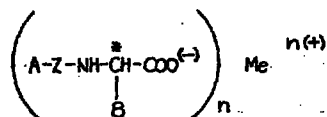
35. Compounds according to claim 1 which are hereinbefore specifically mentioned other than those according to one of claims 22 to 33.

36. A process for the production of a compound which is a penicillin of the general formula I given in claim 1 in which the symbols are as defined below, or a salt thereof, comprising the steps of:—

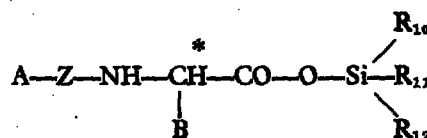
(i) producing a reactive intermediate by reacting a carboxylic acid of the following general formula (V), a carboxylic acid salt of the following general formula Va, or a carboxylic acid silyl or hemisilyl ester of the general formula Vb or Vc:



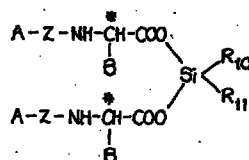
V



Va



Vb



Vc

in an aqueous or anhydrous organic solvent when a compound of the general formula V or Va is reacted, or in an anhydrous inert organic solvent free of hydroxyl groups when a compound of general formula Vb or Vc is reacted, at -70°C to $+30^{\circ}\text{C}$, with either:

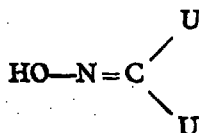
(a) a compound of one of the following general formulae VI to IX:—

25

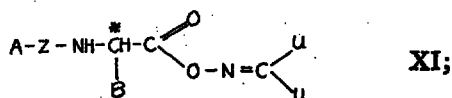
25



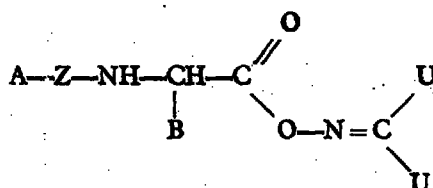
X



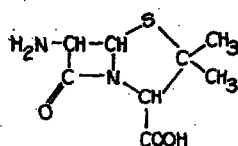
II.



XI.



(ii) reacting the reactive intermediate with 6-aminopenicillanic acid of the following general formula II or silyl- or di-silyl-6-aminopenicillanic acid of the general formula III or IV:—

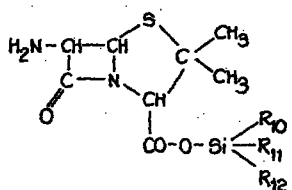


II

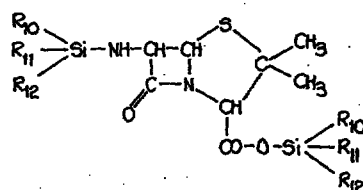


1,392,850

41



III



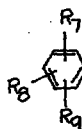
IV

in a solvent in the presence of a base when 6-aminopenicillanic acid is used, or in an anhydrous solvent free of hydroxyl groups when a compound of the general formulae III or IV is used, at a temperature in the range of -70°C to $+50^{\circ}\text{C}$, to produce the desired penicillin compound of any preceding claim;

[in which general formula II to XIIa:

A, C*, R and Z are as defined above;

B is a radical of the formula:—



or



[in which R_7 , R_8 and R_9 are identical or different radicals selected from hydrogen, halogen, R —, R —O—, R —S—, R —SO—, R —SO₂—, nitro (R_2)=N—, R —CO—NH, HO and R —CO—O— radicals, R having the meanings given in claim 1];

$\text{Me}^{n(+)}$ is a cation of an n -valent alkali metal or alkaline earth metal or an aluminium cation;

R_{10} , R_{11} and R_{12} are the same or different lower alkyl radicals;

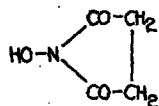
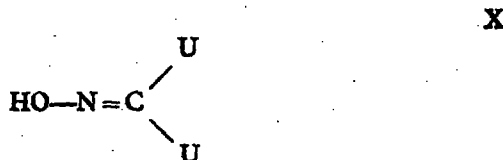
R_{13} can have any of the meanings given for R and can also be a phenyl radical;

R_{14} is a $-(\text{CH}_2)_4-$, $-(\text{CH}_2)_5-$, or $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$ radical;

the groups U which can be same or different are $-\text{C}\equiv\text{N}$ or $-\text{CO}-\text{O}-$ (lower alkyl) radicals; and

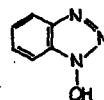
W is a halogen atom].

37. A process according to claim 36 in which the reaction in step (i)(a) is carried out in the presence of about 1 mol equivalent of an N-hydroxy compound of the formula:—



Xa

or



Xb

in which U is as defined in claim 36.

38. A process according to claim 36 in which an optical activity present at the chirality centre C* is protected against possible racemization by carrying out the reaction in step (i)(a) or (b) either in the absence of any organic base or in the presence of a weak organic base as hereinbefore defined.

39. The process of claim 38 in which the reaction in step (i)(a) is carried out in the presence of N-methylmorpholine, N-ethylmorpholine, N,N-dimethylaniline, pyridine, a weak inorganic base, or a buffer.

40. A process according to any of claims 36 to 39 in which the reaction in step (i)(a) is carried out at -50°C to 0°C .

41. A process according to any of claims 36 to 40 in which the reaction in step (ii) is carried out at -50°C to 0°C .

42. A process according to any of claims 36 to 40 in which the reaction in step (ii) is carried out at a pH within the range 2 to 9.

43. A process according to claim 42 in which the reaction in step (ii) is carried out at a pH within the range 2 to 3.

44. A process according to claim 42 in which the said pH is within the range 6.5 to 8.5.

45. A process for the preparation of the penicillin compounds referred to in claim 36, substantially as hereinbefore described or specifically exemplified.

46. Compounds produced by the process of any of claims 36 to 45.

47. A pharmaceutical composition containing as an active ingredient a compound according to any of claims 1 to 35 or 46 in admixture with a solid or liquefied gaseous diluent or in admixture with a liquid diluent other than a solvent of molecular weight less than 200 except in the presence of a surface-active agent.

48. A pharmaceutical composition containing as an active ingredient a compound according to any of claims 1 to 35 and 46 in the form of a sterile or isotonic aqueous solution.

49. A composition according to claim 47 or 48 containing from 0.5 to 95% of active ingredient, by weight.

50. A pharmaceutical composition according to claim 47 or 48 substantially as hereinbefore described or specifically exemplified.

51. A medicament in dosage unit form comprising a compound according to any of claims 1 to 35 or 47 either alone or in admixture with a diluent.

52. A medicament in the form of tablets, pills, dragees, capsules, ampoules or suppositories comprising a compound according to any of claims 1 to 35 or 47, either alone or in admixture with a diluent.

53. A medicament according to claim 51 or 52, substantially as hereinbefore described or specifically exemplified.

54. A method of combating bacterial infection in non-human animals which comprises administering to the animals an active compound according to any of claims 1 to 35 or 47 either alone or in admixture with a diluent or in the form of a medicament according to claim 51, 52 or 53.

55. A method according to claim 54 in which the active compound is administered orally or parenterally at 25,000 to 1,000,000 U/kg of body weight per day.

56. A method according to claim 55 substantially as hereinbefore described or specifically exemplified.

57. An animal feedstuff comprising a nutritious material and a compound of any of claims 1 to 35 and 47.

For the Applicants,
CARPMAELS & RANSFORD,
Chartered Patent Agents,
43 Bloomsbury Square,
London, WC1A 2RA.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1975.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.

