(12)

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1 392 849

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(33) Germany (DT)

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(52) Index at acceptance

C2C 1313 1341 1380 1412 1414 1470 1510 1532 1603 200 20Y 214 215 220 221 225 226 22Y 247 248 250 251 252 253 254 256 258 25Y 27X 280 281 28X 292 29Y 30Y 313 316 318 31Y 320 333 339 342 347 34Y 350 351 352 355 357 35X 35Y 366 367 368 385 386 387 396 39Y 401 40Y 43X 464 491 49Y 511 512 513 514 519 51X 51Y 520 52X 52Y 531 535 553 560 574 575 581 584 594 600 613 614 615 625 627 628 62X 635 638 63X 65X 66X 675 678 699 728 72Y 761 766 775 790 79Y KA KE KM KN KS QG QS RF SB SD TA TM

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

(54) NEW PENICILLINS, 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:—

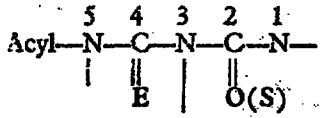
The present invention relates to the production of certain penicillin compounds, to a group of penicillin compounds selected therefrom, and to the use of these compounds in human and veterinary medicine, as therapeutic agents in poultry and mammals, and as feedstuff additives and as growth-promoting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

The 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 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 by *Klebsiella-Aerobacter* if given in a continuous high dosage, such as is only achieved by infusion.

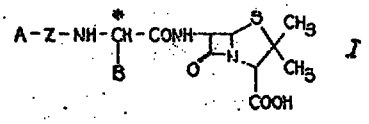
The penicillin compounds of the invention may be regarded as methylpenicillins which are substituted in the methyl group by a radical B and an acyl-biureido radical, of which the carbonyl group in the acyl group can be replaced by a $-SO_2-$ group:



(E is: =O, =S or =N—)

6-(α-Biureido)-acetamido-penicillanic acids are described in British Patent Specifications Nos. 1,265,670 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 now provides penicillin compounds which are penicillins of the following general formula or their salts:—

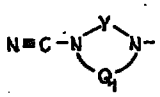


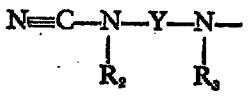
I

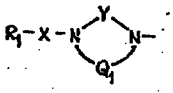
in which

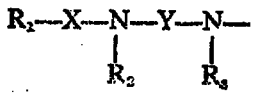
C* is a carbon atom constituting a centre of chirality;

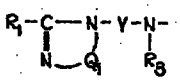
A is a radical of the general formula:—

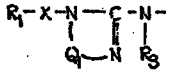


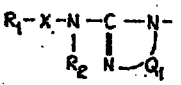


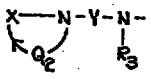




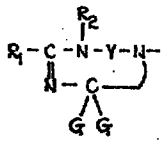




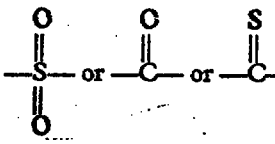


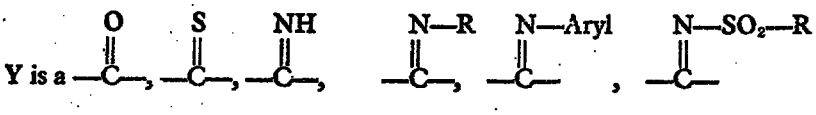


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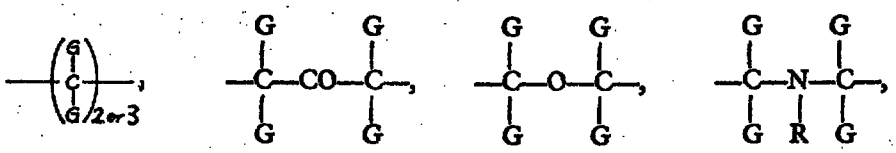


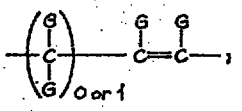
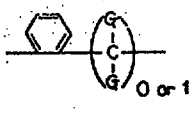
[in which:—

X is a  radical;

Y is a  radical;

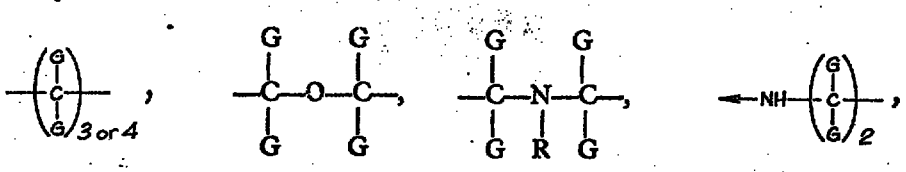
Q_1 is a

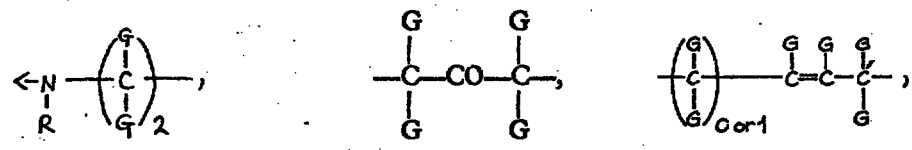


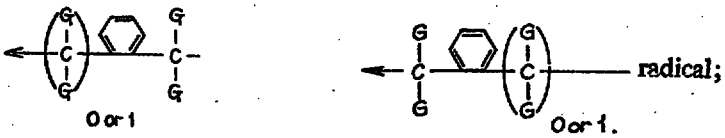



radical;

Q_2 is a



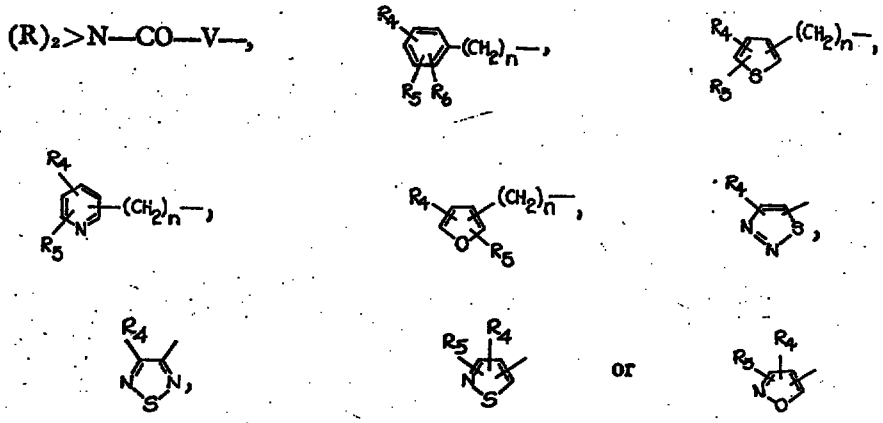




(in which

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

R_1 is an alkyl, cycloalkyl, alkenyl or cycloalkenyl radical with up to 10 carbon atoms, or a vinyl, arylvinyl, mono-, di- or tri-halo-lower alkyl, H_2N—, R—NH—, $(R)_2N$—, Aryl-NH—, 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—, H_2N—CO—V—, R—NH—CO—V—,



radical;

R_1 can also be a hydrogen atom when X is —CO;

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

n is 0, 1 or 2;

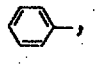
R_2 and R_3, which may be the same or different, are each a hydrogen atom or an alkyl or alkenyl radical with up to 8 carbon atoms, or a vinyl, allyl or propenyl radical, or a cycloalkyl or cycloalkenyl radical with up to 6 carbon atoms, or a mono-, di- or tri-halo- lower alkyl radical or an aryl radical;

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 one of the radicals mentioned above for R, and can also be hydrogen; the meanings marked * not being available when X is $—SO_2—$)];

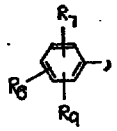
Z is a —CO— or —SO— radical;

B is a radical of the formula:—

,  or  and

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 being as defined above.

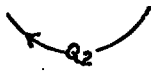
Compounds of the general formula I in which B is

, , or ,

(where R_7, R_8 and R_9 are identical or different radicals selected from hydrogen, halogen, R—, R—O—, R—S—, R—SO—, $R—SO_2—$, nitro, $(R_2 \neq N—$, R—CO—NH—, HO— and R—CO—O— radicals, R being as defined above, provided that when two of R_7, R_8, and R_9 are hydrogen the other cannot be hydrogen and that R_7, R_8 and R_9 cannot in the same compound all be hydrogen) are claimed in our copending Patent Application No. 48700/72. (Serial No. 1 392 850)

The term " lower alkyl " is intended to be understood, in the present specification, as meaning a straight-chain or branched alkyl group with up to 6 carbon atoms. In connection with other groups, such as " di-lower alkylamino ", the term " lower alkyl " only refers to the alkyl part of the group in question.

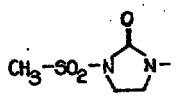
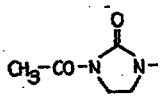
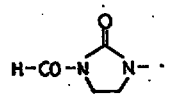
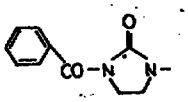
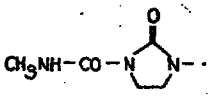
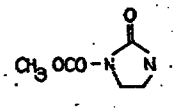
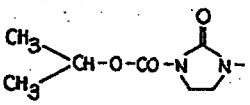
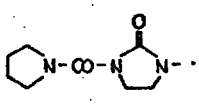
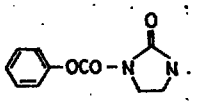
The arrow in the divalent linking group

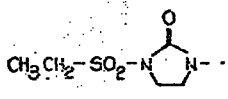
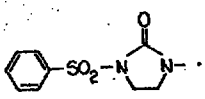


means that the linkage of two atoms by the two free valencies of this group must take place as indicated by the arrow.

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

Preferred radicals A are the following:—

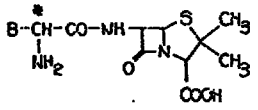










The chirality centre C* is preferably in the R— configuration. Among the penicillin compounds of the invention that are salts of penicillins of the general formula I, those that are pharmaceutically acceptable are preferred.

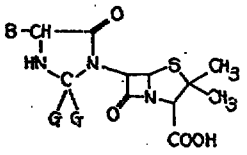
Of the compounds of the invention that are salts, those that are non-toxic and pharmaceutically acceptable are preferred. These include salts of the acid carboxyl group, such as sodium, potassium, magnesium, calcium, aluminium and ammonium salts, and non-toxic substituted ammonium salts with amines, such as di- and tri-lower alkylamines, procaine, dibenzylamine, N,N'-dibenzylethylenediamine, N-benzyl-β-phenylethylamine, N-methyl- and N-ethylmorpholine, 1-ephenamine, dehydroabietylamine, N,N'-bis-dehydroabietylethylenediamine, N-lower alkylpiperidine.

The invention further provides a process for the production of a compound which is a penicillin of the general formula I given above (in which the symbols are as defined below), or a salt thereof, in which process, a 6-amino-penicillanic acid derivative of the general formula:—



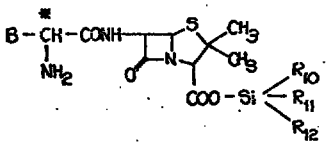
II

or a product of the condensation of such a derivative with a carbonyl compound, the said product having the general formula

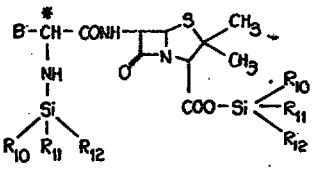


III

or a silyl or disilyl derivative of the said derivative of the general formula:

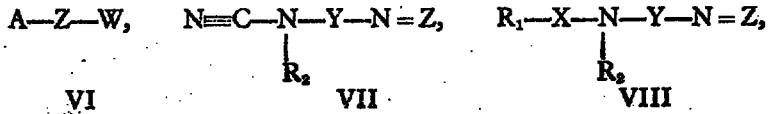


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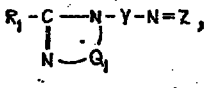


V,

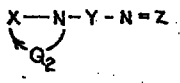
respectively, is reacted with a compound of the general formula:



VI VII VIII



or

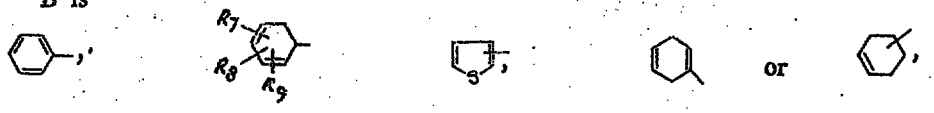


IX X

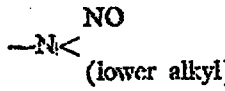
in an anhydrous or aqueous solvent in the presence of a base, when a compound of the general formula II or III is reacted, or in an anhydrous solvent free of hydroxyl groups, with or without a base, when a compound of the general formula IV or V is reacted, at a temperature of −50° to +50°C. [in which general formulae II to IV:

R_{10}, R_{11} and R_{12}, which can be the same or different, are each an alkyl group with up to 6 carbon atoms;

A, C*, G, Q_1, Q_2, R_1, R_2, X, Y and Z are as defined above;
B is



[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 being as defined above]; and
W is a halogen, azide or



radical].

Our copending Patent Application No. 48700/72 (Serial No. 1 392 850) claims other processes for the production of these penicillin compounds.

The carbonyl compounds may, for example, be acetone (see British Patent Specification Nos. 938 321 and 962 719.

If a compound of the general formula II or III is used as the starting material for the synthesis of the penicillin compounds according to the invention, and is reacted with a compound of the general formula VI, VII, VIII, IX or X, the reaction can be carried out, for example, in a mixture of water and an organic solvent which is miscible with water, such as acetone, tetrahydrofuran, dioxane, acetonitrile, dimethylformamide, dimethylsulphoxide or isopropanol. During the reaction, the pH of the reacting mixture is preferably kept at from 2.0 to 9.0 by addition of a base or the use of a buffer solution. The reaction according to the invention is however preferably carried out at a pH of from 4.5 to 9.0 or from 2.0 to 3.0. It is also possible to carry out the reaction in a water-immiscible solvent, for example in chloroform or methylene chloride, with the addition of, preferably, triethylamine, diethylamine or N-ethylpiperidine. The reaction can further be carried out in a mixture of water and a water-immiscible solvent, such as ether, chloroform, methylene chloride, carbon disulphide, isobutyl methyl ketone, ethyl acetate or benzene, when it is preferred to stir the mixture vigorously and to keep the pH at from 4.5 to 9.0 or 2.0 to 3.0, by adding a base or using a buffer solution.

If a compound of the general formula IV or V is used as the starting material for the process of the invention and is reacted with a compound of the general formula VI, VII, VIII, IX or X, the reaction must be carried out in an anhydrous solvent free of hydroxyl groups. Examples of suitable solvents are methylene chloride, chloroform, benzene, tetrahydrofuran, acetone and dimethylformamide. The addition of a base is not necessary, but it can in some cases improve the yield and purity of the products. The base, of added, should generally be either a tertiary amine, such as pyridine or triethylamine, or a secondary amine which as a result of steric hindrance is difficult to acylate, such as dicyclohexylamine. The available choice of usable bases is therefore very wide.

As with most chemical reactions, higher or lower temperatures than those indicated in the Examples can be used. However, if the values given in the Examples are significantly exceeded, side-reactions will increasingly take place, which reduce the yield or adversely influence the purity of the products. On the other hand, excessively lowered reaction temperatures reduce the speed of reaction so greatly that reductions in yield can arise. Reaction temperatures in the range of −20°C to +50°C are therefore preferred, a temperature of 0°C to +20°C being particularly preferred.

The reactants can be reacted with one another in equimolecular amounts. It may however be advisable to use one of the two reactants in excess in order to facilitate the purification, or pure preparation, of the desired penicillin and to increase the yield. For example, the reactants of the general formulae II or III can be employed in an excess of 0.1 to 0.3 mol equivalent and as a result a smaller degree of decomposition of the reactants of the general formulae VI, VII, VIII, IX or X in the aqueous solvent mixture can be achieved. The excess of the reactants of the general formulae II or III can easily be removed, because of their good solubility in aqueous mineral acid, when working up the reaction mixture. On the other hand however, it is also possible with advantage to employ the reactants of the general formulae VI, VII, VIII, IX or X in an excess of, for example, 0.1 to 1.0 mol equivalent. By doing this, the reactants, for example of the general formulae II or III, are more economically used and the decomposition of the reactants of the general formulae VI, VII, VIII, IX or X, which takes place as a side reaction in aqueous solvents, is compensated. Since the compounds of the general formulae VI, VII, VIII, IX or X added in excess are rapidly converted, in water, into

neutral compounds, which can easily be removed, the purity of the penicillins is thereby hardly impaired.

The amount of the bases used is determined, for example, by the desired maintenance of a particular pH. Where 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, 2 mol equivalents of base are preferably added when the compounds of the general formulae II or III are used, whilst either no base at all, or, preferably, 1 mol equivalent of base is added when the compounds of the general formulae IV or V are used.

The working up of the reaction batches for the manufacture of the penicillins according to the invention, and of their salts, can throughout be effected in the manner generally known for penicillins.

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

The compounds of the general formula II used as starting materials in the process according to the present invention can, as regards the configuration of the asymmetric centre in the side chain (C*) occur in the D-=R-form or L-=S-form. They are described in British Patent Specifications Nos. 902,703, 1,011,843, and 873,049, and in U.S. Patents Nos. 3,342,677, and 3,140,282, in South African Patent No. 68/P290 and (an anhydrous form) in British Patent Specification No. 1,003,868. All crystal forms and configurations of the compounds of the general formula II are suitable as the starting material for the reaction according to the invention. The compounds of the general formulae III, IV or V used as the starting materials in the process according to the present invention can, as regards the configuration at the asymmetric centre in the side chain (C*), also occur in the D-=R-form or L-=S-form. The configuration of the asymmetric centres of the 6-amino-penicillanic acid nucleus in the compounds of the general formulae II, III, IV and V should be identical with the corresponding asymmetric centres of 6-amino-penicillanic acid which has been obtained, for example, from penicillin-G by a fermentative process.

The preparation of the compounds of the general formulae IV and V used as the starting material is described in British Patent Specification No. 1,246,495.

The preparation of the compounds of the general formulae VI, VII, VIII, IX or X used as the starting material in the present invention is illustrated in more detail in the following examples.

The chemotherapeutic activity of the new penicillin compounds was tested *in vivo* and *in vitro*. Table I below gives the *in vitro* inhibitory values (MIC) in U/ml*) of nutrient medium. The determination was carried out in a liquid medium in the test tube series dilution test, the reading being taken after 24 hours incubation at 37°C. The MIC is indicated by the non-turbid test tube in the dilution series. The growth 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

(The word DIFCO is a Registered Trade Mark)

*) 1 mol of penicillin contains $5{,}9514 \times 10^8$ Units (U)

The numbers here allocated to the penicillin compounds correspond to the numbers of the Examples in which the preparation of the particular penicillin compound is described.

The spectrum of action of the penicillin compounds of the invention encompasses both Gram-negative and Gram-positive bacteria. The particular advantage of the penicillin compounds 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 ampicillin- and carbenicillin-resistant *Pseudomonas aeruginosa* and *Serratia marcescens* bacteria.

The concentrations required for destruction are reached in the serum after parenteral administration. The results of animal experiments for some of the penicillin compounds according to the invention are summarised in Table 3.

The generally excellent action is achieved both on single and on repeated administration. The penicillin compounds according to the invention are stable to stomach acid. Some of the penicillin compounds show excellent toleration, which is made particularly 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. (Table 4).

Table 1 gives a series of minimum inhibitory concentrations of penicillin No. 4 (see Example 4a) in comparison with carbenicillin.

TABLE 1

Type of bacteria		Minimum inhibitory concentrations in U/ml	
		Penicillin No. 4	Carbenicillin
Pseudomonas aeruginosa	Bonn	16 – 32	200
	Walter	7	100
	F 41	25	100
	E 27 500	12.5	100
	V 10 818	25	100
	V 10 797	12.5	50
	V 10 887	12.5	100
	V 10 900	12.5	50
	A	12.5	25
Klebsiella-Aerobacter	60	<0.8	100
	62	1.6	100
	63	4 – 16	400
	69	1.6	>400
	70	3	400
	1852	>400	>400
	K 10	4 – 16	>400
	1871	6	400
	75	6	>400
aerogenes	418	3	400
Escherichia coli	14	<1	1.6
	A 261	32 – 64	400
	C 165	1 – 4	12.5
	183/58	1 – 4	12.5
	B	<0.8	–
	B 94	<0.8	1.6
	55 B 5	<0.8	–
	T 7	>400	>400
	T 20/2	>400	>400
	1465	>400	>400
	26/6	<0.8	3
	N	1.6	6
	S	32	400

TABLE 1 (Continued)

Type of bacteria		Minimum inhibitory concentrations in U/ml	
		Penicillin No. 4	Carbenicillin
Serratia marcescens	2	1.6	12.5
	3	12.5	400
	4	1.6	12.5
	6	1.6	12.5
	7	1.6	100
	9	<0.8	6
	13	<0.8	6
	K	<0.8	6
Providencia	930	<0.8	6
	933	12.5	3
	945	<0.8	3
Bacillus Proteus rettgeri	Sp.	0.8	1.6
	1 050	>400	>400
	824	>400	>400
mirabilis	Sp.	1.6	1.6
	G.	<0.4	1.6
	605	3	400
	1 235	1.6	3
morganii	Sp.	3	3
	932	6	6
	1 102	200	>800
vulgaris	1 017	1.6	3
	3 400	6	50
Haemophilus influenzae	2 689	0.25	1.6
	2 718	0.1	0.8
	2 786	0.06	1.6
	2 788	0.5	<0.4
	2 684	0.1	–

TABLE 1 (Continued)

Type of bacteria		Minimum inhibitory concentrations in U/ml	
		Penicillin No. 4	Carbenicillin
Streptococcus	8 709	12.5	200
faecalis	8 711	3	50
	8 698	1.6	100
Staphylococcus	BRL 1 756	200	200
aureus	133	1	1
	P 209	<0.8	<0.8
	SG 511	<0.8	<0.8

Table 2 gives the minimum inhibitory concentrations (MIC values) in U/ml of some penicillin compounds of the present invention, for a series of types of bacteria:

TABLE 2

Penicillin No.	Type of bacteria												
	Escherichia coli				*Prot. vulg.*	*Prot. morg.*	*Psdm. aerug.*		*Klebsiella*		*Staph. aur.*		*Strept. faec.*
	14	A 261	C 165	183/58	1017	932	Bonn	Walter	K 10	63	1756 E	133	ATCC 9790
1	<0.8	400	3	3	6	6	25	50	100	25	400	<0.8	25
2	<0.8	100	1.6	1.6	6	1.6	50	25	50	12.5	200	<0.8	50
3	<1	256	4	4	8	8	16	16	16	16	>256	4	64
4	<1	32–64	1–4	1–4	1.6	6	16–32	8	4–16	4–16	64–256	1	16–32
5	<1	256	4	4	4	32	32	32	32	16	>256	<1	32
6	4	>256	4	4	16	64	32	32	16	32	64	<1	32
7	<1	>256	4	<1	16	4	16	8	4	4	128	<1	16
8	4	>256	4	4	32	64	32	32	8	32	128	4	128
9	<1	>256	4	4	32	32	64	32	4	8	>256	4	128
10	<1	>256	4	4	8	4	64	256	8	8	>256	4	128
11	<1	>256	4	<1	16	8	32	16	4	4	64	<1	16
12	<1	64	4	<1	4	8	32*	32	4	8	256	<1	32
13	<1	128	4	<1	4	<1	16*	16	4	8	128	<1	16
14	<1	128	4	<1	4	<1	32*	32	4	4	128	<1	32

* = *Pseudomonas aeruginosa* F 41.

TABLE 2 (Continued)

Penicillin No.	Type of bacteria												
	Escherichia coli				*Prot. vulg.*	*Prot. morg.*	*Psdm. aerug.*		*Klebsiella*		*Staph. aur.*		*Strept. faec.*
	14	A 261	C 165	183/58	1017	932	Bonn	Walter	K 10	63	1756 E	133	ATCC 9790
19	4	>256	8	16	16	32	–	–	–	–	–	–	–
20	4	>256	8	64	16	8	8*	16	32	64	128	<1	32
21	<1	256	4	<1	4	4	32*	32	8	8	256	<1	64
Ampicillin	0.8	>400	6	200	400		200	200	100–200	100–200		<1	12.5
Carbenicillin	1.6	400	12.5	12.5	3	6	200	100	>400	400	200	1	

* = *Pseudomonas aeruginosa* F 41.

TABLE 2 (Continued)

Penicillin No.	Type of Bacteria												
	Escherichia coli				*Prot. vulg.*	*Prot. morg.*	*Psdm. aerug.*		*Klebsiella*		*Staph. aur.*		*Strept. faec.*
	14	A 261	C 165	183/58	1017	932	F 41	Walter	K 10	63	1756 E	133	ATCC 9790
22	4	>256	8	8	16	128	16	32	32	64	128	4	32
23	<1	128	4	<1	4	<1	16	32	8	8	64	<1	32
24	<1	512	2	<1	2	2	32	32	4	8	32	<1	16
25	8	>256	16	32	16	4	64	32	64	64	64	<1	16
26	4	>256	4	4	4	4	32	64	32	16	64	<1	8
27	0.5	>256	1	0.5	1	<1	32	32	4	4	64	<0.25	4
29	4	>256	16	32	64	128	16	16	64	64	256	<1	16
30	<1	>256	8	64	4	8	32	32	128	64	256	4	128
31	8	>256	32	128	>256	64	256	256	>256	>256	64	<1	32
32	4	>256	8	8	8	8	256	128	32	16	64	<1	16

Tables 1 and 2 indicate the superiority of the penicillin compounds in their *in vitro* action, as compared to the commercially available products ampicillin and carbenicillin.

Table 3 shows the effective dose (ED_{50}- values) in the case of mice infected intraperitoneally with the bacterium indicated. This demonstrates the superiority of the penicillin compounds according to the invention in animal experiments with Gram-negative bacteria as compared to carbenicilliin. Further, Table 3 also shows the good action against Gram-positive bacteria.

TABLE 3

Results of animal experiments with white mice for some of the penicillin compounds according to the invention (ED_{50} on subcutaneous treatment, in U/kg)

		Penicillin No.		
Type of bacteria	Carbenicillin	1	2	4
Klebsiella 63	>2 × 300,000	2 × 60,000	2 × 40,000	2 × 40,000
Klebsiella 1871	>1 × 500,000			1 × 350,000
Prot. vulg. 1017	2 × 50,000		2 × 25,000	2 × 25,000
Prot. morg. 932	2 × 75,000			2 × 75,000
Psdm. aerug. Walter	4 × 150,000			4 × 150,000
Psdm. aerug. F 41	4 × 100,000			4 × 25,000
	Propicillin			
Staph. aur. 133	2 × 2,000	2 × 3,000	2 × 4,000	2 × 2,500

Table 4 shows the extremely high level to which some of the penicillins according to the invention are tolerated.

TABLE 4

Penicillin No.	LD_{50} on intravenous injection into the vein of the tail of mice, in mg/kg
2	>3,000
4	>3,000

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 submultiple (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, gelatine 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. 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. C_{14}-alcohol with C_{16}-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, silicic 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 compositions 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 ground nut oil], glycerol, tetrahydrofufuryl 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 subjects of the medicaments of the invention is 500,000 to 90,000,000 units of active ingredient.

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 compounds will be administered perorally, parenterally (for example intramuscularly, intraperitoneally or, in particular, intravenously, and intravenously by continuous drip), rectally or locally.

In general it has proved advantageous to administer amounts of from 25,000 to 1,000,000 U/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 cases 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.

Finally, the invention provides an animal feedstuff comprising a penicillin compound according to the invention and a nutritious material.

The Examples which follow illustrate the invention without limiting it.

The α-aminobenzylpenicillin used in the Examples contained about 14% of water

but anhydrous α-aminobenzylpenicillins [compare British Patent Specification No. 1,003,868] can be employed equally well.

Unless expressly stated otherwise, "ampicillin" is intended to mean α-aminobenzylpenicillin with the D(−)-=R-configuration in the side-chain.

The β-lactam content was determined iodometrically. All penicillin compounds described here showed an IR-spectrum corresponding to their structure.

The NMR-spectra were recorded in CD_3OD solution and the signals indicated in the examples agree with the particular structure; the position of the signals is given in τ-values.

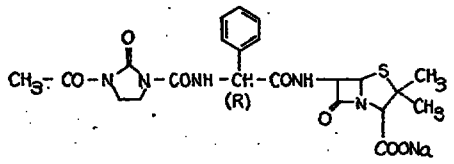
In calculating the analytical data, the water content is taken into account.

Under the heading: "Activity in animal experiments", "A" means that the particular penicillin, when used subcutaneously in mice against *Pseudomonas aeruginosa* F 41, is more active than carbenicillin, "B" denotes that it is more active against *Klebsiella* 63 than carbenicillin, "C" denotes that it is more active against *Klebsiella* 63 than cephalothin and "D" denotes that it is more active against *Klebsiella* 63 than cephalexin.

The figures (U/ml) quoted in the activities against certain bacteria are minimum inhibitory concentrations in the test tube series dilution test after 24 hours incubation.

Example 1.

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

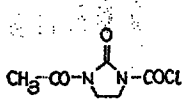


17.5 parts by weight of ampicillin were suspended in 80% (volume/volume) aqueous tetrahydrofuran (140 parts by volume) and sufficient triethylamine (approx. 6.3 parts by volume) was added dropwise whilst stirring, at 20°C, just to produce a clear solution and to give a pH value of from 7.5 to 8.2 (glass electrode). The mixture was cooled to 0°C and 7.6 parts by weight of 3-acetyl-imidazolidin-2-one-1-carbonyl chloride were added gradually in portions over the course of 30 minutes, while the mixture was stirred and kept at a pH value of from 7 to 8 by simultaneous addition of triethylamine. The mixture was stirred for 10 minutes at 0°C and subsequently further stirred at room temperature until no further addition of triethylamine was necessary to maintain a pH value of 7—8. 150 parts by volume of water were now added and the tetrahydrofuran was largely removed in a rotary evaporator at room temperature. The residual aqueous solution was extracted once by shaking with ethyl acetate, covered with 250 parts by volume of fresh ethyl acetate and acidified to pH 1.5—2.0 with dilute hydrochloric acid whilst being cooled with ice. The organic phase was separated off, washed twice with 50 parts by volume of water at a time and dried for 1 hour over anhydrous $MgSO_4$ in a refrigerator. After filtration, about 45 parts by volume of a 1 molar solution of sodium 2-ethyl-hexanoate in ether containing methanol were added to the solution of the penicillin. The mixture was now concentrated on a rotary evaporator until it had an oily consistency and was dissolved in a sufficient amount of methanol by vigorous shaking, and the solution was rapidly added dropwise, with vigorous stirring, to 500 parts by volume of ether which contained 10% by volume of methanol. The precipitate was allowed to settle for 30 minutes, the solution was decanted from the precipitate, and the latter was again suspended in ether, filtered off and washed with anhydrous ether. After drying over P_2O_5 in a vacuum desiccator, the sodium salt of the penicillin was obtained in the form of a white solid substance.

Yield: 95%
β-Lactam content: 84%
Calculated: C 48.3 H 4.9 N 12.8 S 5.8 wt %.
Found: C 48.6 H(6.2) N 11.7 S 5.6 wt %.
NMR-signals at τ = 2.3—2.7 (5H), 4.3 (1H), 4.5 (2H), 5.8 (1H), 6.15 (4H), 7.5 (3H), 8.4 (3H) and 8.45 ppm (3H).

The product showed only one antibiotically active spot in the electropherogram.
Activity in animal experiments: B and C
Activity against *E. coli* 183/58: 3
Activity against *Prot. morg.* 932: 6
Activity against *Psdm. aerug.* Bonn: 25
Activity against *Klebs.* 63: 25

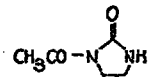
B) 3-Acetyl-imidazolidin-2-one-1-carbonyl chloride:



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

Yield: 81% Melting point = 104°C
Calculated: C 37.7 H 3.7 Cl 18.6 N 14.7 wt %.
Found: C 39.3 H 4.3 Cl 17.7 N 14.7 wt %.
IR-bands at 1798, 1740, 1690 and 1660 cm^{-1}.
NMR-signals at $\tau = 5.65$—6.3 (4H) and 7.45 ppm (3H)
According to the NMR-spectrum, the product still contained 5—10% of N-acetyl-imidazolidone, which however does not interfere in the reaction with ampicillin (Example 1A).

C) N-acetyl-imidazolid-2-one

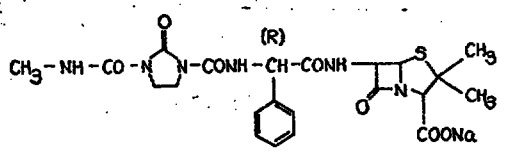


23.6 parts by weight of acetyl chloride in 100 parts by volume of tetrahydrofuran were added dropwise over the course of 60 minutes to a suspension of 25.8 parts by weight of imidazol-2-one in 350 parts by volume of dry tetrahydrofuran, at 0°C. The mixture was stirred for 3 hours at room temperature, 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 wt %.
Found: C 47.0 H 6.2 N 22.5 wt %.
IR-bands at 3230, 1730 and 1640 cm^{-1}.
NMR-signals at $\tau = 6.2$ (2H), 6.5 (2H) and 7.6 ppm (3H).

Example 2.

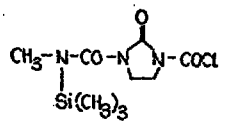
A) Sodium D - α - [(3 - methylaminocarbonyl - imidazolidin - 2 - on - 1 - yl)-carbonylamino] - benzylpenicillin:



This penicillin was produced as described in Example 1A from 6.5 parts by weight of 3-(N-methyl-N-trimethylsilyl-amino-carbonyl)-imidazolid-2-one-1-carbonyl chloride and 14 parts by weight of ampicillin.

Yield: 27%
β-Lactam content: 83%
Calculated: C 46.5 H 4.9 N 14.8 S 5.6 wt %.
Found: C 46.0 H 5.6 N 14.0 S 5.2 wt %.
IR-bands at 3330, 1765, 1722, 1672 and 1266 cm^{-1}.
NMR-signals at $\tau = 2.3$—2.8 (5H), 4.4 (1H), 4.55 (2H), 5.85 (1H), 6.25 (4H), 7.15 (3H), 8.45 (3H) and 8.5 ppm (3H).
Activity in animal experiments: B, C and D.
Activity against *E. coli* 183/68: 1.6
Activity against *Prot. morg.* 932: 1.6
Activity against *Psdm. aerug.* Walter: 25
Activity against *Klebsiella* 63: 12

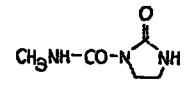
B) 3 - (N - methyl - N - trimethylsilyl - aminocarbonyl) - imidazolidin - 2 - one - 1-carbonyl chloride:



A suspension of 7.1 parts by weight of N-methylaminocarbonyl-imidazolid-2-one in 150 parts by volume of benzene and 12 parts by weight of triethylamine was treated dropwise over the course of 30 minutes with 13 parts by weight of trimethylchlorosilane, at room temperature, with stirring and the exclusion of moisture, and the mixture was subsequently kept under reflux for 24 hours. It was then cooled, the triethylamine hydrochloride was filtered off and rinsed with benzene, and the filtrate was treated with 5 parts by weight of phosgene in 20 parts by volume of benzene. The mixture was left to stand in a refrigerator overnight, the solvent was stripped off *in vacuo* and the residue was dried under an oil pump. The residue was suspended in a 1:1 (volume:volume) mixture of benzene and pentane and filtered off, the filtrate was evaporated to dryness and the residue was suspended in dry ether and again filtered off. The filtrate thus obtained was cooled in ice for approx. 1 hour, the precipitate which formed was again filtered off and the resulting solution was evaporated to dryness. The semi-solid mass was dried under an oil pump.

According to the NMR-spectrum the substance thus obtained consisted of a 3:1 mixture of 1-methylaminocarbonyl-imidazolid-2-one (NMR-signals at 6.1, 6.5 and 7.15 τ) and 3-(N-methyl-N-trimethylsilylamino-carbonyl)-imidazolidin-2-one-1-carbonyl chloride (NMR-signals at 6.0, 7.0 and 9.7 ppm) which could be reacted with ampicillin to give the corresponding penicillin (Example 2A).

C) N-(methylaminocarbonyl)-imidazolidin-2-one:



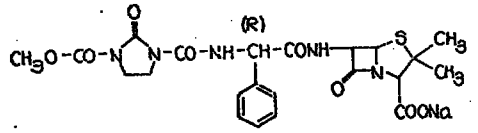
14.9 parts by weight of N-chlorocarbonylimidazolidone-2 were added in portions, under cooling with ice, to a solution of 20 parts by weight of a 50 wt % aqueous methylamine solution in 50 parts by weight of tetrahydrofuran which had been adjusted to a pH value of 8.5 with concentrated hydrochloric acid, and at the same time a pH value of 8.5 was maintained by simultaneous addition of triethylamine. Thereafter the mixture was further stirred until the pH value had not changed further in 15 minutes, even without addition of triethylamine. A pH value of 6.5 was established by adding HCl and the tetrahydrofuran was stripped off *in vacuo*. The product was filtered off, rinsed with a little ice-water and recrystallised from methanol.

Yield: 72% Melting point = 198°C.
Calculated: C 41.9 H 6.3 N 29.4 wt %.
Found: C 41.7 H 6.5 N 30.2 wt %.

IR-bands at 3220, 1728 and 1645 cm^{-1}.
NMR-signals at $\tau = 2.0$ (1H), 2.5 (1H), 6.2 (2H), 6.6 (2H) and 7.2 ppm (3H).

Example 3.

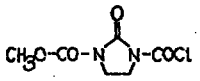
Sodium D - α[(3 - methoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino]-benzylpenicillin:



This penicillin was produced as described in Example 1 from 7.8 parts by weight of 3 - methoxy - carbonyl - imidazolidin - 2 - one - 1 - carbonyl chloride and 17.5 parts by weight of ampicillin.

Yield: 97%
β-Lactam content: 87%
Calculated: C 48.8 H 4.4 N 12.9 S 5.9 wt %.
Found: C 48.6 H(6.7) N 11.0 S 5.5 wt %.
IR-bands at 3300, 1775, 1740, 1667, 1605 and 1262 cm^{-1}.
NMR-signals at $\tau = 2.3$—2.8 (5H), 4.4 (1H), 4.5 (2H), 5.8 (1H), 6.15 (3H), 6.0—6.3 (4H), 8.4 (3H) and 8.5 ppm (3H).
The product only shows one antibiotically active spot in the electropherogram.
Activity in animal experiments: B and C.
Activity against *E. coli* 183/58: 4
Activity against *Prot. morg.* 932: 8
Activity against *Psdm. aerug.* Walter: 16
Activity against *Klebsiella* K 10: 16

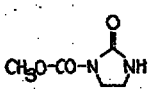
B) 3-Methoxycarbonyl-imidazolidin-2-one-1-carbonyl chloride



This carbamic acid chloride was produced as described in Example 1 B 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 wt %.
Found: C 34.8 H 3.4 Cl 17.1 N 13.6 wt %.
IR-bands at 1820, 1737, 1690 and 1260 cm^{-1}.
NMR-signals at $\tau = 5.7$—6.3 (4H) and 6.1 ppm (3H).

C) N-methoxycarbonyl-imidazolid-2-one

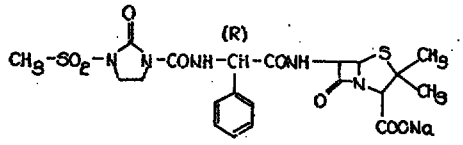


14.9 parts by weight of N-chlorocarbonyl-imidazolid-2-one were introduced into 70 parts by volume of ice-cold methanol and the mixture was stirred for 1 hour at room temperature and subsequently for 1 hour at 40—50°C. After the excess methanol had been stripped off, the residue was recrystallised from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

Yield: 55% Melting point = 185°C
Calculated: C 41.6 H 5.5 N 19.4 wt %.
Found: C 41.8 H 4.8 N 19.2 wt %.
IR-bands at 3320, 1745 and 1670 cm^{-1}.

Example 4.

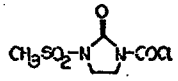
A) Sodium D - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin



This penicillin was produced as described in Example 1 A from 5.1 parts by weight of 3-methyl-sulphonyl-imidazolidin-2-one-1-carbonyl chloride and 9.3 parts by weight of ampicillin.

Yield: >90%
β-Lactam content: 81%
Calculated: C 42.7 H 4.6 N 11.8 S 10.8 wt %.
Found: C 42.7 H 5.4 N 11.6 S 11.4 wt %.
IR-bands at 3305, 1760, 1728, 1670, 1605, 1360 and 1174 cm^{-1}.
NMR-signals at $\tau = 2.3$—2.7 (5H), 4.35 (1H), 4.5 (2H), 5.8 (1H), 5.8—6.2 (4H), 6.65 (3H), 8.4 (3H) and 8.5 ppm (3H).
Activity in animal experiments: A, B, C and D
Activity against *E. coli* A 261: 32—64
Activity against *E. coli* 183/58: 1—4
Activity against *Proteus* 1017: 1.6
Activity against *Psdm. aerug.* Walter: 4—16
Activity against *Klebsiella* K 10: 4—16

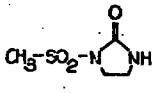
B) 1-Chlorocarbonyl-3-methylsulphonyl-imidazolid-2-one:



16.4 parts by weight of 1-methylsulphonyl-imidazolid-2-one in dioxane were boiled for 3 days with 27 parts by weight of trimethylchlorosilane and 20 parts by weight of triethylamine. The triethylamine hydrochloride with precipitated was filtered off, 11 parts by weight of phosgene were added to the filtrate and the mixture was left to stand overnight at room temperature. It was then evaporated to dryness and the residue 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 wt %.
Found: C 27.2 H 3.4 Cl 15.3 N 12.0 S 14.1 wt %.
NMR-signals at $\tau = 5.6$—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 manufactured successfully from 1-methylsulphonyl-imidazolid-2-one and excess phosgene in methylene chloride.

C) 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 imidazolidone-2 in 400 parts by volume of dry tetrahydrofuran and the mixture was stirred for 1 hour at 30—40°C and then heated under reflux for 1 hour. Thereafter the solvent was distilled off *in vacuo* and the residue was kept under an oil pump for 1 hour at 60°C. 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 wt %.
Found: C 29.0 H 5.0 N 17.2 S 19.6 wt %.
IR-bands at 3250, 3115, 1715, 1350 and 1160 cm^{-1}.
NMR-signals at $\tau = 2.4$ (1H), 6.2 (2H), 6.5 (2H) and 6.8 ppm (3H).

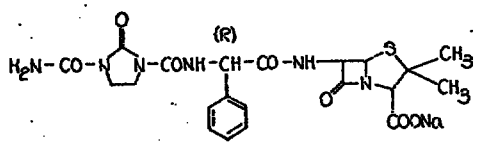
Instructions 2

80 parts by weight of methanesulphochloride followed by 56 parts by weight of triethylamine were added dropwise over the course of 30 minutes, whilst stirring, to a suspension of 43 parts by weight of imidazolidone-2 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 hour at 45°C, the solvent was then stripped off *in vacuo*, the residue which remained was extracted twice with 150 parts by volume of chloroform at a time, and the crystals which remained were recrystallised from methanol.

Yield: 49%. The product agrees, according to melting point and IR-spectrum, with the N-methylsulphonylimidazolid-2-one described above.

Example 5.

A) Sodium D - α - [(3 - aminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonyl-amino] - benzylpenicillin:

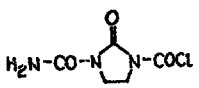


16.2 parts by weight of ampicillin in 170 parts by volume of methylene chloride were stirred with 10 parts by weight of triethylamine and 20 parts by weight of anhydrous sodium sulphate for 90 minutes at room temperature. Thereafter the mixture was filtered and the solution thus obtained was treated, at 0°C, with a suspension of 11 parts by weight of 3-aminocarbonyl-imidazolidin-2-one-1-carbonyl chloride in 30 parts by volume of methylene chloride. The mixture was stirred for 1 hour at 0°C and 1 hour at room temperature and poured into 200 parts by volume of water, the pH was adjusted to 7 and the methylene chloride was stripped off *in vacuo*. The aqueous solution thus obtained was extracted once with 100 parts by volume of ethyl acetate, covered with 300 parts by volume of fresh ethyl acetate and adjusted to pH = 1.5—2.0 with dilute hydrochloric acid, whilst cooling with ice. The precipitate formed which was relatively sparingly soluble in ethyl acetate and consisted of the slightiy contaminated free acid of the penicillin, was filtered off and washed with water. The organic phase was now separated from the water, washed once with water and dried over $MgSO_4$, and after addition of sodium 2-ethylhexanoate the penicillin was obtained in the form of its sodium salt, as described in Example 1A.

Yield: 25%
β-Lactam content: 76%
Calculated: C 45.5 H 4.7 N 15.2 S 5.8 wt %.
Found: C 45.6 H 6.0 N 13.7 S 5.6 wt %.
IR-bands at 3300, 1760, 1725, 1670 and 1275 cm^{-1}.
NMR-signals at $\tau = 2.3$—2.8 (5H), 4.4 (1H), 4.5 (2H), 5.8 (1H), 6.2 (4H), 8.4 (3H) and 8.5 ppm (3H).

The free penicillin-acid obtained in 37% yield showed a β-lactam content of 65% and according to analysis and spectra had the correct structure.
Activity in animal experiments: B, C and D.
Activity against *E. coli* 183/58: 4
Activity against *Proteus* 1017: 4
Activity against *Psdm. aerug.* Walter: 32
Activity against *Klebsiella* 63: 16

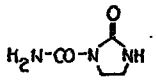
B) 3-Aminocarbonyl-imidazolidin-2-one-1-carbonyl chloride:



The mixture of 7.7 parts by weight of N-aminocarbonyl-imidazolid-2-one, 16.3 parts by weight of trimethylchlorosilane, 15 parts by weight of triethylamine and 100 parts by volume of benzene was converted, in the manner described in Example 2 B, firstly into the silyl compound and subsequently, with 6 parts by weight of phosgene, into the carbamic acid chloride.

Yield: 11.6 parts by weight.
IR-bands at 3400, 3300, 2950, 2895, 1795 and 1600 cm^{-1}.

C) N-aminocarbonyl-imidazolid-2-one



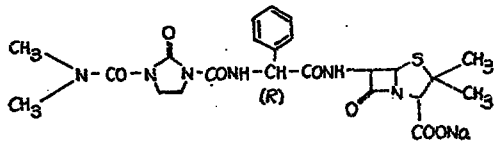
29.7 parts by weight of N-chlorocarbonyl-imidazolid-2-one, were reacted at pH = 8.5 and room temperature with 20 parts by volume of 25% strength aqueous solution of NH_3 in 80% (volume/volume) aqueous tetrahydrofuran. After stripping off the tetrahydrofuran *in vacuo*, the product which precipitated was filtered off and washed with a little ice water. Yield after drying over P_2O_5 in a desiccator: 62%. Melting point = 200°C.

Calculated: C 37.2 H 5.4 N 32.6 wt %.
Found: C 37.7 H 5.3 N 33.2 wt %.
IR-bands at 3345, 3260, 3200, 1740, 1677 and 1590 cm^{-1}.

A further 12% of the product were obtainable from the filtrate of the main precipitation, evaporated to dryness, by extracting it by boiling with several portions of acetone (melting point = 199°C, IR-bands as for the main amount).

Example 6.

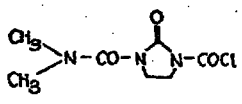
A) Sodium D - α - [(3 - dimethylaminocarbonyl - imidazolidin - 2 - on - 1 - yl)-carbonylamino] - benzylpenicillin:



This penicillin was produced as described in Example 1 A from 7.1 parts by weight of 3-dimethylaminocarbonyl-imidazolidin-2-one-1-carbonyl chloride and 13 parts by weight of ampicillin.

Yield: 76%
β-Lactam content: 93%
Calculated: C 47.9 H 5.1 N 14.6 S 5.5 wt %.
Found: C 48.1 H 5.7 N 14.0 S 6.1 wt %.
IR-bands at 3290, 1760, 1722, 1662, 1600 and 1260 cm^{-1}.
IMR-signals at τ = 2.4—2.75 (5H), 4.4 (1H), 4.53 (2H), 5.8 (1H), 6.2 (4H), 7.0 (6H), 8.43 (3H) and 8.5 ppm (3H).
Activity in animal experiments: B, C and D
Activity against *E. coli* 183/58: 4
Activity against *Proteus* 1017: 16
Activity against *Psdm. aerug.* Walter: 32
Activity against *Klebsiella* K 10: 16

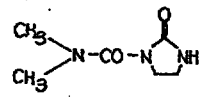
B) 3-Dimethylaminocarbonyl-imidazolidin-2-one-1-carbonyl chloride:



This carbamic acid chloride was produced as described in Example 1 B from 6 parts by weight of N-dimethylaminocarbonyl-imidazolidone-2. Crystalline substance.

Yield: 93%
Calculated: C 38.3 H 4.6 Cl 16.2 N 19.1 wt %.
Found: C 38.8 H 5.0 Cl 16.4 N(17.3) wt %.
IR-bands at 2930, 1800, 1758, 1720 and 1675 cm^{-1}.

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

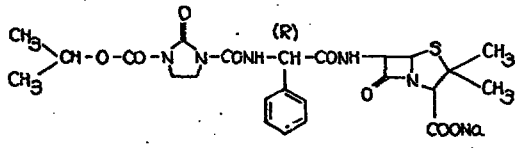


A mixture of 50 parts by volume of a 50 wt %. aqueous dimethylamine solution and 70 parts by volume of tetrahydrofuran was adjusted to pH = 8 with 5 N hydrochloric acid. 14.9 parts by weight of N-chlorocarbonyl-imidazolid-2-one were added gradually thereto whilst stirring and cooling with ice and the pH value was maintained by simultaneous addition of further dimethylamine solution. The mixture was further stirred until the pH was constant, the tetrahydrofuran was then stripped off and the residue was saturated with sodium chloride and repeatedly extracted with ethyl acetae. The organic solution was washed with saturated sodium chloride solution, dried over $MgSO_4$ and filtered, and the solvent was evaporated off. The residue was recrystallised from acetone and dried in a vacuum desiccator over P_2O_5.

Yield: 36% Melting point = 135°C
Calculated: C 45.9 H 6.4 N 26.8 wt %.
Found: C 45.9 H 6.8 N 27.1 wt %.
IR-bands at 3280, 1740, 1715 and 1660 cm^{-1}.

Example 7.

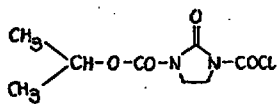
A) Sodium D - α - [(3 - i - propyloxycarbonyl - imidazolidin - 2 - on - 1 - yl)-carbonylamino] - benzylpenicillin:



This penicillin was produced as described in Example 1 A from 6.3 parts by weight of 3-(i-propyloxycarbonyl)-imidazolidin-2-one-1-carbonyl chloride and 10.9 parts by weight of ampicillin.

Yield: 62%
β-Lactam content: 85%
Calculated: C 49.1 H 5.1 N 11.9 S 5.5 wt %.
Found: C 49.2 H 6.2 N 11.6 S 5.6 wt %.
IR-bands at 3300, 1765, 1665, 1600 and 1260 cm^{-1}.
NMR-signals at τ = 2.3—2.8 (5H), 4.3 (1H), 4.5 (2H), 4.5—5.1 (1H), 5.8 (1H), 6.1 (4H), 8.4 (6H) and 8.6 ppm (6H).
Activity in animal experiments: B, C and D.
Activity against *E. coli* 183/58: <1
Activity against *Proteus morg.* 932: 4
Activity against *Psdm. aerug.* Walter: 8
Activity against *Klebsiella* K 10: 4

B) 3-(i(Propyloxycarbonyl)-imidazolidin-2-one-1-carbonyl chloride:

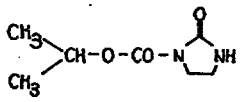


This carbamic acid chloride was produced as described in Example 1 B from 11 parts by weight of N-i-propyloxycarbonyl-imidazolidone-2, 13.5 parts by weight of trimethylchlorosilane and 7 parts by weight of phosgene.

Recrystallisation from acetone/pentane.
Yield: 6.8 parts by weight. Melting point = 98—102°C.
According to the NMR-spectrum and the analysis, the substance consisted of 65% of end product and 35% of starting material, which however did not interfere with the reaction to give the penicillin.

Calculated for 65% of end product and 35% of starting material:
C 43.7 H 5.5 Cl 9.9 N 13.5 wt %.
Found: C 44.3 H 5.5 Cl 10.1 N 14.5 wt %.
IR-bands at 3220, 1820, 1760, 1740, 1695 and 1685 cm^{-1}
NMR-signals at $\tau = 4.85$, 6.1 and 8.6 ppm (end product and at $\tau = 4.9$, 6.4 and 8.7 ppm (starting material)

C) N-(i(propyloxycarbonyl)-imidazolid-2-one

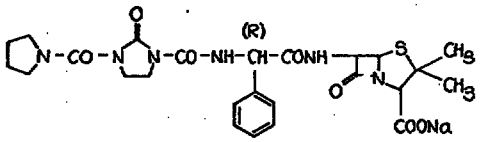


14.9 parts by weight of N-chlorocarbonylimidazolid-2-one in 100 parts by volume of i-propanol and 100 parts by volume of dioxane were warmed to 50°C for 3 hours. After stripping off the solvent, the residue was recrystallised from acetone.

Yield: 67% Melting point = 86°C
IR-bands at 3320, 1764 and 1670 cm^{-1}.
NMR-signals at $\tau = 5.05$ (1H), 5.7—6.75 (5H) and 8.75 ppm (6H).

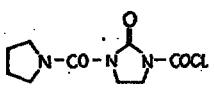
Example 8.

A) Sodium D - α - [(3 - pyrrolidyl - N - carbonyl - imidazolidin - 2 - on - 1 - yl)-carbonylamino] - benzylpenicillin



This penicillin was produced as described in Example 1 A from 8 parts by weight of 3-pyrrolidyl-N-carbonyl-imidazolidin-2-one-1-carbonyl chloride and 13.2 parts by weight of ampicillin.
Yield: 82%
β-Lactam content: 95%
Calculated: C 49.2 H 5.3 N 13.8 wt %.
Found: C 49.3 H(7.1) N 13.4 wt %.
IR-bands at 3290, 1760, 1720, 1655, 1600 and 1250 cm^{-1}.
NMR-signals at $\tau = 2.4$—2.8 (5H), 4.4 (1H), 4.55 (2H), 5.8 (1H), 6.2 (4H), 6.3—6.6 (4H), 7.9—8.3 (4H), 8.45 (3H) and 8.5 ppm (3H).
Activity in animal experiments: A, B and C
Activity against *E. coli* 183/58: 4
Activity against *Proteus* 1017: 32
Activity against *Psdm. aerug.* Walter: 32
Activity against *Klebsiella* K 10: 8

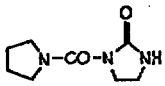
B) 3-(Pyrrolidyl-N-carbonyl)-imidazolidin-2-one-1-carbonyl-chloride



This carbamic acid chloride was produced as described in Example 1 B from 9.2 parts by weight of N-(pyrrolidyl-N-carbonyl)-imidazolidone-2, 13.6 parts by weight of trimethylchlorosilane and 5.6 parts by weight of phosgene. Recrystallisation from acetone/ether.

Yield: 1st fraction of melting point = 125°C: 71%
2nd fraction of melting point = 120—122°C: 25%
1st fraction:
Calculated: C 44.0 H 4.9 Cl 14.5 N 17.1 wt %.
Found: C 44.1 H 5.3 Cl 15.0 N 16.8 wt %.
IR-bands at 1795, 1755, 1725 and 1660 cm^{-1}.

C) N-(pyrrolidyl-N-carbonyl)-imidazolid-2-one

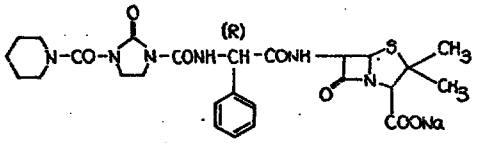


This substance was produced as described in Example 6 C from N-chlorocarbonyl-imidazolidone-2 and pyrrolidine.

Yield: 56% Melting point = 155°C
Calculated: C 52.3 H 7.1 N 22.9 wt %.
Found: C 51.5 H 7.0 N 22.6 wt %.
IR-bands at 3240, 1720, 1698, 1647 and 1620 cm^{-1}.
NMR-signals at τ = 6.0—6.8 (8H) and 8.0—8.3 (4H)

Example 9.

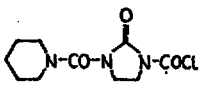
A) Sodium D - α - [(3 - piperidyl - N - carbonyl - imidazolidin - 2 - on - 1 - yl)-carbonylamino] - benzylpenicillin



This penicillin was manufactured in the manner described in Example 1 A from 5.0 parts by weight of 3-(piperidyl-N-carbonyl)-imidazolidin-2-one-1-carbonyl chloride and 7.6 parts by weight of ampicillin.

Yield: 92%
β-Lactam content: 94%
Calculated: C 51.0 H 5.4 N 13.7 S 5.2 wt %.
Found: C 50.7 H(6.8) N 13.5 S 5.7 wt %.
IR-bands at 3295, 3050, 1765, 1725, 1667, 1608 and 1265 cm^{-1}.
NMR-signals at τ = 2.3—2.7 (5H), 4.3 (1H), 4.65 (2H), 5.8 (1H), 6.2 (4H), 6.3—6.6 (4H) and 8.1—8.5 ppm (12H).
Activity in animal experiments: B and C
Activity against *E. coli* 183/58: 4
Activity against *Proteus* 1017: 32
Activity against *Psdm. aerug.* Walter: 32
Activity against *Klebsiella* K 10: 4

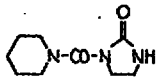
B) 3-(Piperidyl-N-carbonyl)-imidazolidin-2-one-1-carbonyl chloride



This carbamic acid chloride was produced as described in Example 1 B from 15.7 parts by weight of N-(piperidyl-N-carbonyl)-imidazolidone-2, 21.7 parts by weight of trimethylchlorosilane and 8.4 parts by weight of phosgene.

Recrystallisation from acetone/ether.
Yield: 1st fraction of melting point = 117°C: 27.5%
2nd fraction of melting point = 112°C: 49%
1st fraction:
Calculated: C 46.3 H 5.4 Cl 13.7 N 16.2 wt %.
Found: C 46.3 H 5.8 Cl 14.6 N 15.8 wt %.
IR-bands at 3060, 1793, 1710, 1659 and 1234 cm^{-1}.

C) N-(piperidyl-N-carbonyl)-imidazolid-2-one

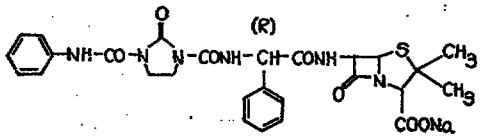


This substance was produced as described in Example 6 C from N-chlorocarbonyl-imidazolid-2-one and piperidine.

Recrystallisation from nitromethane.
Yield: 85% Melting point = 187°C
Calculated: C 54.8 H 7.6 N 21.3 wt %.
Found: C 55.2 H 7.8 N 20.3 wt %.
IR-bands at 3240, 1710, 1675 and 1640 cm^{-1}.
NMR-signals at τ = 6.0—7.0 (8H) and 8.0—8.6 ppm (6H).

Example 10.

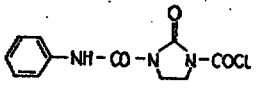
A) Sodium D - α - [(3 - phenylaminocarbonyl - imidazolidin - 2 - on - 1 - yl)-carbonylamino] - benzylpenicillin



This penicillin was produced as described in Example 1 A from 2.4 parts by weight of 3-(phenylaminocarbonyl)-imidazolidin-2-one-1-carbonyl chloride and 4.4 parts by weight of ampicillin.

Yield: 54%
β-Lactam content: 86%
Calculated: C 50.9 H 4.9 N 13.2 S 5.0 wt %.
Found: C 51.3 H 5.5 N 12.2 S 5.2 wt %.
IR-bands at 3390, 3290, 1782, 1720, 1678 and 1598 cm^{-1}.
NMR-signals at τ = 2.3—3.0 (10H), 4.4 (1H), 4.5 (2H), 5.8 (1H), 6.1 (4H), 8.4 (3H) and 8.5 ppm (H).
Activity in animal experiments: B and C
Activity against *E. coli* 183/58: 4
Activity against *Proteus morg.* 932: 4
Activity against *Klebsiella* K 10: 8

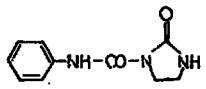
B) 3-(Phenylaminocarbonyl)-imidazolidin-2-one-1-carbonyl chloride



This carbamic acid chloride was produced as described in Example 1 B from 15.0 parts by weight of N-phenylaminocarbonyl-imidazolid-2-one, 15.8 parts by weight of trimethylchlorosilane and 7.2 parts by weight of phosgene.

Recrystallisation from acetone/pentane.
Yield: 12% Melting point = 198—200°C
A further precipitate of 8.3 parts by weight was considerably less pure.
IR-bands at 3240, 1785, 1715, 1690 and 1598 cm^{-1}.

C) N-phenylaminocarbonyl-imidazolid-2-one



10.2 parts by weight of aniline were first introduced into 120 parts by volume of 80% (volume/volume) aqueous tetrahydrofuran at pH = 8 and 14.9 parts by weight of N-chlorocarbonyl-imidazolid-2-one were added in portions at room temperature whilst stirring and keeping the pH value at 7—8 by simultaneous addition of triethylamine. The mixture was further stirred until the pH was constant, 80 parts by volume of water were added, the tetrahydrofuran was stripped off *in vacuo*, the pH was adjusted to 2.5 and after standing for one hour in an ice bath the product which had precipitated was filtered off. It was washed with ice water and dried over P_2O_5 in a vacuum desiccator.

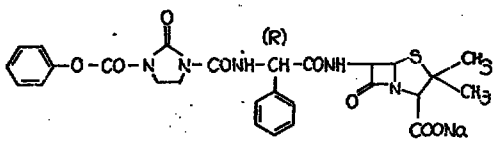
Yield: 91% Melting point = 164°C

Recrystallisation from acetone gave a product also melting at 164°C, in a yield of 78%.

Calculated: C 58.5 H 5.4 N 20.5 wt %.
Found: C 59.0 H 5.4 N 20.7 wt %.
IR-bands at 3275, 3090, 1735—1715, 1658, 1616 and 1600 cm^{-1}.

Example 11.

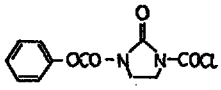
A) Sodium D - α - [(3 - phenoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin



This penicillin was produced as described in Example 1 A from 5 parts by weight of 3-phenoxycarbonyl-imidazolidin-2-one-1-carbonyl chloride and 8.1 parts by weight of ampicillin.

Yield: 42%
β-Lactam content: 88% (determined from the analytical Craig distribution chromatogram)
Calculated: C 53.7 H 4.3 N 11.6 S 5.3 wt %.
Found: C 53.5 H(5.8) N 11.1 S 5.4 wt %.
IR-bands at 3300, 3050, 1775, 1740 (shoulder), 1670, 1600 and 1198 cm^{-1}.
NMR-signals at $\tau = 2.3$—2.9 (10H), 4.3 (1H), 4.5 (2H), 5.8 (1H), 6.05 (4H), 8.4 (3H) and 8.5 ppm (3H).
Activity in animal experiments: B and C
Activity against *E. coli* 183/58: ≤ 1
Activity against *Prot. morg.* 932: 8
Activity against *Psdm. aerug.* Walter: 16
Activity against *Klebsiella* K 10: 4

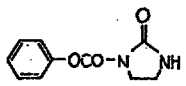
B) 3-Phenoxycarbonyl-imidazolidin-2-one-1-carbonyl chloride:



This carbamic acid chloride was produced as described in Example 1 B from 11 parts by weight of N-phenoxycarbonyl-imidazolidone-2, 11.7 parts by weight of trimethylchlorosilane and 5.3 parts by weight of phosgene. Recrystallisation from acetone/pentane.

Yield: 21% Melting point approx. 130°C
IR-bands at 1780, 1758, 1682 and 1594 cm^{-1}.

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

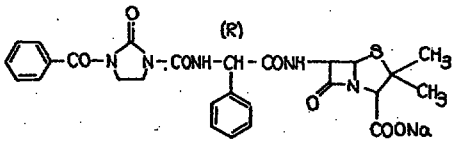


12.7 parts by weight of sodium phenolate were dissolved in 120 parts by volume of 80% (volume/volume) tetrahydrofuran and the solution was adjusted to pH = 8. 14.9 parts by weight of N-chlorocarbonyl-imidazolid-2-one were now introduced whilst stirring and keeping the pH value constant at 8 by simultaneous addition of triethylamine. The mixture was further stirred until the pH remained constant even without addition of triethylamine. 100 parts by volume of water were now added, the tetrahydrofuran was stripped off *in vacuo*, the residue was adjusted to pH = 10 with sodium hydroxide solution, and the solution was extracted with ethyl acetate. The organic solution was washed with water, dried over $MgSO_4$ and evaporated and the residue was dried under an oil pump at 60°C for 1 hour and recrystallised from acetone.

Yield: 56% Melting point = 182°C
Calculated: C 58.3 H 4.9 N 13.6 wt %.
Found: C 58.5 H 5.1 N 13.6 wt %.
IR-bands at 3260, 3110, 3050, 1780—1760, 1695, 1684, 1597 and 1182 cm^{-1}.

Example 12.

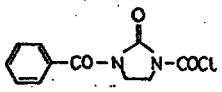
A) Sodium D - α - [(3 - benzoyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:



This penicillin was produced as described in Example 1 A from 5.5 parts by weight of 3-benzoyl-imidazolidin-2-one-1-carbonyl chloride and 10.1 parts by weight of ampicillin.

Yield: 92%
β-Lactam content: 89%
Calculated: C 49.2 H 5.2 N 10.8 S 4.9 wt %.
Found: C 49.2 H 5.3 N 10.8 S 5.2 wt %.
IR-bands at 3220, 3050, 1755, 1725 and 1667 cm^{-1}.
NMR-signals at τ = 2.2—2.8 (10H), 4.4 (1H), 4.55 (2H), 5.85 (1H), 6.05 (4H), 8.4 (3H) and 8.5 ppm (3H).

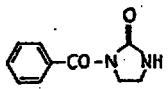
B) 3-Benzoyl-imidazolidin-2-one-1-carbonyl chloride:



This carbamic acid chloride was produced as described in Example 1 B from 4.8 parts by weight of N-benzoyl-imidazolid-2-one, 4.4 parts by weight of trimethylchlorosilane and 2.8 parts by weight of phosgene.

Yield: 100% Melting point = 153—4°C
Calculated: C 52.2 H 3.6 Cl 14.0 N 11.1 wt %.
Found: C 51.2 H 4.4 Cl 13.2 N 11.1 wt %.
IR-bands at 3060, 1768, 1725 and 1672 cm^{-1}.
NMR-signals at τ = 2.5 (5H) and 6.0 ppm (4H)

C) N-benzoyl-imidazolid-2-one

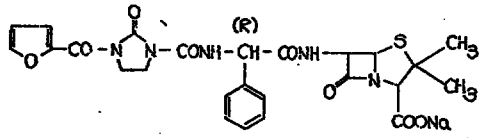


8.6 parts by weight of imidazolid-2-one in 100 parts by volume of dry tetrahydrofuran were treated with 15.5 parts by weight of benzoyl chloride in 30 parts by volume of tetrahydrofurane over the course of 15 minutes, at 5—10°C, and the mixture was subsequently stirred for 3 hours at 10°C. The solvent was stripped off, the residue was shaken with a mixture of chloroform and aqueous $NaHCO_3$ solution for 15 minutes, the chloroform was separated off, the water was again extracted with chloroform and the combined organic phases were washed with water, dried over $MgSO_4$ and evaporated. The residue was recrystallised from ethyl acetate/ether.

Yield: 30% Melting point = 169—70°C
Calculated: C 63.2 H 5.3 N 14.8 wt %.
Found: C 63.0 H 5.3 N 14.8 wt %.
IR-bands at 3190, 3110, 1742, 1718 and 1655 cm^{-1}.
NMR-signals at τ = 2.2—2.9 (5H), 3.9 (1H), 6.0 (2H) and 6.6 ppm (2H).

Example 13.

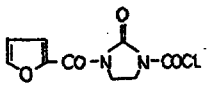
A) Sodium D - α - [(3 - furoyl(2) - imidazolidin - 2 - on - 1 - yl) - carbonyl-amino] - benzylpenicillin



This penicillin was produced as described in Example 1 A from 6.0 parts by weight of 3-furoyl(2)-imidazolidin-2-one-1-carbonyl chloride and 12.1 parts by weight of ampicillin.

Yield: 90%
β-Lactam content: 97%
Calculated: C 50.0 H 4.4 N 11.6 S 5.3 wt %.
Found: C 49.9 H 4.9 N 11.1 S 6.1 wt %.
IR-bands at 3300, 1770 (shoulder), 1740, 1670, 1605 and 1260 cm^{-1}.
NMR-signals at τ = 2.2 (1H), 2.3—2.8 (6H), 3.4 (1H), 4.35 (1H), 4.55 (2H), 5.8 (1H), 6.1 (4H), 8.45 (3H) and 8.5 ppm (3H).

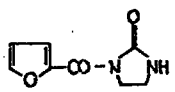
B) 3-Furoyl(2)-imidazolidin-2-one-1-carbonyl chloride



This carbamic acid chloride was produced as described in Example 1 B from 9 parts by weight of N-furoyl(2)-imidazolid-2-one, 8.7 parts by weight of trimethylchlorosilane and 6.0 parts by weight of phosgene.

Recrystallisation from benzene.
Yield: 55% Melting point = 119°C
Calculated: C 44.5 H 2.9 Cl 14.6 N 11.5 wt %.
Found: C 45.0 H 3.6 Cl 13.4 N 11.5 wt %.
IR-bands at 3150, 3100, 1800, 1745, 1715, 1650, 1620 and 1255 cm^{-1}.
NMR-signals at τ = 2.3 (1H), 2.5 (1H), 3.4 (1H) and 5.9 ppm (4H).

C) N-furoyl(2)-imidazolid-2-one

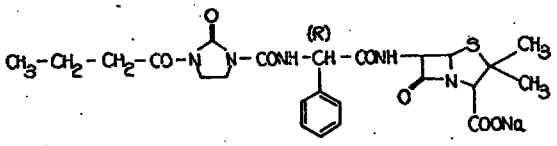


This substance was produced as described in Example 12 C from imidazolid-2-one and furane-α-carboxylic acid chloride. Instead of stirring at 10°C, the mixture was stirred for a further 3 hours at 30—40°C. Recrystallisation from nitromethane.

Yield: 53% Melting point = 144—6°C.
Calculated: C 53.2 H 4.5 N 15.6 wt %.
Found: C 51.2 H 4.5 N 15.3 wt %.
IR-bands at 3245, 3120, 1740, 1622, 1560, 1257 and 1240 cm^{-1}.
NMR-signals at τ = 2.25 (1H), 2.6 (1H), 3.35 (1H), 6.0 (2H) and 6.4 ppm (2H).

Example 14.

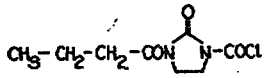
A) Sodium D - α - [(3 - n - butyryl - imidazolidin - 2 - on - 1 - yl) - carbonyl-amino] - benzylpenicillin



This penicillin was produced as described in Example 1 A from 6.0 parts by weight of 3-n-butyryl-imidazolidin-2-one-1-carbonyl chloride and 11.3 parts by weight of ampicillin.

Yield:—100%
β-Lactam content: 93.5%.
Calculated: C 50.5 H 5.3 N 12.2 S 5.6 wt %.
Found: C 50.1 H 6.0 N 11.8 S 6.7 wt %.
IR-bands at 3310, 3055, 1760, 1730, 1680, 1603, 1265 and 1230 cm^{-1}.
NMR-signals at τ = 2.3—2.8 (5H), 4.4 (1H), 4.5 (2H), 5.8 (1H), 6.25 (4H), 7.1 (2H), 8.2 (2H), 8.4 (3H), 8.5 (3H) and 9.0 ppm (3H).

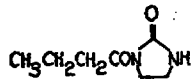
B) 3-n-Butyryl-imidazolidin-2-one-1-carbonyl chloride



This carbamic acid chloride was produced as described in Example 1 B from 10.0 parts by weight of N-n-butyryl-imidazolid-2-one, 11.4 parts by weight of trimethyl-chlorosilane and 7.0 parts by weight of phosgene. It was twice recrystallised from acetone/pentane.

Yield: 65% Melting point = 103°C
Calculated: C 40.2 H 4.4 Cl 14.9 N 11.8 wt %.
Found: C 40.2 H 4.8 Cl 14.7 N 11.7 wt %.
IR-bands at 3060, 1792, 1722, 1686 and 1220 cm^{-1}.
NMR-signals at τ = 6.0 (4H), 7.1 (2H), 8.4 (2H) and 9.0 ppm (3H).

C) N-n-butyryl-imidazolid-2-one



This substance was produce as described in Example 12 C from imidazolidone-2 and n-butyryl chloride. Instead of stirring at 10°C, the mixture was stirred for a further hour at room temperature and an hour at 50°C. Recrystallise twice from methanol.

Yield: 36% Melting point = 96°C
Calculated: C 53.9 H 7.7 N 18.0 wt %.
Found: C 53.5 H 7.6 N 18.3 wt %.
IR-bands at 3200, 3120, 1740, 1662 and 1262 cm^{-1}.
NMR-signals at τ = 6.15 (2H), 6.5 (2H), 7.2 (2H), 8.4 (2H), and 9.1 ppm (3H).

Example 15.

If, as described in Example 1 A, 0.05 mol of:—
3-acetyl-imidazolidin-2-one-1-carbonyl chloride,
3-methylaminocarbonyl-imidazolidin-2-one-1-carbonyl chloride,
3-methoxycarbonyl-imidazolidin-2-one-1-carbonyl chloride,
3-methylsulphonyl-imidazolidin-2-one-1-carbonyl chloride,
3-aminocarbonyl-imidazolidin-2-one-1-carbonyl chloride,
3-phenoxycarbonyl-imidazolidin-2-one-1-carbonyl chloride,
3-furoyl(2)-imidazolidin-2-one-1-carbonyl chloride or
3-ethyl-sulphonyl-imidazolidin-2-one-1-carbonyl chloride
are reacted with 0.05 mol of:—
α-amino-p-methylbenzylpenicillin,
α-amino-p-methoxy-benzylpenicillin,
α-amino-p-methylthio-benzylpenicillin,
α-amino-p-hydroxy-benzylpenicillin,
α-amino-p-chlorobenzylpenicillin,
α-amino-p-nitro-benzylpenicillin,
α-amino-α-thienyl(2)-methylpenicillin or
α-amino-α-thienyl(3)-methylpenicillin,
the following penicillins are obtained in the form of their sodium salts:—
α-[(3-acetyl-imidazolidin-2-on-1-yl)-carbonylamino]-p-methylbenzylpenicillin,
α-[(3-acetyl-imidazolidin-2-on-1-yl)-carbonylamino]-p-methoxybenzylpenicillin,
α-[(3-acetyl-imidazolidin-2-on-1-yl)-carbonylamino]-p-methylthiobenzylpenicillin,
α-[(3-acetyl-imidazolidin-2-on-1-yl)-carbonylamino]-p-hydroxybenzylpenicillin,
α-[(3-acetyl-imidazolidin-2-on-1-yl)-carbonylamino]-p-chlorobenzylpenicillin,
α-[(3-acetyl-imidazolidin-2-on-1-yl)-carbonylamino]-p-nitrobenzylpenicillin,
α-[(3-acetyl-imidazolidin-2-on-1-yl)-carbonylamino]-α-thienyl(2)-methylpenicillin,
α-[(3-acetyl-imidazolidin-2-on-1-yl)-carbonylamino]-α-thienyl(3)-methylpenicillin,
α - [(3 - methoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - methoxybenzylpenicillin,
α - [(3 - methoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p-methylthiobenzylpenicillin,
α - [(3 - methoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p-hydroxybenzylpenicillin,
α - [(3 - methoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p-chlorobenzylpenicillin,
α - [(3 - methoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - nitrobenzylpenicillin,
α - [(3 - methoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α-thienyl(2) - methylpenicillin,
α - [(3 - methoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α-thienyl(3) - methylpenicillin,
α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p-methylbenzylpenicillin,
α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p-methoxybenzylpenicillin,
α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p-methylthiobenzylpenicillin,
α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p-hydroxybenzylpenicillin,
α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p-chlorobenzylpenicillin,
α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - nitrobenzylpenicillin,
α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α-thienyl(2) - methylpenicillin,
α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α-thienyl(3) - methylpenicillin,
α - [(3 - aminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p-methylbenzylpenicillin,
α - [(3 - methylaminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p-methylbenzylpenicillin,
α - [(3 - methylaminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p-methoxybenzylpenicillin,

α - [(3 - methylaminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p-methylthiobenzylpenicillin,
α - [(3 - methylaminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p-hydroxybenzylpenicillin,
α - [(3 - methylaminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p-chlorobenzylpenicillin,
α - [(3 - methylaminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p-nitrobenzylpenicillin,
α - [(3 - methylaminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α-thienyl(2) - methylpenicillin,
α - [(3 - methylaminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α-thienyl(3) - methylpenicillin,
α - [(3 - methoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p-methylbenzylpenicillin,
α - [(3 - aminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - methoxybenzylpenicillin,
α - [(3 - aminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - methylthiobenzylpenicillin,
α - [(3 - aminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - hydroxybenzylpenicillin,
α - [(3 - aminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - chlorobenzylpenicillin,
α - [(3 - aminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - nitrobenzylpenicillin,
α - [(3 - aminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl-(2) - methylpenicillin,
α - [(3 - aminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl-(3) - methylpenicillin,
α - [(3 - phenoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - methylbenzylpenicillin,
α - [(3 - phenoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - methoxybenzylpenicillin,
α - [(3 - phenoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - methylthiobenzylpenicillin,
α - [(3 - phenoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - hydroxybenzylpenicillin,
α - [(3 - phenoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - chlorobenzylpenicillin,
α - [(3 - phenoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - nitrobenzylpenicillin,
α - [(3 - phenoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl(2) - methylpenicillin,
α - [(3 - phenoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl(3) - methylpenicillin,
α - [(3 - furoyl(2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - methylbenzylpenicillin,
α - [(3 - furoyl(2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - methoxybenzylpenicillin,
α - [(3 - furoyl(2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - methylthiobenzylpenicillin,
α - [(3 - furoyl(2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - hydroxybenzylpenicillin,
α - [(3 - furoyl(2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - chlorobenzylpenicillin,
α - [(3 - furoyl(2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - nitrobenzylpenicillin,
α - [(3 - furoyl(2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl(2)-methylpenicillin,
α - [(3 - furoyl(2) - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl(3)-methylpenicillin,
α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - methylbenzylpenicillin,
α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - methoxybenzylpenicillin,

α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - methylthiobenzylpenicillin,
α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - hydroxybenzylpenicillin,
α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - chlorobenzylpenicillin,
α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - p - nitrobenzylpenicillin,
α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl(2) - methylpenicillin,
or α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - α - thienyl(3) - methylpenicillin.

Example 16.

If, as described in Example 1 A, 0.05 mol of:—
1-chlorocarbonyl-1,3-dimethyl-3-acetyl-urea,
1-chlorocarbonyl-1,3-dimethyl-3-methylsulphonyl-urea,
1-chlorocarbonyl-1,3-dimethyl-3-methoxycarbonyl-urea,
N-(isothiazolidine-1,1-dioxide-2-yl-carbonyl)-N-methyl-carbamic acid chloride,
1-chlorocarbonyl-3-p-methoxybenzoyl-imidazolidone-(2),
1-chlorocarbonyl-3-methylsulphonyl-4-methyl-imidazolidone-(2),
1-chlorocarbonyl-3-methylsulphonyl-5-methyl-imidazolidone-(2),
1-chlorocarbonyl-1-methyl-3-methylsulphonyl-urea,
1-chlorocarbonyl-1,3-diaza-4-thia-cyclohexan-2-one-4,4-dioxide or
1-chlorocarbonyl-4-thia-imidazolidin-2-one-4,4-dioxide
are reacted with 0.05 mol of ampicillin,
the following penicillins are obtained in the form of their sodium salts:—
D-α-(5-acetyl-3,5-dimethyl-biureido)-benzylpenicillin,
D-α-(5-methylsulphonyl-3,5-dimethyl-biureido)-benzylpenicillin,
D-α-(5-methoxycarbonyl-3,5-dimethyl-biureido)-benzylpenicillin,
D-α-[(3-isothiazolidine-1,1-dioxide-2-yl-carbonyl)-3-methylureido]-benzylpenicillin,
D-α-[(3-(p-methoxybenzoyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin,
D - α[(3 - methylsulphonyl - 4 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin,
D - α - [(3 - methylsulphonyl - 5 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin,
D-α-(3-methyl-5-methylsulphonyl-biureido)-benzylpenicillin,
D - α - (1,3 - diaza - 4 - thia - cyclohexan - 2 - one - 4,4 - dioxide - 1 - yl - carbonylamino) - benzylpenicillin or
D-α-(4-thia-imidazolidin-2-one-4,4-dioxide-1-yl-carbonylamino)-benzylpenicillin.

Example 17.

If, as described in Example 1 A, 0.05 mol of:—
N-benzoyl-N-methyl-carbamoylisocyanate,
N-benzoyl-N-methyl-carbamoylisothiocyanate,
N-acetyl-N-methyl-carbamoylisocyanate,
N-acetyl-N-methyl-carbamoylisothiocyanate,
imidazolid-2-on-1-yl-carbonylisocyanate,
imidazolid-2-on-1-yl-carbonylisothiocyanate,
pyrrolid-2-on-1-yl-carbonylisocyanate,
pyrollid-2-one-1-yl-carbonylisothiocyanate,
1,3,3-trimethyl-ureido-1-carbonylisocyanate,
1,3,3-trimethyl-ureido-1-carbonylisothiocyanate,
N-methylsulphonyl-N-methyl-carbamoylisocyanate,
N-methylsulphonyl-N-methyl-carbamoylisothiocyanate,
1,3-dimethylureido-1-carbonylisocyanate,
1,3-dimethylureido-1-carbonylisothiocyanate,
N-furoyl(2)-N-methylcarbamoylisocyanate,
N-furoyl(2)-N-methylcarbamoylisothiocyanate,
isothiazolidine-1,1-dioxide-2-yl-carbonylisocyanate or
isothiazolidine-1,1-dioxide-2-yl-carbonylisothiocyanate
are reacted with 0.05 mol of ampicillin, the following penicillins are obtained in the form of their sodium salts:—
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,
D-α-[3-imidazolidin-2-on-1-yl-carbonyl)-ureido]-benzylpenicillin,
D-α-[3-(imidazolidin-2-on-1-yl-carbonyl)-thioureido]-benzylpenicillin,
D-α-[3-(pyrrolidin-2-on-1-yl-carbonyl)-ureido]-benzylpenicillin,
D-α-[3-(pyrrolidin-2-on-1-yl-carbonyl)-thioureido]-benzylpenicillin,
D-α-[5-dimethylaminocarbonyl-5-methyl-biureido]-benzylpenicillin,
D-α-(5-methylsulphonyl-5-methyl-2-thio-biureido)-benzylpenicillin,
D-α-(5-methylsulphonyl-5-methyl-biuredio)-benzylpenicillin,
D-α-(5-methylsulphonyl-5-methyl-2-thio-biureido)-benzylpenicillin,
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,
D-α-[3-(isothiazolidine-1,1-dioxide-2-yl-carbonyl)-ureido]-benzylpenicillin or
D-α-[3-(isothiazolidine-1,1-dioxide-2-yl-carbonyl)-thioureido]-benzylpenicillin.

Example 18.

If, as described in Example 1 A, 0.05 mol of:—
1-chlorocarbonyl-3-propionyl-imidazolid-2-one,
1-chlorocarbonyl-3-acetyl-4-methyl-imidazolid-2-one,
1-chlorocarbonyl-3-acetyl-5-methyl-imidazolid-2-one,
1-chlorocarbonyl-3-acetyl-1,3-diaza-cyclohexan-2-one,
1-chlorocarbonyl-3-n-propylsulphonyl-imidazolid-2-one,
1-chlorocarbonyl-3-ethylsulphonyl-4-methyl-imidazolid-2-one,
1-chlorocarbonyl-3-ethylsulphonyl-5-methyl-imidazolid-2-one,
1-chlorocarbonyl-3-ethylsulphonyl-1,3-diaza-cyclohexan-2-one,
1-chlorocarbonyl-3-methylsulphonyl-1,3-diaza-cyclohexan-2-one,
1-chlorocarbonyl-3-n-propylsulphonyl-1,3-diaza-cyclohexan-2-one,
1-chlorocarbonyl-3-i-propylsulphonyl-1,3-diaza-cyclohexan-2-one,
1-chlorocarbonyl-3-i-propylsulphonyl-imidazolid-2-one,
1-chlorocarbonyl-3-i-propylsulphonyl-4-methyl-imidazolid-2-one,
1-chlorocarbonyl-3-i-propylsulphonyl-5-methyl-imidazolid-2-one,
1-chlorocarbonyl-3-n-propylsulphonyl-4-methyl-imidazolid-2-one,
1-chlorocarbonyl-3-n-propylsulphonyl-5-methyl-imidazolid-2-one,
1-chlorocarbonyl-3-phenylsulphonyl-imidazolid-2-one,
1-chlorocarbonyl-3-p-methylphenylsulphonyl-imidazolid-2-one,
1-chlorocarbonyl-3-cyclohexylsulphonyl-imidazolid-2-one,
1-chlorocarbonyl-3-thienyl(2)-sulphonyl-imidazolid-2-one,
1-chlorocarbonyl-3-formyl-4-methyl-imidazolid-2-one,
1-chlorocarbonyl-3-formyl-5-methyl-imidazolid-2-one,
1-chlorocarbonyl-3-formyl-1,3-diazacyclohexan-2-one,
1-chlorocarbonyl-3-methylaminocarbonyl-4-methyl-imidazolid-2-one,
1-chlorocarbonyl-3-methylaminocarbonyl-5-methyl-imidazolid-2-one,
1-chlorocarbonyl-3-methylaminocarbonyl-1,3-diaza-cyclohexan-2-one,
1-chlorocarbonyl-3-methoxycarbonyl-4-methyl-imidazolid-2-one,
1-chlorocarbonyl-3-methoxycarbonyl-5-methyl-imidazolid-2-one,
1-chlorocarbonyl-3-methoxycarbonyl-1,3-diazacyclohexan-2-one,
1-chlorocarbonyl-3-i-propyloxycarbonyl-4-methyl-imidazolid-2-one,
1-chlorocarbonyl-3-i-propyloxycarbonyl-5-methyl-imidazolid-2-one,
1-chlorocarbonyl-3-i-propyloxycarbonyl-1,3-diazacyclohexan-2-one,
1-chlorocarbonyl-3-methylsulphonyl-4,5-dimethyl-imidazolid-2-one,
1-chlorocarbonyl-3-methylsulphonyl-4,4-dimethyl-imidazolid-2-one, or
1-chlorocarbonyl-3-methylsulphonyl-5,5-dimethyl-imidazolid-2-one

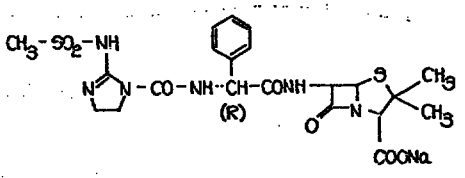
are reacted with 0.05 mod of ampicillin, the following penicillins are obtained in the form of their sodium salts:—

D-α-[(3-propionyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin,
D-α-[(3-acetyl-4-methyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin,
D-α-[(3-acetyl-5-methyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin,
D-α-[(3-acetyl-1,3-diaza-cyclohexan-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)-carbonylamino]-benzylpenicillin,
D-α-[(3-ethylsulphonyl-5-methyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin,

D - α - [(3 - ethylsulphonyl - 1,3 - diaza - cyclohexan - 2 - on - 1 - yl) - carbonyl-amino] - benzylpenicillin,
D - α - [(3 - methylsulphonyl - 1,3 - diaza - cyclohexan - 2 - on - 1 - yl) - carbonyl-amino] - benzylpenicillin,
D - α - [(3 - n - propylsulphonyl - 1,3 - diaza - cyclohexan - 2 - on - 1 - yl) - carbonyl-amino] - benzylpenicillin,
D - α - [(3 - i - propylsulphonyl - 1,3 - diaza - cyclohexan - 2 - on - 1 - yl) - carbonyl-amino] - benzylpenicillin,
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,
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,
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 -1 imidazolidin - 2 - on - 1 - yl) - carbonylamino]-benzylpenicillin,
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,
D-α-[(3-formyl-5-methyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin,
D-α-[(3-formyl-1,3-diaza-cyclohexan-2-on-1-yl)-carbonylamino]-benzylpenicillin,
D - α - [(3 - methylaminocarbonyl - 4 - methyl - imidazolidin - 2 - on - 1 - yl) - carb-onylamino] - benzylpenicillin,
D - α - [(3 - methylaminocarbonyl - 5 - methyl - imidazolidin - 2 - on - 1 - yl) - carb-onylamino] -benzylpenicillin,
D - α - [(3 - methylaminocarbonyl - 1,3 - diaza - cyclohexan - 2 - on - 1 - yl) - carb-onylamino] - benzylpenicillin,
D - α - [(3 - methoxycarbonyl - 4 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonyl-amino] - benzylpenicillin,
D - α - [(3 - methoxycarbonyl - 5 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonyl-amino] - benzylpenicillin,
D - α - [(3 - methoxycarbonyl - 1,3 - diaza - cyclohexan - 2 - on - 1 - yl) - carbonyl-amino] - benzylpenicillin,
D - α - [(3 - i - propyloxycarbonyl - 4 - methyl - imidazolidin - 2 - on - 1 - yl) - carb-onylamino] - benzylpenicillin,
D - α - [(3 - i - propyloxycarbonyl - 5 - methyl - imidazolidin - 2 - on - 1 - yl) - carb-onylamino] - benzylpenicillin,
D - α - [(3 - i - propyloxycarbonyl - 1,3 - diazacyclohexan - 2 - on - 1 - yl) - carb-onylamino] - benzylpenicillin,
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 or
D - α - [(3 - methylsulphonyl - 5,5 - dimethyl - imidazolidin - 2 - on - 1 - yl) -carb-onylamino] - benzylpenicillin.

Example 19.

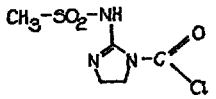
A) Sodium D - α - [(2 - methylsulphonylamino - imidazolin(2) - 1 - yl) - carbonyl-amino] - benzylpenicillin:



This penicillin was produced as described in Example 1 A from 4.8 parts by weight of 1-chlorocarbonyl-2-methylsulphonylamino-4,5-dihydroimidazole and 9 parts by weight of ampicillin.

Yield: 38%.
β-Lactam content: 96%
IR-bands at 3060, 1764, 1670, 1605 and 1130 cm^{-1}.
NMR-signals at $\tau = 2.3$—2.9 (5H), 4.45 (1H), 4.55 (2H), 5.8 (1H), 5.9—6.5 (4H), 6.95 (3H), 8.4 (3H) and 8.5 ppm (3H).
Activity against *E. coli* C 165: 8
Activity against *Prot. vulg.* 1017: 16

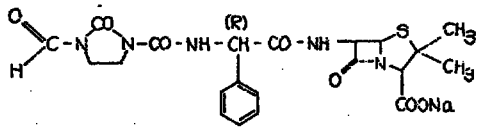
B) 1-Chlorocarbonyl-2-methylsulphonylamino-4,5-dihydroimidazole:



8.2 parts by weight of 2-(N-methylsulphonyl-imino)-imidazoline and 8.0 parts by weight of phosgene were reacted in anhydrous dioxane at 60—70°C. The resulting crude product however, on reaction with ampicillin, gave the penicillin of the expected structure.

Example 20.

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



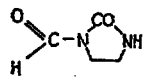
D-α-aminobenzylpenicillin (5.7 parts by weight) was suspended in 80% (volume/volume) aqueous tetrahydrofuran (60 parts by volume) and sufficient triethylamine was then added dropwise at 30°C, whilst stirring, just to produce a clear solution and to give a pH value of the mixture of between 7.5 and 8.2 (glass electrode). The mixture was then cooled to 0°C and a solution of 3-formyl-imidazolidin-2-one-1-carbonyl chloride (2.2 parts by weight) in tetrahydrofuran (20 parts by volume) was added dropwise. At the same time the pH of the mixture was kept at 7.5 to 8.0 by appropriate addition of triethylamine. The mixture was stirred for a further 30 minutes at 0°C. Thereafter, no further addition of triethylamine was necessary to maintain the pH value of 7.5 to 8.0. After addition of water (60 parts by volume) the pH was adjusted to 6.5 with dilute hydrochloric acid and the tetrahydrofuran was largely removed in a rotary evaporator. The aqueous solution which remained was once extracted by shaking with ether (the ether extract was discarded) and was subsequently covered with a 1:1 mixture (vol:vol) of ether and ethyl acetate and the pH was adjusted to 1—2 by means of dilute hydrochloric acid whilst stirring and cooling with ice. The organic phase was then separated off, washed with water, dried for about one hour over magnesium sulphate at 0°C and, after filtration, diluted with about half its volume of ether. The sodium salt was then precipitated by adding an approx. 1 molar solution of sodium 2-ethylhexanoate in ether containing methanol. The precipitate was initially oily but could be converted into an amorphous solid substance after decanting off the supernatant solution and trituration with ether.

Yield: 0.9 parts by weight (crude product)
β-Lactam content: 77%
According to the NMR-spectrum, the substance contained 3.5 mols of H_2O and 0.3 mol of sodium 2-ethylhexanoate per mol. This was taken into account in the calculated values of the analytical data:
Calculated: C 45.1 H 5.4 N 11.2 S 5.1 wt %.
Found: C 45.2 H 5.3 N 11.0 S 5.3 wt %.
NMR-signals at $\tau = 1.0$ (1H), 2.4—2.8 (5H), 4.3—4.6 (3H), 5.8 (1H), 6.1—6.3 (4H) and 8.3—8.5 ppm (6H)

Activity against *E. coli* C 165: 8
Activity against *Prot. morg.* 932: 8
Activity against *Psdm.* F 41: 8
Activity against *Klebs.* K 10: 32

The 3-formyl-imidazolidin-2-one-1-carbonyl chloride used in the production of this penicillin was obtained as follows:

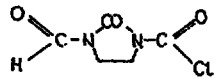
N-formyl-imidazolidin-2-one:



Imidazolidin-2-one (8.6 parts by weight) was suspended in tetrahydrofuran (100 parts by volume), formic acid-acetic acid anhydride (10 parts by weight) was added at room temperature whilst stirring and thereafter the mixture was stirred at the same temperature for 3¼ hours. The precipitate present was filtered off, washed with tetrahydrofuran and dried.

Yield: 6.4 parts by weight
Melting point: 156—158°C
Calculated: C 42.1 H 5.3 N 24.6 wt %.
Found: C 42.2 H 5.4 N 25.3 wt %.
NMR-signals at $\tau = 1.2$ (1H) and 5.9 to 6.5 ppm (4H).

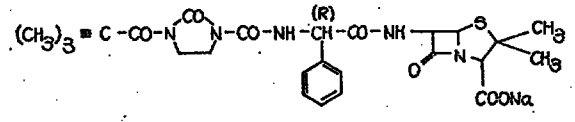
3-Formyl-imidazolidin-2-one-1-carbonyl chloride:



A mixture of N-formyl-imidazolidin-2-one (6.0 parts by weight), benzene (40 parts by volume) and triethylamine (11.8 parts by volume) was boiled under reflux and at the same time a solution of trimethylchlorosilane (8.5 parts by weight) in benzene (20 parts by volume) was added dropwise. Thereafter the mixture was boiled for a further 5 hours and then left to stand overnight at room temperature and the precipitate present was filtered off and washed with benzene. The combined benzene solutions, on standing overnight, formed further amounts of precipitate which were filtered off. A solution of phosgene (15.6 parts by weight) in dichloromethane (30 parts by volume) was then added dropwise to the filtrate and the mixture was subsequently left to stand overnight in a refrigerator. It was then completely evaporated to dryness in a rotary evaporator. The residue, a mass which did not crystallise throughout to give a solid, was used, at it was, for the reaction with ampicillin.

Example 21.

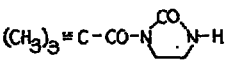
Sodium D-α-[(3-pivaloyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin:



This penicillin was produced as described in Example 20 from ampicillin (9.8 parts by weight) and 3-pivaloyl-imidazolidin-2-one-1-carbonyl chloride (4.9 parts by weight).

Yield: 8.6 parts by weight
β-Lactam content: 97.8%.
Calculated: C 50.3 H 5.6 N 12.2 S 5.6 wt %.
Found: C 50.6 H 5.9 N 11.6 S 5.6 wt %.
NMR-signals at $\tau = 2.4$—2.8 (5H), 4.3—4.7 (3H), 5.8 (1H), 6.0—6.4 (4H) and 8.3—8.9 ppm (15 H).
Activity against *E. coli* C 165: 4
Activity against *Prot. morg.* 932: ≤ 1
Activity against *Psdm.* F 41: 4
Activity against *Klebs.* K 10: 8

N-pivaloyl-imidazolidin-2-one:



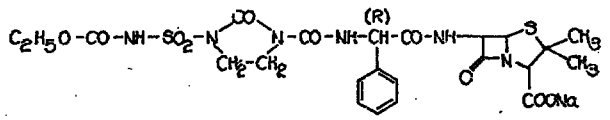
A suspension, cooled to 0°C, of imidazolidin-2-one (17.2 parts by weight) in tetrahydrofuran (200 parts by volume) was treated dropwise over the course of one hour, with pivaloyl chloride (24.2 parts by weight) at the same temperature. The mixture was then stirred for a further 3 hours at 0°C, triethylamine (27.8 parts by volume) was subsequently added dropwise whilst cooling with ice water, and the mixture was then left to stand overnight at room temperature. The triethylamine hydrochloride which had separated out was then filtered off, the filtrate was completely concentrated *in vacuo* by means of a rotary evaporator and the residue was further warmed for 1 hour, *in vacuo*, in a bath at 60°C. The oily product (crude yield: 32.8 parts by weight) was further processed, as it was. When an attempt was made to distil the substance *in vacuo*, severe decomposition occurred.

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

A solution of trimethylchlorosilane (16.65 parts by weight) in benzene (15 parts by volume) was added dropwise, over the course of one hour, to a boiling mixture if N-pivaloyl-imidazolidin-2-one (17.5 parts by weight), benzene (100 parts by volume) and triethylamine (23 parts by volume), the mixture was subsequently boiled for a further 6 hours and the triethylamine hydrochloride which had separated out was then filtered off. The filtrate was combined with a solution of phosgene (13 parts by weight) in benzene (20 parts by volume) and the mixture was then left to stand overnight at room temperature. The reaction mixture was then completely evaporated *in vacuo* and the oily residue was dried in a desiccator over NaOH. Crude yield 22.2 parts by weight. The product was reacted in this form with ampicillin.

Example 22.

Sodium D - α - {[3 - (ethoxy - carbonyl - amino - sulphonyl) - imidazolidin - 2 - on-1 - yl] - carbonylamino} - benzylpenicillin:

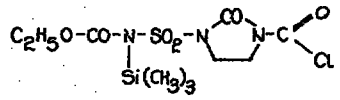


This penicillin was produced as described in Example 20 from ampicillin (9.8 parts by weight) and 3-(ethoxy-carbonyl-trimethylsilylaminosulphonyl)-imidazolidin-2-one-1-carbonyl chloride (8.0 parts by weight).

Yield: 2.8 parts by weight
β-Lactam content: 76.8%
NMR-signals at $\tau = 2{,}4$—2.7 (5H), 6.3—6.7 (3H), 5.8 (1H), 5.85—6.4 (6H), 8.3—8.6 (6H) and 8.6—8.95 ppm (3H).

The 3-(ethoxy-carbonyl-trimethylsilylaminosulphonyl)-imidazolidin-2-one-1-carbonyl chloride used in the manufacture of this penicillin was obtained as follows:

3 - (Ethoxy - carbonyl - trimethylsilylaminosulphonyl) - imidazolidin - 2 - one - 1-carbonyl chloride

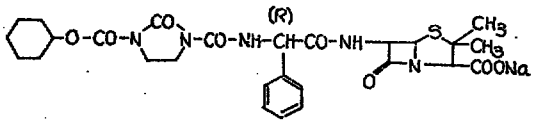


A mixture of the internal salt of ethyl(carboxysulphamoyl)triethylammonium hydroxide (G. M. Atkins, Jr., E. M. Burgers, J. Amer. Chem. Soc. *90*, 4744 (1968)) (12.5 parts by weight) and imidazolidin-2-one (4.0 parts by weight) was warmed in a bath at 100°C. for 2 hours, the resulting thick oil was dissolved in dichloromethane (80 parts by volume), triethylamine (10.9 parts by volume) was added, this solution was then heated to the boil and at the same time a solution of trimethylchlorosilane (15.8 parts by weight) in benzene (30 parts by volume) was added dropwise. Thereafter the

mixture was boiled under reflux for a further 3 hours. A further 80 parts by volume of benzene were then added and the mixture was again boiled under reflux for 3 hours. After standing overnight at 20°C, solvent was distilled off under normal pressure up to a boiling point of 70—75°C, the triethylamine hydrochloride was then filtered off whilst still hot and after cooling the filtrate was combined with a solution of phosgene (5.3 parts by weight) in benzene (20 parts by volume). This mixture was left to stand, well sealed, for 24 hours at 20°C. Undissolved material was then filtered off and the filtrate was completely evaporated in a rotary evaporator. An oil remained, which in the IR-spectrum possesses, in the carbonyl region, a double band with peaks at 1790 and 1730 cm^{-1} (in dichloromethane). The substance was used without further purification for the reaction with ampicillin.

Example 23.

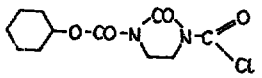
Sodium D - α 1 [(3 - cyclohexyloxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:



This penicillin was produced as described in Example 20 from ampicillin (6.6 parts by weight) and 3-cyclohexyloxycarbonyl-imidazolidin-2-one-1-carbonyl chloride (4.0 parts by weight).

Yield: 1.6 parts by weight
β-Lactam content: 63.7%
Calculated: C 48.3 H 5.8 N 10.5 S 4.8 wt %.
Found: C 47.5 H 7.0 N 10.5 S 5.1 wt %.
NMR-signals at $\tau = 2.5$—2.7 (5H), 4.3—4.7 (3H), 5.8 (1H), 6.0—6.3 (5H) and 8.1—9.2 ppm (16H).

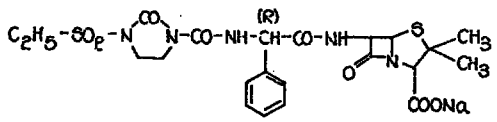
3-Cyclohexyloxycarbonyl-imidazolidin-2-one-1-carbonyl chloride:



Triethylamine (5.8 parts by weight) was added dropwise to a mixture of imidazolidin-2-one-1-carbonyl chloride (7.4 parts by weight), tetrahydrofuran (50 parts by volume) and cyclohexanol (5.5 parts by weight) whilst stirring, and cooling with ice, the mixture was then slowly stirred overnight at room temperature and subsequently boiled for 1 hour under reflux, and the triethylamine hydrochloride was filtered off hot. The filtrate was completely evaporated *in vacuo*, the residue was triturated with cyclohexane and the solid product was filtered off and dried 3 days in a desiccator. Yield: 5.0 parts by weight. This substance (5.0 parts by weight) was then suspended in tetrahydrofuran, triethylamine (5.2 parts by volume) was added, the mixture was boiled under reflux and a solution of trimethychlorosilane (3.8 parts by weight) in tetrahydrofuran (10 parts by volume) was at the same time added dropwise. Thereafter the mixture was boiled overnight under reflux and insoluble matter was then filtered off hot. A solution of phosgene (2.6 parts by weight) in tetrahydrofuran (10 parts by volume) was slowly added to the filtrate at room temperature and the mixture was left to stand well sealed at room temperature for 24 hours. A precipitate which was present (largely triethylamine hydrochloride) was then filtered off and the filtrate was completely evaporated *in vacuo*. The crystalline residue was dried in a desiccator. The substance has a broad absorption between 1680 and 1820 cm^{-1} in the carbonyl region of the IR-spectrum (Nujol). It was reacted, in this form, with ampicillin.

Example 24.

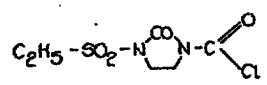
Sodium D - α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:



This penicillin was produced as described in Example 20 from ampicillin (9.4 parts by weight) and 3-ethanesulphonyl-imidazolidin-2-one-1-carbonyl chloride (5.0 parts by weight).

Yield: 5.7 parts by weight
β-Lactam content: 89.1%
The penicillin contains about 3.3 wt % of sodium 2-ethyl-hexanoate and 6.7 wt % of water. This was taken into account in the calculated values of the analytical data.
Calculated: C 43.2 H 5.1 N 11.0 S 10.0 wt %.
Found: C 43.3 H 5.8 N 10.8 S 9.9 wt %.

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



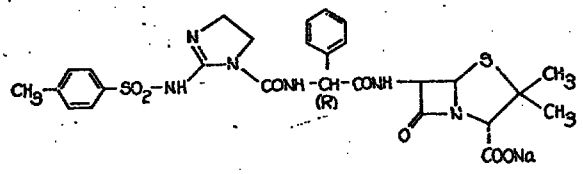
A mixture of imidazolidin-2-one (21.5 parts by weight) and ethanesulphonic acid chloride (32.5 parts by weight) was warmed for 4 hours in a bath at 150°C. to 180°C. The evolution of HCl had by then largely ended. The reaction product was then successively extracted by boiling twice with benzene, twice with acetone and twice with ethyl acetate on a water bath and the extracts were decanted. The combined extracts were completely evaporated *in vacuo* and the residue was recrystallised once from ethyl acetate and once from acetone (in the latter case with the addition of charcoal powder). Yield 8.1 parts by weight of N-ethanesulphonyl-imidazolidin-2-one. Melting point: 114°C.

The N-ethanesulphonyl-imidazolidin-2-one was then suspended in dichloromethane, a large excess of phosgene was introduced at 0°C, a little pyridine was added and the mixture was left to stand overnight. The excess phosgene was then largely removed by passing in dry air and the product (3-ethane-sulphonyl-imidazolidin-2-one-1-carbonyl chloride) was suspended in dichloromethane and filtered off. Melting point: 174°C.

Calculated: C 30.0 H 3.8 Cl 14.8 N 11.6 S 13.3 wt %.
Found: C 30.1 H 3.8 Cl 14.7 N 11.8 S 13.3 wt %.

Example 25.

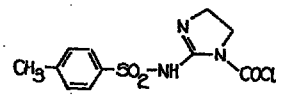
A) Sodium D - α - [(2 - tosylamino - imidazolin(2) - 1 - yl) - carbonylamino]-benzylpenicillin:



This penicillin was produced as described in Example 1 A from 7.5 parts by weight of 1-chloro-carbonyl-2-tosylamino-4,5-dihydroimidazole and 11 parts by weight of ampicillin.

Yield: 77%
β-Lactam content: 90%
Calculated (the water content of 6.1 wt % was taken into account):
C 47.9 H 5.0 N 12.4 S 9.5 wt %.
Found: C 48.3 H 4.8 N 10.8 S 9.1 wt %.
IR-bands at 3360—3200, 1775, 1725, 1675, 1608, 1538, 1290 and 1146 cm^{-1} (in Nujol).
NMR-signals at $\tau = 2.2$ (2H), 2.4—2.9 (7H), 4.5 (3H), 5.8 (1H), 6.25 (4H), 7.6 (3H), 8.4 (3H) and 8.5 ppm (3H).

B) 1-Chlorocarbonyl-2-tosylamino-4,5-dihydro-imidazole:

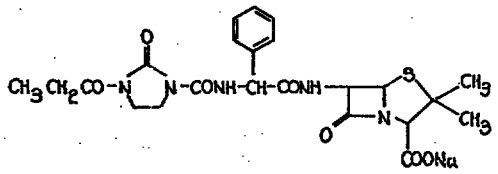


12 parts by weight of 2-tosylimino-imidazolidine (produced as described by Gompper and Hägele, Ber. *99*, 2892 [1966]) were partly dissolved by 10 minutes' boiling in 150 parts by volume of absolute tetrahydrofuran, and thereafter rapidly cooled to 0°C by swirling in an ice bath. 6 parts by weight of phosgene were added to the suspension whilst stirring, the mixture was stirred for 30 minutes at 0°C, 5 parts by weight of triethylamine were then added dropwise and the whole was then stirred for a further 3 hours at room temperature. The excess phosgene was blown out by means of a stream of dry air and the precipitated triethylamine hydrochloride was removed from the tetrahydrofuran solution by filtration and was thoroughly eluted with absolute tetrahydrofuran. The combined solutions were evaporated to dryness *in vacuo* and the residual oil yas caused to crystallise by trituration with methylene chloride and ether, filtered off and dried *in vacuo*. Melting point = 101°C (decomposition).

Yield: 59%.
Calculated: C 43.8 H 4.0 Cl 11.8 N 13.9 S 10.6 wt %.
Found: C 43.0 H 4.3 Cl 13.5 N 12.4 S 10.0 wt %.
IR-bands at 3340, 3050, 1796, 1765, 1628, 1265, 1145, 1087 and 905 cm^{-1} (in Nujol).

Example 26.

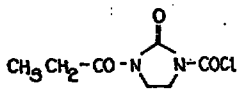
A) Sodium D - α - [(2 - oxo - 3 - propionyl - 1 - imidazolidinyl) - carbonylamino]-benzylpenicillin:



This penicillin was produced as described in Example 1 A from 9 parts by weight of 1-chloro-carbonyl-2-oxo-3-propionyl-imidazolidine and 17.5 parts by weight of ampicillin.

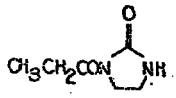
Yield: 38%.
β-Lactam content: 89%
Calculated: (the water content of 2 wt % was taken into account):
C 50.1 H 5.0 N 12.7 S 5.8 wt %.
Found: C 49.8 H 6.3 N 12.7 S 5.6 wt %.
IR-bands at 3290, 1760, 1732, 1670, 1603, 1525 and 1250 cm^{-1} (in Nujol).
NMR-signals at $\tau = 2.3$—2.8 (5H), 4.35 (1H), 4.5 (2H), 5.8 (1H), 6.0—6.3 (4H), 7.1 (2H), 8.4 (3H), 8.5 (3H) and 8.8 ppm (3H).

B) 1-Chlorocarbonyl-2-oxo-3-propionyl-imidazolidine:



12 parts by weight of 1-propionyl-2-oxo-imidazolidine, 18.4 parts by weight of trimethylchlorosilane, 15.1 parts by weight of triethylamine and 80 parts by volume of toluene were together kept under reflux overnight, whilst stirring, and after cooling the precipitate was filtered off and eluted with toluene. 9 parts by weight of phosgene were added to the combined solutions, the mixture was left to stand overnight at room temperature and then evaporated *in vacuo*, and the residue was dried under an oil pump. The product was reacted in this form with ampicillin (Example 26 A).
IR-bands at 1822, 1770—1680, 1385 and 1280—1210 cm^{-1}.

C) 1-Propionyl-2-oxo-imidazolidine:

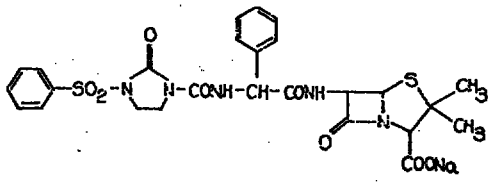


This substance was produced as described in Example 1 C from 17.2 parts by weight of 2-oxo-imidazolidine and 20.4 parts by weight of propionic acid chloride. Melting point = 147°C (from chloroform).

Yield: 45%
Calculated: C 50.7 H 7.0 N 19.7 wt %.
Found: C 49.2 H 7.1 N 20.2 wt %.
IR-bands at 3240, 1760—1736, 1678 and 1280 cm^{-1}.
NMR-signals at $\tau = 3.8$ (1H), 6.1 (2H), 6.4 (2H), 7.1 (2H) and 8.8 ppm (3H) (in $CDCl_3$).

Example 27.

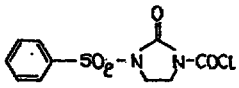
Sodium D - α - [(2 - oxo - 3 - benzenesulphonyl - 1 - imidazolidinyl) - carbonyl-amino] - benzylpenicillin:



This penicillin was produced as described in Example 1 A from 5 parts by weight of 1-chloro-carbonyl-2-oxo-3-benzenesulphonyl-imidazolidine and 7.5 parts by weight of ampicillin.

Yield: 94%.
β-Lactam content: 95%
Calculated (the water content of 3.5% was taken into account):
C 48.0 H 4.4 N 10.8 S 9.9 wt %.
Found: C 48.1 H 4.6 N 10.9 S 10.5 wt %.
IR-bands at 3300, 1770, 1740, 1680, 1610, 1530, 1260, 1184 and 1136 cm^{-1}.
NMR-signals at $\tau = 1.8$—2.1 (2H), 2.2—2.8 (8H), 4.4 (1H), 4.5 (2H), 5.8 (1H), 6.15 (4H), 8.45 (3H) and 8.5 ppm (3H).

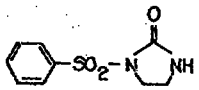
B) 1-Chlorocarbonyl-2-oxo-3-benzenesulphonyl-imidazolidine:



A mixture of 80 parts by weight of 1-benzenesulphonyl-2-oxo-imidazolidine, 69 parts by weight of phosgene, 31.6 parts by weight of pyridine and 350 parts by volume of dichloromethane, brought together at 0°C, was stirred overnight at room temperature and subsequently evaporated to dryness. Thereafter the material was suspended in 500 parts by volume of ice water and filtered off, the residue was taken up in 500 parts by volume of dichloromethane, the solution was dried over $MgSO_4$, filtered and again evaporated to dryness, and the residue was recrystallised from acetone/petroleum ether. Melting point = 161°C.

Yield: 64%
Calculated: C 41.6 H 3.5 Cl 12.3 N 9.7 S 11.1 wt %.
Found: C 41.6 H 3.0 Cl 12.2 N 9.7 S 10.7 wt %.
IR-bands at 1802, 1732, 1318 and 1200 cm^{-1}. (in Nujol).
NMR-signals at $\tau = 1.8$—2.1 (2H), 2.1—2.5 (3H) and 5.7—6.1 ppm (4H).

C) 1-Benzenesulphonyl-2-oxo-imidazolidine:

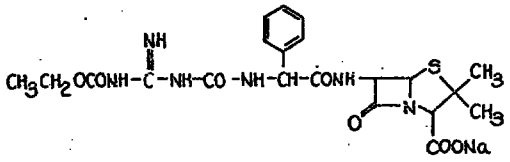


86 parts by weight of 2-oxo-imidazolidine, 194 parts by weight of benzenesulphonyl chloride, 800 parts by volume of tetrahydrofuran, 500 parts by volume of chloroform and 101 parts by weight of triethylamine were stirred overnight at 50°C and spbsequently evaporated to dryness *in vacuo*. The residue was gradually added, whilst stirring, to 1,000 parts by volume of ice water, the mixture was filtered and the residue was recrystallised from ethanol. Melting point = 155°C.

Yield: 35%
Calculated: C 47.7 H 4.4 N 12.4 S 14.2 wt %.
Found: C 47.8 H 4.5 N 12.2 S 14.3 wt %.
IR-bands at 3280, 1740, 1700, 1280, 1178, 1095 and 1060 cm^{-1} (in Nujol).
NMR-signals at $\tau = 1.8$—2.6 (6H), 6.1 (2H) and 6.7 ppm (2H) (in DMSO—d_6).

Example 28.

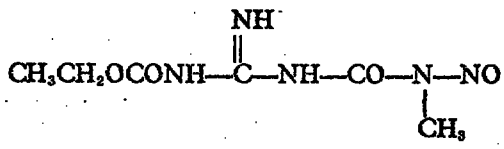
Sodium D-α-(4-imino-5-ethoxycarbonyl-biureido)-benzylpenicillin:



8 parts by weight of 1-(N-nitroso-N-methyl-aminocarbonyl)-3-ethoxycarbonyl-guanidine were added in portions, over the course of 15 minutes, to a stirred solution of 16.3 parts by weight of ampicillin and 5.7 parts by weight of triethylamine in 100 parts by volume of water. The initially foaming mixture was stirred for 4 hours at room temperature, insoluble matter was filtered off and the filtrate was covered with 200 parts by volume of ethyl acetate and acidified to pH = 2 with dilute hydrochloric acid, whilst cooling with ice. The penicillin was isolated as the sodium salt from the ethyl acetate solution of the penicillin-acid, as described in Example 1 A, by precipitation with sodium 2-ethyl-hexanoate solution.

Yield: 15%
β-Lactam content: 66%.
IR-bands at 3250, 1760 and 1665 cm^{-1}.
NMR-signals at $\tau = 2.4$—2.8 (5H), 4.4 (1H), 4.5 (2H), 5.8 (3H), 8.4 (3H), 8.5 (3H) and 8.8 ppm (3H).

B) 1-(N-Nitroso-N-methyl-aminocarbonyl)-3-ethoxycarbonyl-guanidine:

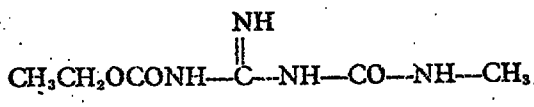


A solution of 7.3 parts by weight of sodium nitrite in 13 parts by volume of water was added dropwise over the course of 20 minutes to an ice-cooled solution of 11 parts by weight of 1-(methylaminocarbonyl)-3-ethoxycarbonyl-guanidine in 58 parts by volume of 5 N hydrochloric acid. The mixture was stirred for a further hour at 0°C and the yellow precipitate formed was filtered off and eluted with a little ice water.

Yield: 8.4 parts by weight. The product, in the moist form, was reacted analogously to Example 28 A to give the penicillin. A small sample was dried over P_2O_5 *in vacuo*. Melting point = 116°C (decomposition).

Calculated (a content of 15 wt % NaCl was taken into account in the calculation):
C 28.1 H 4.3 N 27.4 wt %.
Found: C 27.0 H 4.3 N 28.2 wt %.
IR-bands at 3400—2400, 1790, 1762 and 1725 cm^{-1}.

C) 1-(Methylaminocarbonyl)-3-ethoxycarbonyl-guanidine:

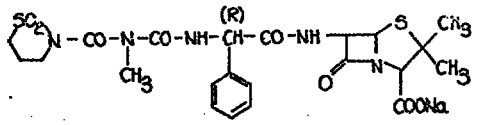


5.1 parts by weight of methylisocyanate were added to a suspension of 10 parts by weight of ethoxycarbonylguanidine (manufactured according to Isr. J. Chem. *8*, 651 [1970]) in 60 parts by volume of anhydrous dioxane, in the course of which the temperature rose to 45°C and the precipitate dissolved. After a short time, a crystalline precipitate separated out again, which was filtered off after cooling and washed with ether. It was dried *in vacuo* over P_2O_5 and paraffin chips. Melting point = 150°C.

Yield: 80%
Calculated: C 38.2 H 6.4 N 29.8 wt %.
Found: C 38.8 H 6.4 N 29.1 wt %.
IR-bands at 3380, 3300, 1730, 1700—1600, 1580—1520, 1300, 1260 and 155 cm^{-1} (in Nujol).
NMR-signals at $\tau = 1.0$ (3H), 2.8 (1H), 5.95 (2H), 7.3 (3H) and 8.8 ppm (3H) (in DMSO—d_6).

Example 29.

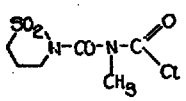
A) Sodium D - α - {3 - [N - (1,1 - dioxo - isothiazolidin - 2 - yl) - carbonyl] - 3-methyl} - ureido - benzylpenicillin:



This penicillin was produced as described in Example 20 from 12.0 parts by weight of ampicillin and 6.3 parts by weight of N-[(1,1-dioxo-isothiazolidin-2-yl)-carbonyl]-N-methylcarbamic acid chloride. However, when acidifying the penicillin salt solution, it was acidified to pH 2.0, the solution was at the same time kept at 0°C, and the solution of the free penicillin-acid in an ether-ethyl acetate mixture was only dried for 15 minutes at 0°C over $MgSO_4$.

Yield: 11.2 parts by weight.
β-Lactam content: about 100%
Electrophoresis of the penicillin showed that only one antibiotically active substance was present:
Specific rotation: $[\alpha]_{589} + 141°$ (methanol/water).
NMR-signals at $\tau = 2.4$—2.8 (5H), 4.3—4.6 (3H), 5.8 (1H), 5.9—6.3 (2H), 6.4—6.8 (2H), 6.6 (3H), 7.3—7.7 (2H) and 8.3—8.5 ppm (6H).

B) N - [(1,1 - Dioxo - isothiazolidin - 2 - yl) - carbonyl] - N - methylcarbamic acid chloride:



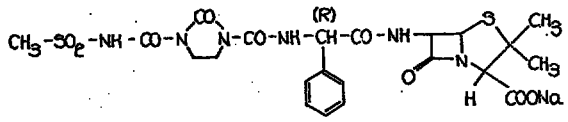
A solution of 7.7 parts by weight of 1,1-dioxo-isothiazolidine and 8.8 parts by volume of triethylamine in 30 parts by volume of tetrahydrofuran was added dropwise at room temperature to a solution of 10.0 parts by weight of bis-chlorocarbonyl-methylamine (Farbenfabriken Bayer: German Offenlegungschrift No. 1,932,830) in tetrahydrofuran (100 parts by volume). The mixture was stirred for a further hour at room temperature and the triethylamine hydrochloride formed was filtered off and washed

with tetrahydrofuran. The combined filtrates were completely evaporated *in vacuo* and the residue was recrystallised from hot tetrahydrofuran with addition of a little pentane.

Yield: 13.1 parts by weight.
Melting point = 102—103°C.
Calculated: C 30.0 H 3.8 Cl 14.7 N 11.6 S 13.3 wt %.
Found: C 30.1 H 3.9 Cl 14.3 N 11.6 S 13.3 wt %.
NMR-signals at $\tau = 6.15$ (triplet) (2H), 6.65 (triplet) (2H), 6.8 (3H) and 7.3—7.9 ppm (multiplet) (2H).
IR-spectrum: 1700 and 1740 cm^{-1} (C=0).

Example 30.

A) Sodium D - α - [3 - (methylsulphonyl - amino - carbonyl) - imidazolidinon - 2-yl - 1] - carbonylamino - benzylpenicillin:

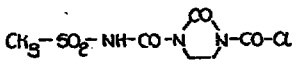


This penicillin was produced from 10.0 parts by weight of ampicillin and 5.9 parts by weight of 3-(methyl-sulphonyl-amino-carbonyl)-1-chlorocarbonyl-imidazolidinone-(2) as described in Example 20.

Yield: 9.8 parts by weight.
β-Lactam content: 82%.
NMR-signals at $\tau = 2.4$—2.8 (5H), 4.3—4.65 (3H), 5.8 (1H), 6.05—6.45 (4H), 6.95 (3H) and 8.35—8.75 ppm (6H).
Calculated: *) C 40.1 H 5.2 N 11.7 S 8.9 wt %.
Found: C 40.4 H 5.2 N 11.7 S 8.8 wt %.
*) (a content of 5.8 wt % of sodium 2-ethylhexanoate and 10 wt % of water was taken into account).

One electrophoresis (micro-biological evaluation with *Subtilis*) the penicillin shows only one spot.

B) 1-(Methylsulphonly-amino-carbonyl)-3-chlorocarbonyl-imidazolid-2-one:

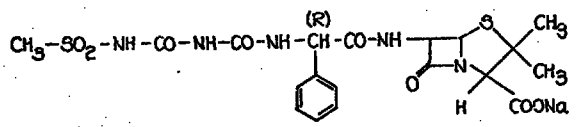


7.0 parts by weight of 1-chlorocarbonylimidazolidinone-(2) were dissolved or suspended in 50 parts by volume of tetrahydrofuran, 5.7 parts by weight of methanesulphonyl isocyanate were added and the mixture was first stirred for 26 hours at room temperature. Since practically no reaction had yet occurred at that time, 5 drops of pyridine were added and the mixture was stirred for a further 65 hours at room temperature. A crystalline precipitate was then filtered off.

Yield: 10.5 parts by weight.
Melting point = 218—220°C.
Calculated: C 26.7 H 3.0 Cl 13.1 N 15.6 S 11.9 wt %.
Found: C 27.2 H 3.2 Cl 12.8 N 15.5 S 11.9 wt %.
NMR-signals at $\tau = 5.8$—6.2 (multiplet) (4H) and 6.7 ppm (3H).
IR-spectrum: 1800 and 1730 cm^{-1} (C=0).

Example 31.

A) Sodium D-α-(5-mesyl-biureido)-benzylpenicillin:



This penicillin was produced as described in Example 20 from 11.2 parts by weight of ampicillin and 6.4 parts by weight of N-mesyl-N'-chlorocarbonyl-urea.

Yield: 3.4 parts by weight.
β-Lactam content: 66.5%.
Calculated: *) C 39.3 H 5.1 N 10.9 S 10.0 wt %.
Found: C 39.6 H 6.1 N 10.2 S 10.0 wt %.
*) (a content of 6.6 wt % of sodium 2-ethyl-hexanoate and 9 wt % of water was taken into account).

A microbiologically (*Bact. Subtilis*) developed electropherogram showed, in addition to one large inhibition halo, a second though very small inhibition halo.

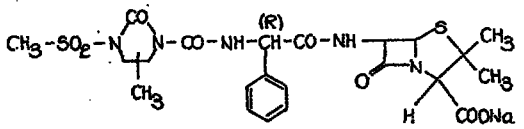
B) N-Mesyl-N'-chlorocarbonyl-urea:

$$CH_3—SO_2—NH—CO—NH—CO—Cl$$

6.1 parts by volume of pyridine were added dropwise, whilst cooling, to a mixture of 10.5 parts by weight of N-mesyl-urea, 60 parts by volume of dichloromethane and 15.0 parts by weight of phosgene, whilst cooling, and after some hours at 0°C the excess of the phosgene was removed, the precipitate present was filtered off and the filtrate was completely concentrated *in vacuo*. A viscous oil remained, which had an absorption at 1800 cm^{-1} in the carbonyl region of the IR-spectrum. The substance was used without further purification for the production of the penicillin.

Example 32.

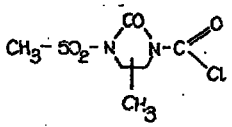
A) Sodium D - α - [(3 - methylsulphonyl - 4 - or 5 - methyl - imidazolidin - 2-on - 1 - yl) - carbonylamino] - benzylpenicillin:



This penicillin was produced from 12.0 parts by weight of ampicillin and 7.7 parts by weight of 1-methyl-sulphonyl-3-chlorocarbonyl-4- or -5-methyl-imidazolidin-2-one as described in Example 20.

Yield: 9.3 parts by weight.
β-Lactam content 94%
Calculated: (with 1.33 mol H_2O): C 44.0 H 4.8 N 11.7 S 10.7 wt %.
Found: C 44.0 H 5.0 N 11.4 S 10.6 wt %.
Specific rotation: $[\alpha]_{589}+135.9°$ (methanol-water).
NMR-signals at $\tau = 2.3—2.65$ (5H), 4.25—4.6 (3H), 5.75 (1H), 5.8—6.4 (3H), 6.6 (3H), 8.3—8.5 (6H) and 8.6—8.8 ppm (3H).

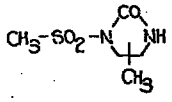
B) 1-Methanesulphonyl-3-chlorocarbonly-4- or -5-methyl-imidazolidin-2-one:



13.4 parts by weight of 1-methanesulphonyl-4- or -5-imidazolidin-2-one were added to a solution of 15.0 parts by weight of phosgene in 60 parts by volume of dichloromethane and 6.1 parts by volume of pyridine were added dropwise at 0°C. The mixture was then left to stand overnight at room temperature, phosgene which was still present was removed by means of a dry stream of air and the solution was then completely concentrated *in vacuo*. The residue, an oil, was dried in a desiccator over P_2O_5.

Yield: 27 parts by weight.
IR-bands in the carbonyl region: 1800, 1760 and 1720 cm^{-1}.

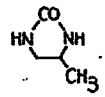
C) 1-Methanesulphonyl-4- or -5-methyl-imidazolidin-2-one



A mixture of 53.8 parts by weight of 4-methylimidazolidin-2-one and 64.6 parts by weight of methanesulphonic acid chloride was heated in a bath at 90°C. until the evolution of HCl had ceased (approx. 7 hours). The resulting crude product (yield 34.2 parts by weight) melted at 131—133°C. A product of melting point 135°C is obtained by recrystallisation from water on a waterbath.

Calculated: C 33.7 H 5.7 N 15.7 S 18.0 wt %.
Found: C 33.5 H 5.5 N 15.3 S 18.2 wt %.
NMR-signals at $\tau = 5.9$—6.7 (multiplet) (3H), 6.75 (3H) and 8.65 u. 8.75 ppm (3H) (doublet).

D) 4-Methylimidazolidin-2-one:

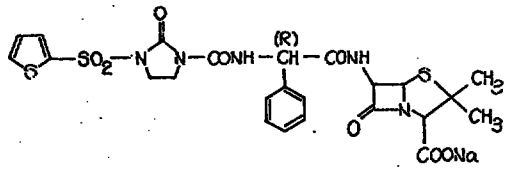


This substance was obtained by heating a mixture of 383 parts by weight of 1,2-diaminopropane and 611 parts by weight of carbonic acid diethyl ester to 180°C. in an autoclave for 10 hours and recrystallising from isopropanol and methanol.

Yield 109 parts by weight.
Melting point = 130°C.

Example 33.

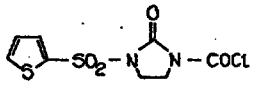
A) Sodium D - α - [3 - (thienyl(2) - sulfonyl) - imidazolidin - 2 - on - 1 - yl-carbonylamino] - benzylpenicillin:



This penicillin was produced as described in Example 1A from 3.3 parts by weight of 1 - chloro - carbonyl - 2 - oxo - 3 - (thienyl(2) - sulfonyl) - imidazolidine and 5.0 parts by weight of ampicillin.

Yield: 89%.
β-Lactam content: 83%.
Calculated (the water content of 6.4 wt %. and the sodium-2-ethyl-hexanoate content of 2.1 wt % were taken into account):
C 43.4 N 10.2 H 4.4 S 14.1 wt %.
Found: C 43.7 N 10.0 H 4.2 S 14.1 wt %.
IR-bands at 3320, 1770, 1742, 1680, 1610, 1530, 1258 and 1188 cm^{-1}.
NMR-signals at $\tau = 2.0$—2.2 (2H), 2.4—2.9 (6H), 4.4 (1H), 4.5 (2H), 5.8 (1H), 6.2 (4H), 8.45 (3H), and 8.5 ppm (3H).

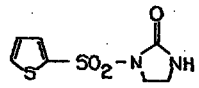
B) 1-Chlorocarbonyl-2-oxo-3-(thienyl(2)-sulfonyl)-imidazolidine:



This carbamic acid chloride was produced as described in Example 27B from 2.9 parts by weight of 1-thienyl(2)-carbonyl)-2-oxo-imidazolidine and 2.7 parts by weight of phosgene.

Yield: 80%. Melting point = 166°C.
IR-bands at 3080, 1800, 1728, 1300 and 1178 cm^{-1} (in nujol).

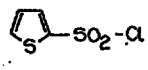
C) 1-(Thienyl(2)-sulfonyl)-2-oxo-imidazolidine:



The mixture of 14 parts by weight of 2-chlorosulfonyl-thiophene and 6.6 parts by weight of imidazolidone-2 were heated with stirring to 150°C until the evolution of HCl had finished (ca. 4 hours). After cooling the reaction product was extracted with 150 parts by volume of chloroform/H_2O (2:1 volume:volume), the chloroform-layer was separated, dried over $MgSO_4$ and evaporated to dryness. The residue was recrystallised from acetone.

Yield: 20.2%. Melting point = 174°C.
Calculated: C 36.1 H 3.5 N 12.0 S 27.5 wt %.
Found: C 35.8 H 3.5 N 11.9 S 27.5 wt %.
IR-bands at 3230, 3080, 1738, 1705, 1175 and 1062 cm^{-1} (in nujol).
NMR-signals at τ 2.—2.4 (2H), 2.8—3.0 (1H), 4.0 (1H), 5.9—6.2 (2H), and 6.3—6.7 ppm (2H) (in $CDCl_3$).

D) 2-Chlorosulfonyl thiophene:

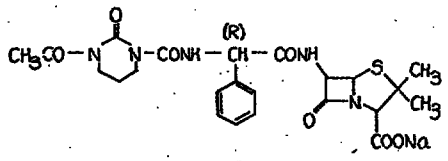


This compound was produced as described for chlorosulfonyl-methylthiophene in J. org. Chem. *33*, 1357 (1968) from thiophene, chlorosulfonic acid and PCl_5. The yield was 70%. The substance was a low melting solid.

Boiling point = 117°C (2 mm Hg).
Calculated: C 26.3 H 1.6 Cl 19.4 S 35.0 wt %.
Found: C 25.9 H 2.6 Cl 19.4 S 34.2 wt %.
IR-bands at 3110, 1196, 1032 and 740 cm^{-1}.
NMR-Signals at τ = 2.08 (2H) and 2.75 ppm (1H).

Example 34.

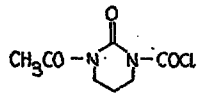
A) Sodium D - α - [(2 - oxo - 3 - acetyl - 1,3 - diaza - cyclohex - 1 - yl) - carbonyl-amino] - benzylpenicillin:



This penicillin was produced as described in Example 1A from 7.6 parts by weight of 1-chlorocarbonyl-2-oxo-3-acetyl-1,3-diaza-cyclohexane and 16.5 parts by weight of ampicillin.

Yield: 93%.
β-Lactam content: 94%.
Calculated (the water content of 6 wt% was taken into account).
C 48.1 H 5.2 N 12.2 S 5.5 wt %.
Found: C 48.0 H 5.5 N 12.2 S 6.2 wt %.
IR-bands at 3250, 1772, 1700, 1615, 1520, 1305 and 1180 cm^{-1}.
NMR-signals at τ = 2.3—2.8 (5H), 4.4 (1H), 4.5 (2H), 5.8 (1H), 6.0—6.4 (4H), 7.5 (3H), 7.8—8.3 (2H), 8.4 (3H) and 8.5 ppm (3H).

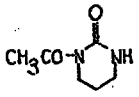
B) 1-Chlorocarbonyl-2-oxo-3-acetyl-1,3-diaza-cyclohexane:



This carbamic acid chloride was produced as described in Example 27B from 7.1 parts by weight of 1-acetyl-2-oxo-1,3-diaza-cyclohexane and 10 parts by weight of phosgene.

Oil. Yield: 89%.
Calculated: C 41.1 H 4.4 Cl 17.4 N 13.7 wt %.
Found: C 41.1 H 4.5 Cl 17.1 N 13.3 wt %.
IR-bands at 2950, 1800, 1730, 1706, 1400, 1376, 1320, 1295, 1202, 1178 and 1054 cm^{-1}.
NMR-signals at $\tau = 5.9$—6.3 (4H), 7.45 (3H) and 7.65—8.15 ppm (2H).

C) 1-Acetyl-2-oxo-1,3-diaza-cyclohexane:

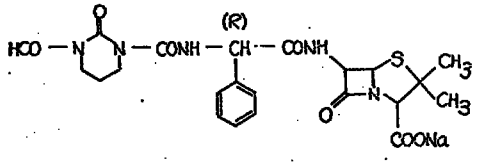


The mixture of 10 parts by weight of 1,3-diaza-cyclohexan-2-one, 11.8 parts by weight of acetylchloride, 8.7 parts by weight of pyridine, 50 parts by volume of tetrahydrofuran and 50 parts by volume of chloroform was stirred for 24 hours at room temperature, filtered and washed out with tetrahydrofuran/chloroform (1:1 volume/volume). The combined solutions were evaporated to dryness, recrystallised from acetone/ethanol; 50 parts by volume of $NaHCO_3$-solution were added, and the mixture was extracted 3 times with 50 parts by volume of ethylacetate at a time. The combined organic solutions were dried over $MgSO_4$, evaporated to dryness, and the residue was recristallised from acetone/petrolether.

Yield: 53%. Melting point = 132°C.
Calculated: C 50.7 H 7.0 N 19.7 wt %.
Found: C 50.5 H 7.1 N 20.1 wt %.
IR-bands at 3345, 1708, 1664, 1320, 1281, 1250, 1175, 1130 and 1022 cm^{-1} (in nujol).
NMR-signals at $\tau = 6.1$—6.4 (2H), 6.6—6.85 (2H), 7.5 (3H) and 7.8—8.3 ppm (2H) (in CD_3OD).

Example 35.

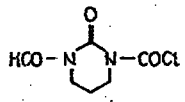
A) Sodium D - α - [(3 - formyl - 1,3 - diaza - cyclohexan - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:



This penicillin was produced as described in Example 1A from 8.1 parts by weight of 1-chlorocarbonyl-2-oxo-3-formyl-1,3-diaza-cyclohexane and 18.9 parts by weight of ampicillin.

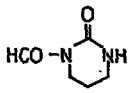
Yield: 41%.
β-Lactam content: 94%.
Calculated (the water content of 3 wt % was taken into account):
C 48.7 H 4.8 N 12.9 S 5.9 wt %.
Found: C 48.4 H 5.4 N 11.3 S 6.5 wt %.
IR-bands at 3270, 1765, 1700, 1675, 1603, 1310 and 1183 cm^{-1}.
NMR-signals at $\tau = 0.6$ (1H), 2.3—2.8 (5H), 4.4 (1H), 4.5 (2H), 5.8 (1H), 6.0—6.5 (4H), 7.75 (2H), 8.4 (3H) and 8.5 ppm (3H).

B) 1-Chlorocarbonyl-2-oxo-3-formyl-1,3-diaza-cyclohexane:



This carbamic acid chloride was produced as described in Example 27B from 5 parts by weight of 1-formyl-2-oxo-1,3-diaza-cyclohexane and 6 parts by weight of phosgene. The substance, an oil, was used without further purification for the production of the penicillin of Example 35A. IR-bands at 1790, 1685, 1300 and 1165 cm^{-1}.

C) 1-Formyl-2-oxo-1,3-diaza-cyclohexane:

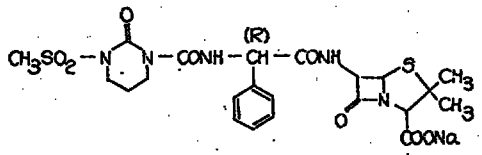


The mixture of 10 parts by weight of 1,3-diaza-cyclohexane-2-one, 49 parts by weight of trimethylchlorosilane, 25 parts by weight of triethylamine and 150 parts by volume of dioxane were boiled for 3 days with stirring and exclusion of moisture, then filtered, evaporated to 50 parts by volume *in vacuo* and stirred over night with 11.5 parts by volume of formic acid-acetic acid anhydride. The mixture was evaporated to dryness in vacuo, and the residue was recrystallised from ethanol/ether.

Yield: 40%. Melting point: 100°C.
Calculated: C 46.9 H 6.9 N 21.9 wt %.
Found: C 46.7 H 6.3 N 22.0 wt %.
IR-bands at 3250, 3120, 1690, 1312 and 1166 cm^{-1} (in nujol).

Example 36.

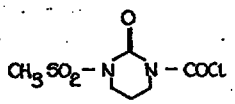
A) Sodium D - α - [(3 - mesyl - 1,3 - diaza - cyclohexan - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:



This penicillin was produced as described in Example 1A from 5.6 parts by weight of 1-chlorocarbonyl-2-oxo-3-mesyl-1,3-diaza-cyclohexane and 10 parts by weight of ampicillin.

Yield: 52%.
β-Lactam content: 94%.
Calculated (the water content of 2.9 wt % and the sodium-2-ethylhexanoate content of 2.9 wt % were taken into account):
C 44.8 H 4.8 N 11.4 S 10.4 wt %.
Found: C 44.9 H 5.1 N 11.0 S 10.3 wt %.
IR-bands at 3300, 1765, 1705—1665, 1605, 1515, 1345 and 1165 cm^{-1}.
NMR-signals at $\tau = 2.3$—2.8 (5H), 4.4 (1H), 4.5 (2H), 5.8 (1H), 6.0—6.4 (4H), 6.6 (3H), 7.7—8.3 (2H), 8.4 (3H) and 8.5 ppm (3H).

B) 1-Chlorocarbonyl-2-oxo-3-mesyl-1,3-diaza-cyclohexane:

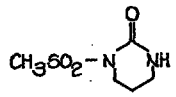


This carbamic acid chloride was produced as described in Example 4B from 4.5 parts by weight of 1-mesyl-2-oxo-1,3-diaza-cyclohexane, 6.9 parts by weight of tri-

methylchlorosilane and 5.2 parts by weight of phosgene. The oily reaction product was used without further purification for the reaction with ampicillin (Example 36A).

Yield: 83%.
IR-bands at 2980, 2950, 1790, 1760—1680, 1472, 1355, 1215, 1162, 982 and 855 cm^{-1}.

C) 1-Mesyl-2-oxo-1,3-diaza-cyclohexane:

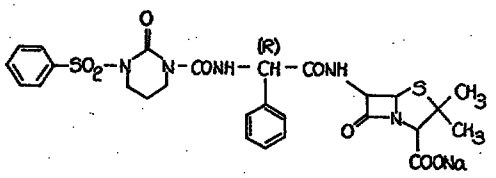


This compound was produced as described in Example 35C from 10 parts by weight of 1,3-diaza-cyclohexan-2-one, 49 parts by weight of trimethylchlorosilane and 30 parts by weight of mesylchloride. The reaction product was recrystallised from acetone at low temperature and thereafter from acetone/ethanol.

Yield: 34%. Melting point: 172°C.
Calculated: C 33.7 H 5.6 N 15.8 S 18.0 wt %.
Found: C 33.4 H 5.7 N 15.6 S 17.3 wt %.
IR-bands at 3210, 3070, 1692, 1340 and 1170 cm^{-1} (in nujol).
NMR-signals at $\tau = 6.25$ (2H), 6.5—6.8 (2H), 6.7 (3H) and 7.8—8.3 ppm (2H) (in CD_3OD).

Example 37.

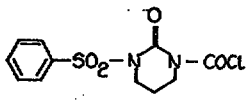
A) Sodium D - α - [(3 - phenylsulfonyl - 1,3 - diaza - cyclohexan - 2 - on - 1 - yl)-carbonylamino] - benzylpenicillin:



This penicillin was produced as described in Example 1A from 2.6 parts by weight of 1-chlorocarbonyl-2-oxo-3-phenylsulfonyl-1,3-diaza-cyclohexane and 3.8 parts by weight of ampicillin.

Yield: 82%.
β-Lactam content: 85%.
IR-bands at 3300, 1770, 1695, 1610, 1520 and 1180 cm^{-1}.
NMR-signals at $\tau = 1.9$—2.1 (2H), 2.3—2.6 (3H), 2.6 (5H), 4.54 (1H), 4.6 (2H), 5.85 (1H), 5.9—6.5 (4H), 7.8—8.25 (2H), 8.47 (3H) and 8.52 ppm (3H).

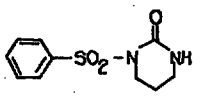
B) 1-Chlorocarbonyl-2-oxo-3-phenylsulfonyl-1,3-diaza-cyclohexane:



This carbamic acid chloride was produced as described in Example 27A from 6 parts by weight of 1-phenylsulfonyl-1,3-diaza-cyclohexane-2-one and 5 parts by weight of phosgene. The product was recrystallised from acetone/petrolether.

Yield: 35%. Melting point = 123°C.
IR-bands at 3350, 1790, 1692 and 1162 cm^{-1} (in nujol).

C) 1-Phenylsulfonyl-2-oxo-1,3-diaza-cyclohexane:

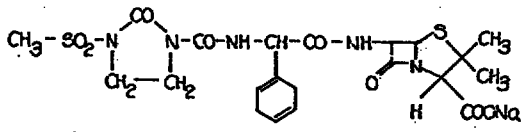


20.4 Parts by weight of benzenesulfochloride in 20 parts by volume of tetrahydrofuran were added dropwise at 10—15°C over the course of 15 minutes to a stirred mixture of 10 parts by weight of 1,3-diaza-cyclohexan-2-one, 80 parts by volume of tetrahydrofuran and 80 parts by volume of chloroform, followed by 10.1 parts by weight of triethylamine at the same temperature. The mixture was stirred at 10—15°C for 30 minutes and then overnight at 50°C. Subsequently the mixture was evaporated to dryness; the residue was stirred with 100 parts by volume of water, filtered, stirred with water once more, filtered and washed with ethanol.

Yield: 28%. Melting point: 207°C.
Calculated: C 50.0 H 5.0 N 11.7 S 13.3 wt %.
Found: C 49.0 H 5.0 N 11.7 S 12.5 wt %.
IR-bands at 3320, 1665, 1348, 1300 and 1175 cm^{-1} (in nujol).
NMR-signals at $\tau = 1.8$—2.2 (2H), 2.3—2.7 (3H), 6.0 (2H), 6.7 (2H) and 8.0 ppm (2H) (in $CDCl_3$).

Example 38.

Sodium D - α - [(3 - methylsulfonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 1,4 - cyclohexadien - yl - 1 - methylpenicillin:

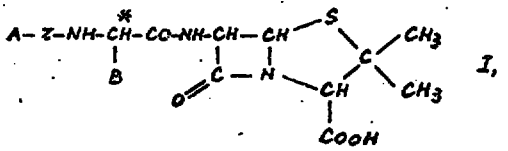


This penicillin was produced as described in Example 20 from 2.5 parts by weight of D - α - Amino - 1,4 - cyclohexadien - yl - 1 - methylpenicillin and 1.6 parts by weight of 1-methylsulfonyl-3-chlorocarbonyl-imidazolidin-2-one.

Yield: 2.6 parts by weight
β-Lactam content: 93%
NMR-signals at $\tau = 4.0$ (1H), 4.3 (2H), 4.4 (2H), 4.9 (1H), 5.8 (1H), 6.0 (4H), 6.6 (3H), 7.2 (4H) and 8.2—8.4 ppm (pH).

WHAT WE CLAIM IS:—

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

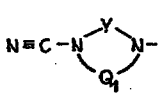


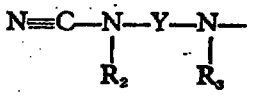
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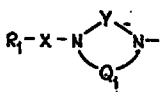
in which

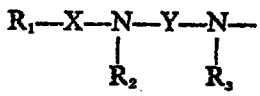
C* is a carbon atom constituting a centre of chirality;

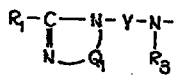
A is a radical of the general formula:—

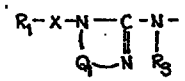










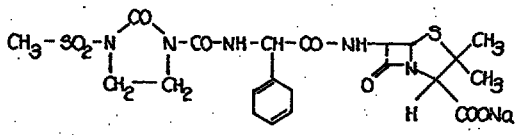


20.4 Parts by weight of benzenesulfochloride in 20 parts by volume of tetrahydrofuran were added dropwise at 10—15°C over the course of 15 minutes to a stirred mixture of 10 parts by weight of 1,3-diaza-cyclohexan-2-one, 80 parts by volume of tetrahydrofuran and 80 parts by volume of chloroform, followed by 10.1 parts by weight of triethylamine at the same temperature. The mixture was stirred at 10—15°C for 30 minutes and then overnight at 50°C. Subsequently the mixture was evaporated to dryness; the residue was stirred with 100 parts by volume of water, filtered, stirred with water once more, filtered and washed with ethanol.

Yield: 28%. Melting point: 207°C.
Calculated: C 50.0 H 5.0 N 11.7 S 13.3 wt %.
Found: C 49.0 H 5.0 N 11.7 S 12.5 wt %.
IR-bands at 3320, 1665, 1348, 1300 and 1175 cm^{-1} (in nujol).
NMR-signals at $\tau = 1.8$—2.2 (2H), 2.3—2.7 (3H), 6.0 (2H), 6.7 (2H) and 8.0 ppm (2H) (in $CDCl_3$).

Example 38.

Sodium D - α - [(3 - methylsulfonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 1,4 - cyclohexadien - yl - 1 - methylpenicillin:

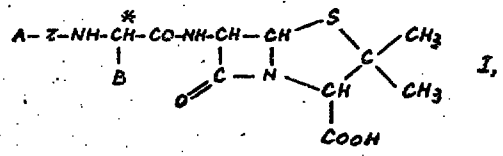


This penicillin was produced as described in Example 20 from 2.5 parts by weight of D - α - Amino - 1,4 - cyclohexadien - yl - 1 - methylpenicillin and 1.6 parts by weight of 1-methylsulfonyl-3-chlorocarbonyl-imidazolidin-2-one.

Yield: 2.6 parts by weight
β-Lactam content: 93%
NMR-signals at $\tau = 4.0$ (1H), 4.3 (2H), 4.4 (2H), 4.9 (1H), 5.8 (1H), 6.0 (4H), 6.6 (3H), 7.2 (4H) and 8.2—8.4 ppm (pH).

WHAT WE CLAIM IS:—

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

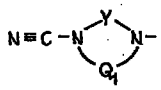


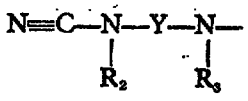
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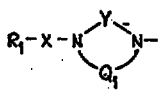
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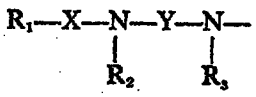
C* is a carbon atom constituting a centre of chirality;

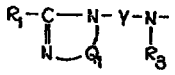
A is a radical of the general formula:—

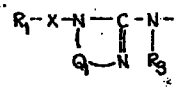


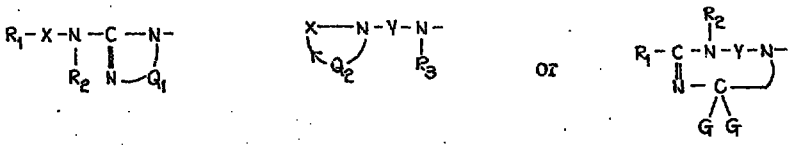




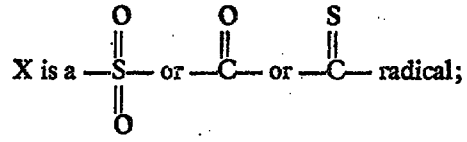


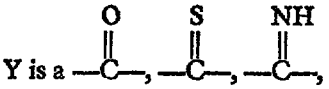


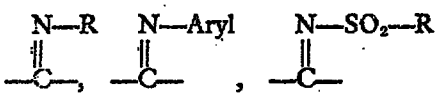


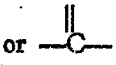


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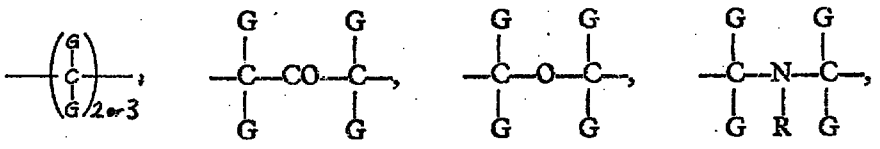
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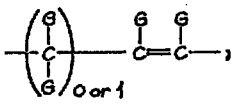
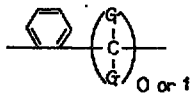
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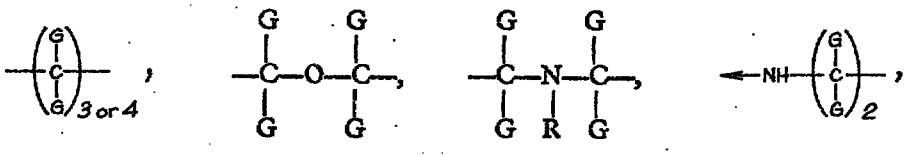
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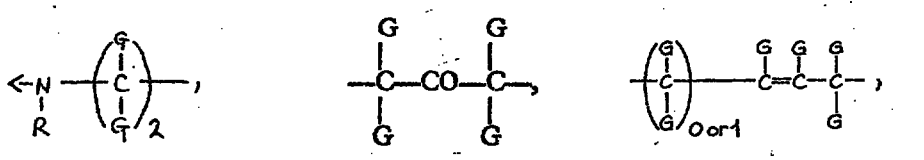
Q_1 is a

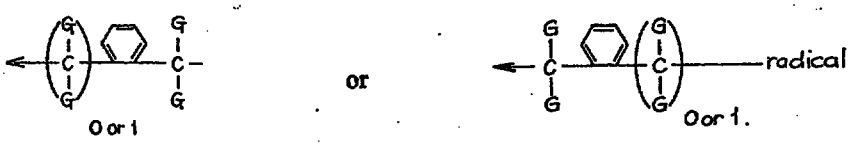


 or  radical and

Q_2 is a



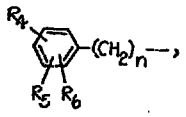
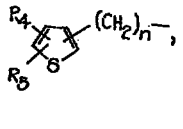
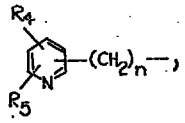
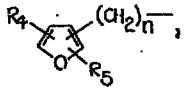
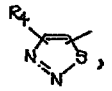
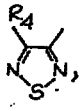




(in which

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

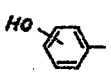
R_1 is an alkyl, cycloalkyl, alkenyl or cycloalkenyl radical with up to 10 carbon atoms, or a vinyl, arylvinyl, mono-, di- or tri-halo-lower alkyl, H_2N—, R—NH—, $(R)_2>N$—, aryl-NH—, aryl-lower alkylamino radical, or an alkoxy* or aralkoxy* radical with up to 8 carbon atoms, or a cycloalkoxy* radical with up to 7 carbon atoms, or an aryloxy*, R—O—V—, R—S—V, N≡C—V—, R—O—CO—V—, H_2N—CO—V—, R—NH—CO—V—, $(R)_2>N$—CO—V—,

or

radical;

R_1 can also be a hydrogen atom when X is —CO—;
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, 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 radical 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 one of the radicals mentioned above for R, and can also be hydrogen;
the meanings marked * not being available when X is —SO_2—)];
Z is a —CO— or —SO— radical; and
B is a radical of the formula:—

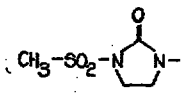
or


the arrow in the divalent linking group

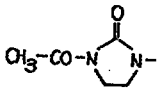


meaning that the linkage of two atoms by the free valencies of this group must take place as indicated by the arrow; the term "lower alkyl" means a straight chain or branched alkyl group with up to 6 carbon atoms.

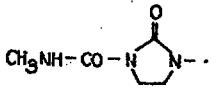
2. The compounds according to claim 1, in which A is



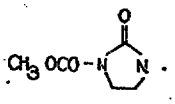
3. The compounds according to claim 1, in which A is



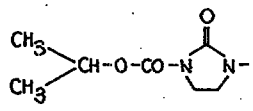
4. The compounds according to claim 1, in which A is



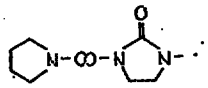
5. The compounds according to claim 1 in which A is



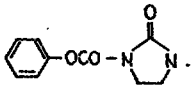
6. The compounds according to claim 1, in which A is



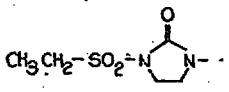
7. The compounds according to claim 1, in which A is



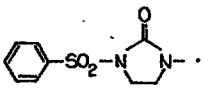
8. The compounds according to claim 1, in which A is



9. The compounds according to claim 1, in which A is

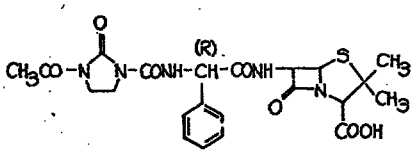


10. The compounds according to claim 1 in which A is

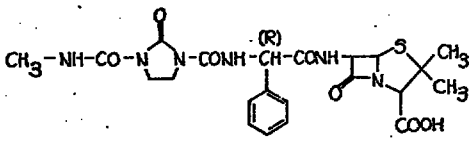


11. The compounds according to any preceding claim in which C* is in the R-configuration.

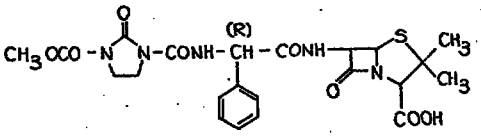
12. D-α-[(3-acetyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin:



13. D - α - [(3 - methylaminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonyl-amino] - benzylpenicillin:

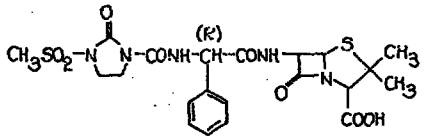


14. D - α - [(3 - methoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonyl-amino] - benzylpenicillin:

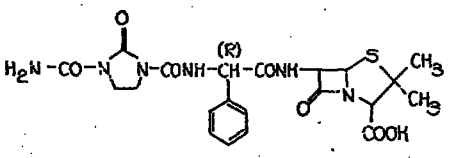


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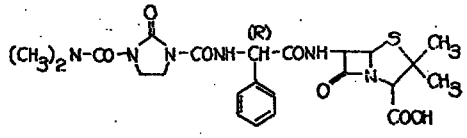
15. α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:



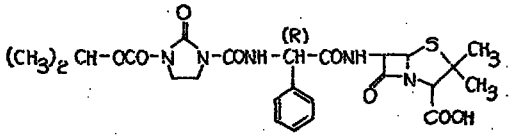
16. D - α - [(3 - aminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:



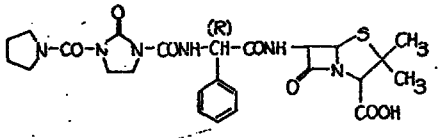
17. D - α - [(3 - dimethylaminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:



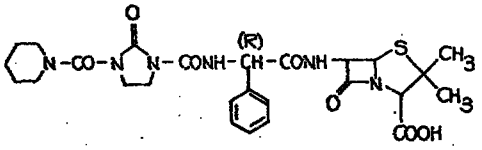
18. D - α - [(3 - i - propyloxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:



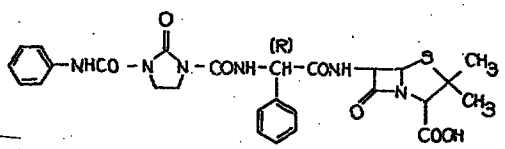
19. D - α - [(3 - pyrrolidyl - N - carbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:



20. D - α - [(3 - piperidyl - N - carbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:

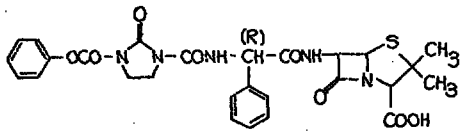


21. D - α - [(3 - phenylaminocarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:

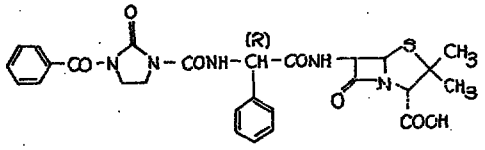


* C L M S *

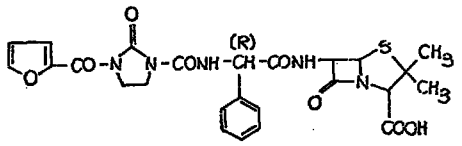
22. D - α - [(3 - phenoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonyl-amino] - benzylpenicillin:



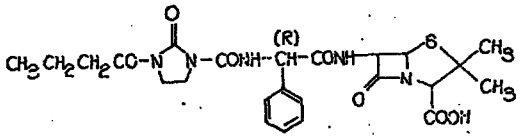
23. D-α-[(3-benzoyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin:



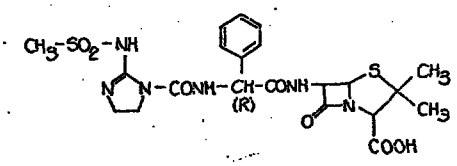
24. D-α-[(3-furoyl(2)-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin:



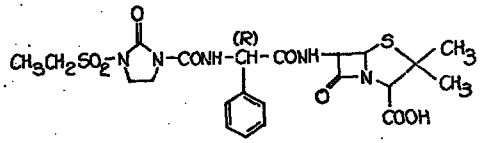
25. D - α - [(3 - n - butyryl - imidazolidin - 2 - on - 1 - yl) - carbonylamino]-benzylpenicillin:



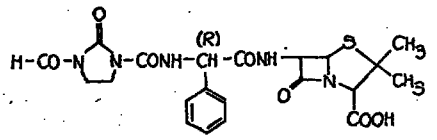
26. D - α - [(2 - methylsulphonylamino - imidazolin(2) - 1 - yl) - carbonyl-amino] - benzylpenicillin:



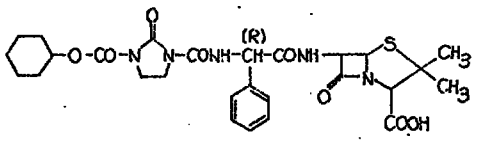
27. D - α - [(3 - ethylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino]-benzylpenicillin:



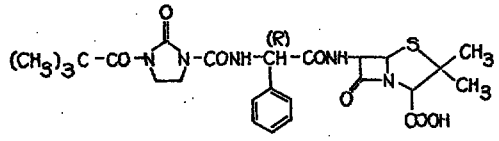
28. D-α-[(3-formyl-imidazolidin-2-on-1-yl)-carbonylamino]-benzylpenicillin:



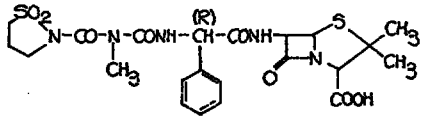
29. D - α - [(3 - cyclohexyloxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:



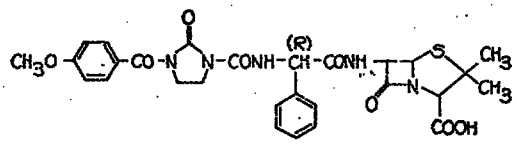
30. D - α - [(3 - pivaloyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:



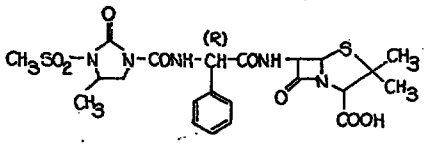
31. D - α - [3 - (isothiazolidine - 1,1 - dioxide - 2 - yl - carbonyl) - 3 - methyl-ureido] - benzylpenicillin:



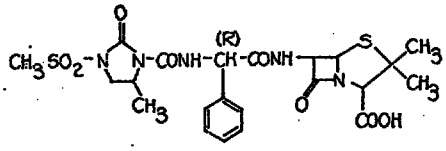
32. D - α - [3 - (p - methoxybenzoyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:



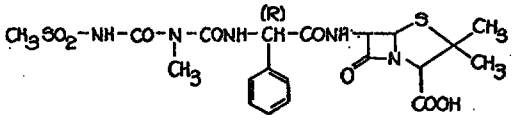
33. D - α - [(3 - methylsulphonyl - 4 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:



34. D - α - [(3 - methylsulphonyl - 5 - methyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - benzylpenicillin:

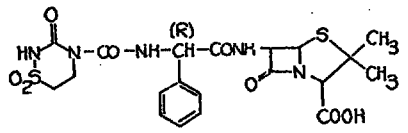


35. D-α-(5-methylsulphonyl-3-methyl-biureido)-benzylpenicillin:

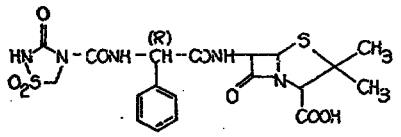


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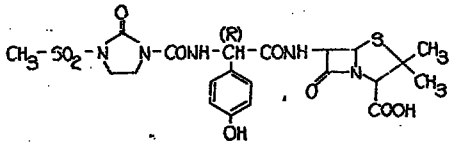
36. D - α - (1,3 - diaza - 4 - thia - cyclohexan - 2 - one - 4,4 - dioxide - 1 - yl-carbonylamino) - benzylpenicillin:



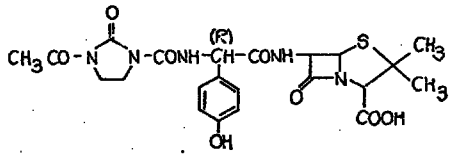
37. D - α - (4 - thia - imidazolidin - 2 - one - 4,4 - dioxide - 1 - ly - carbonyl-amino) - benzylpenicillin:



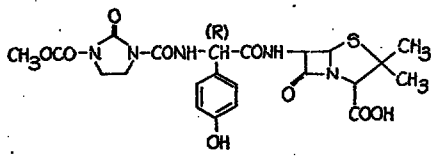
38. D - α - [(3 - methylsulphonyl - imidazolidin - 2 - on - 1 - yl) - carbonyl-amino] - 4 - hydroxy - benzylpenicillin:



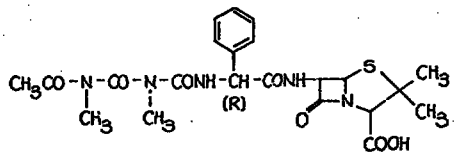
39. D - α - [(3 - acetyl - imidazolidin - 2 - on - 1 - yl) - carbonylamino] - 4-hydroxy - benzylpenicillin:



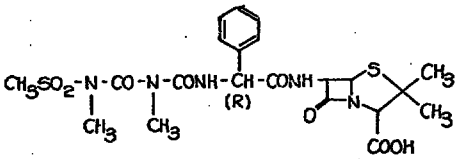
40. D - α - [(3 - methoxycarbonyl - imidazolidin - 2 - on - 1 - yl) - carbonyl-amino] - 4 - hydroxy - benzylpenicillin:



41. D-α-(3,5-dimethyl-5-acetyl-biureido)-benzylpenicillin:

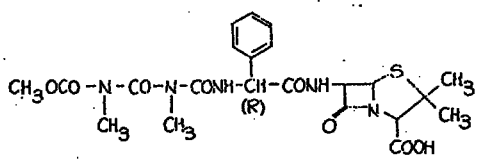


42. D-α-(3,5-dimethyl-5-methylsulphonyl-biureido)-benzylpenicillin:

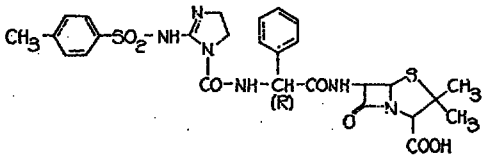


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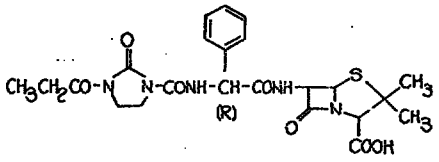
43. D-α-(3,5-dimethyl-5-methoxycarbonyl-biureido)-benzylpenicillin:



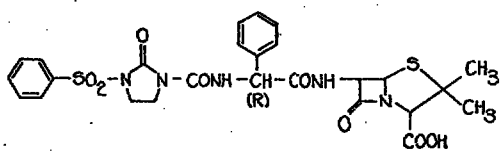
44. D-α-(2-tosylamino-imidazolin(2)-1-yl)-carbonylamino]-benzylpenicillin:



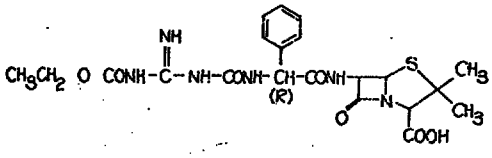
45. D-α-[(2-oxo-3-propionyl-1-imidazolidinyl)-carbonylamino]-benzylpenicillin:



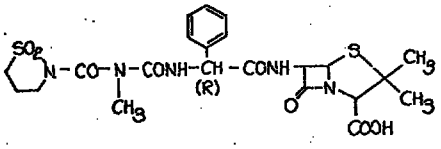
46. D - α - [(2 - oxo - 3 - benzenesulphonyl - 1 - imidazolidinyl) - carbonylamino]-benzylpenicillin:



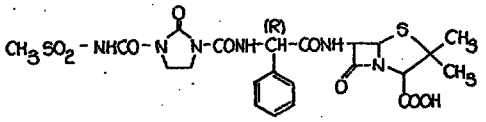
47. D-α-(4-imino-5-ethoxycarbonylbiureido)-benzylpenicillin:



48. D - α - {3 - [N - (1,1 - dioxo - isothiazolidin - 2 - yl) - carbonyl] - 3-methyl} - ureido - benzylpenicillin:

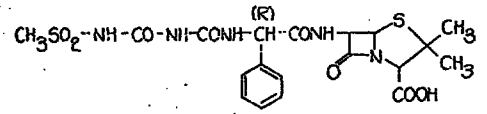


49. D - α - ([3 - (methylsulphonyl - amino - carbonyl) - imidazolidin - 2 - on-1 - yl] - carbonylamino - benzylpenicillin:

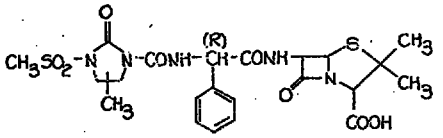


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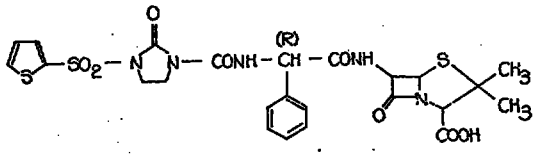
50. D-α-(5-mesyl-biuredio)-benzylpenicillin:



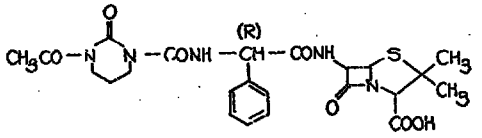
51. D - α - [(3 - mesyl - 4- or 5 - methyl - imidazolidin - 2 - on - 1 - yl)-carbonylamino] - benzylpenicillins:



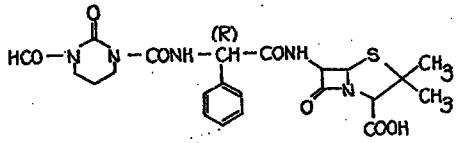
52. D - α - [3(thienyl(2) - sulfonyl) - imidazolidin - 2 - on - 1 - yl - carbonyl-amino] - benzylpenicillin:



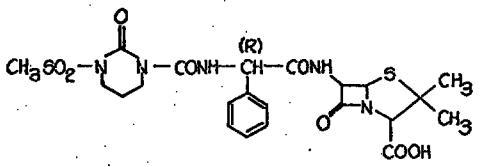
53. D - α - [(2 - oxo - 3 - acetyl - 1,3 - diaza - cyclohex - 1 - yl) - carbonyl-amino] - benzylpenicillin:



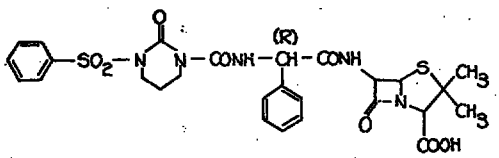
54. D - α - [(3 - formyl - 1,3 - diaza - cyclohexan - 2 - on - 1 - yl) carbonyl-amino] - benzylpenicillin:



55. D - α - [(3 - mesyl - 1,3 - diaza - cyclohexan - 2 - on - 1 - yl) - carbonyl-amino] - benzylpenicillin:



56. D - α - [(3 - phenylsulfonyl - 1,3 - diaza - cyclohexan - 2 - on - 1 - yl)-carbonylamino] - benzylpenicillin:



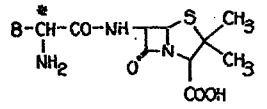
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57. Compounds according to claim 1 which are hereinbefore specifically mentioned in Examples 1 to 24, other than those according to any of claims 12 to 56.

58. Compounds according to claim 1 which are hereinbefore specifically mentioned in any of Examples 25 to 32, other than those according to any of claims 12 to 56.

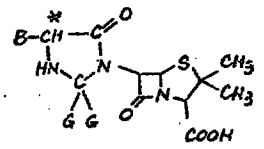
59. Compounds according to claim 1 which are hereinbefore specifically mentioned in any of Examples 33 to 37, other than those according to any of claims 12 to 56.

60. 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, in which process a 6-amino-penicillanic acid derivative of the general formula:



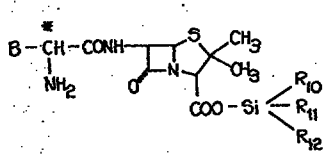
II

or a product of the condensation of such a derivative with a carbonyl compound, the said product having the general formula:—

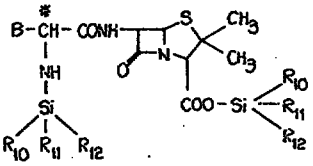


III

or a silyl or disilyl derivative of the said derivative, of the general formula:—

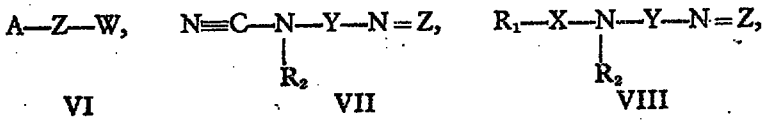


IV

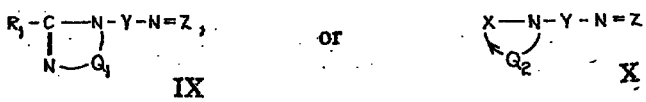


V

respectively is reacted with a compound of the general formula:—



VI VII VIII



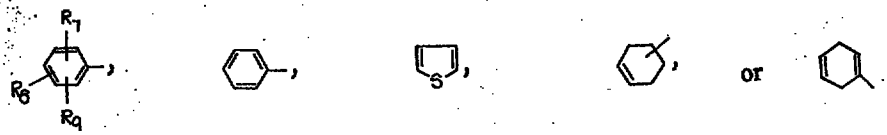
IX X

in an anhydrous or aqueous solvent in the presence of a base, when a compound of the general formula II or III is reacted, and in an anhydrous solvent free of hydroxyl groups, with or without a base, when a compound of the general formula IV or V is reacted, at a temperature in the range of −50° to +50°C;

[in which general formulae:—

A, C*, G, Q_1, Q_2, R_1, R_2, X, Y and Z are as defined in any of claims 1 to 16;

B is a radical of the 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 being as defined above];

R_{10}, R_{11} and R_{12}, which can be the same or different, are each an alkyl group with up to 6 carbon atoms; and

W is a halogen, azide, or

$$-N\langle^{NO}_{\text{(lower alkyl)}}$$

radical].

61. A process according to claim 60 in which the reaction is carried out at a pH in the range 2.0 to 9.0.

62. A process according to claim 61 in which the said pH is from 4.5 to 9.0.

63. A process according to claim 61 in which the said pH is from 2.0 to 3.0.

64. A process according to any of claims 60 to 63 in which the reaction is carried out at a temperature from 0 to +20°C.

65. A process according to any of claims 60 to 64 in which W is a chlorine atom.

66. A process according to any of claims 60 to 65 in which a compound of the general formula II or III is reacted in the presence of a base, the said base being triethylamine, diethylamine, or N-ethylpiperidine.

67. A process according to any of claims 1 to 65 in which a compound of the general formula IV or V is reacted in the presence of a base, the said base being a secondary or tertiary amine.

68. A process according to claim 60, substantially as hereinbefore described in any of Examples 1 to 24.

69. A process according to claim 60 substantially as hereinbefore described in any of Examples 25 to 32.

70. A process according to claim 60 substantially as hereinbefore described in any of Examples 33 to 37.

71. Compounds according to claim 1 whenever produced by the process of any of claims 60 to 68.

72. Compounds according to claim 1 whenever produced by the process of claim 69.

73. Compounds according to claim 1 whenever produced by the process of claim 70.

74. A pharmaceutical composition containing as an active ingredient a compound according to any of claims 1 to 9, 11 to 43, 57 or 71 in admixture with a solid or liquified 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.

75. A pharmaceutical composition containing as an active ingredient a compound according to any of claims 1 to 9, 11 to 43, 57 or 71, in the form of a sterile or isotonic aqueous solution.

76. A composition according to claim 74 or 75 containing from 0.5 to 95% of active ingredient, by weight.

77. A composition according to claim 74, 75 or 76 in which the said compound is a compound according to claim 10, 44 to 51, 58 to 72.

78. A composition according to claim 74, 75 or 76 in which the said compound is a compound according to claim 52 to 56, 59 or 73.

79. A pharmaceutical composition according to claim 74 or 75, substantially as hereinbefore described or specifically exemplified.

80. A medicament in dosage unit form comprising a compound according to any of claims 1 to 9, 11 to 43, 57 or 71 either alone or in admixture with a diluent.

81. A medicament in the form of tablets, pills, dragees, capsules, ampoules or suppositories comprising a compound according to any of claims 1 to 9, 11 to 43, 57 or 71 either alone or in admixture with a diluent.

82. A medicament according to claim 80 or 81, in which the said compound is a compound according to claim 10, 44 to 51, 58 or 72.

83. A medicament according to claim 80 or 81, in which the said compound is a compound according to claim 52 to 56, 59 or 73.

84. A medicament according to claim 80 or 81, substantially as hereinbefore described or specifically exemplified.

85. A medicament according to claim 82, substantially as hereinbefore described or specifically exemplified.

86. A medicament according to claim 83, substantially as hereinbefore described or specifically exemplified.

87. A method of combatting bacterial infections in non-human animals which comprises administering to the animals an active compound according to any of claims 1 to

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9, 11 to 43, 57 to 71 either alone or in admixture with a diluent or in the form of a medicament according to claim 80 or 81.

88. A method according to claim 87 in which the active compound is administered in an amount of 25,000 to 1,000,000 U/kg of body weight/day.

89. A method according to claim 87 or 88 in which the active compound is a compound according to claim 10, 44 to 51, 58 or 72.

90. A method according to claim 87 or 88 in which the active compound is a compound according to claim 52 to 56, 59 or 73.

91. A method according to claim 87 substantially as hereinbefore specifically described or exemplified.

92. An animal feedstuff comprising a nutritious material and a compound according to any of claims 1 to 9, 11 to 43, 57 or 71.

93. An animal feedstuff comprising a nutritious material and a compound according to claim 10, 44 to 51, 58 or 72.

94. An animal feedstuff comprising a nutritious material and a compound according to claim 52 to 56, 59 or 73.

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