

# PATENT SPECIFICATION

(11) 1301961

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## DRAWINGS ATTACHED

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METZGER



## (54) NEW PENICILLINS, THEIR PREPARATION AND THEIR PHARMACEUTICAL USE

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

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

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

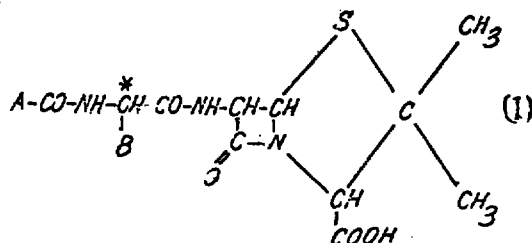
The present invention relates to a process for the production of those 6-( $\alpha$ -3-acylureidoacetamido)-penicillanic acids in which the hydrogen atom of the nitrogen atom present in the 3-position is substituted by other radicals. Some of these penicillins and their salts are claimed in our copending application No. 16881/71 (Serial Number 1301962).

6-( $\alpha$ -3-Acylureidoacetamido)-penicillanic acids are described in Netherlands Patent Applications Nos. 6901646 and 6908909, US Patent Nos. 3,479,339, 3,483,188, 3,481,922 and in German Published Specification 1,959,920, but all 3-acylureidoacetamidopenicillanic acids described and claimed in these Patents possess a hydrogen atom on the nitrogen atom present in the 3-position in the acylureido group. The presence of this hydrogen atom and the absence of another substituent at this position of the acylureido group in part necessarily results from the different way of synthesising these penicillins.

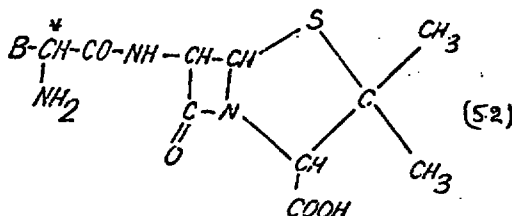
These new compounds, in the treatment of infections by Gram-positive and Gram-negative germs, especially by strains of *Klebsiella aerobacter*, are able, at low doses, to provide a valuable remedy.

[Price 25p]

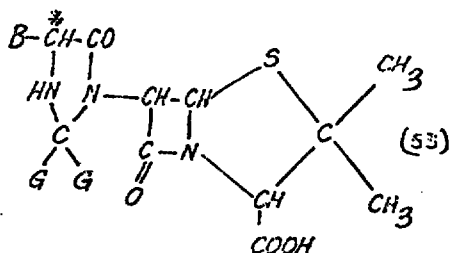
The present invention provides a process for the production of penicillins of the following general formula and their salts:—



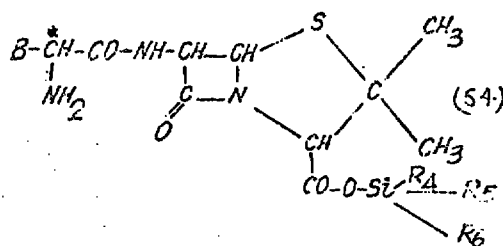
in which process a compound of the general formula:—



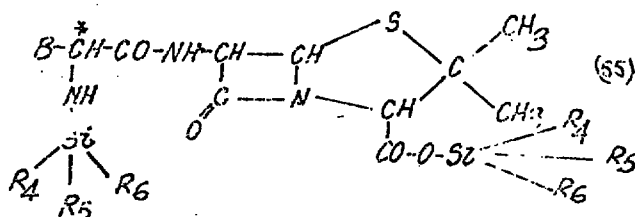
or a condensation product of such a compound with a carbonyl compound, preferably acetone [U.S. Patent No. 3,198,804], the said condensation product being of the general formula:—



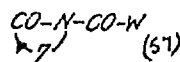
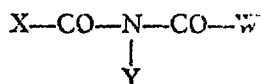
(in the preferred case when the said carbonyl compound is acetone, G is methyl) or a compound of the general formula:—



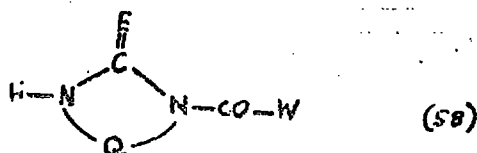
or



is reacted at a temperature of  $-20$  to  $+50^{\circ}\text{C}$  with a compound of the general formula:—



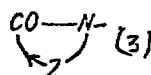
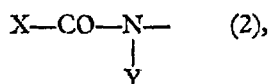
or



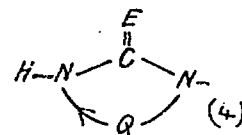
in a solvent and in the presence of a base when a compound of general formula (52) or (53) is used, and in an anhydrous solvent free of hydroxyl groups with or without the presence of a base when a compound of general formula (54) or (55) is used; and, when a salt is desired, converting the penicillin thus produced into the desired salt;

[in which general formulae:—

A denotes a group of the general formula:—

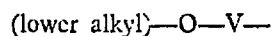


or

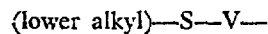


in which general formulae (2), (3) and (4):

X denotes a hydrogen atom or an alkyl, alkenyl, cycloalkyl, or cycloalkenyl group with up to 10 carbon atoms, or a vinyl, arylvinyl, mono-, di- or tri-halo-lower alkyl, mono-lower alkyl-amino, di-lower alkylamino, monoarylamino or aryl-(lower alkyl)-amino group, or an alkoxy or aralkoxy group with up to 8 carbon atoms, or a cycloalkoxy group with up to 7 carbon atoms, or an aryloxy group, or a group of the general formula:—



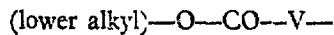
(5);



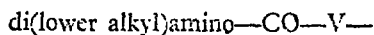
(6);



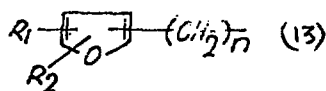
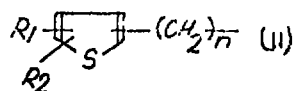
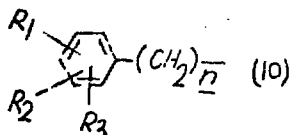
(7);

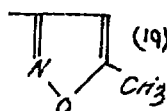
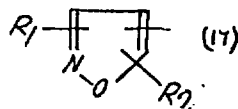
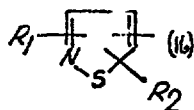
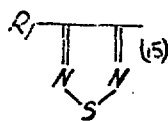
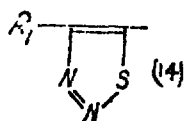


(8);

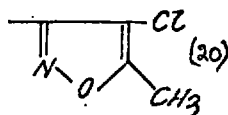


(9);





or



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

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V denotes a divalent organic radical with one to three carbon atoms;  
 n is 0, 1, or 2; and

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R<sub>1</sub>, R<sub>2</sub>, and R<sub>3</sub>, which may be the same or different, each denote a hydrogen, chlorine, bromine, iodine or fluorine atom or a nitro, nitrile, di-(lower alkyl)-amino, di-(lower alkyl)aminocarbonyl, lower alkanoylamino, lower alkoxy carbonyl, lower alkanoyloxy, lower alkyl, lower alkoxy, sulphonyl or trifluoromethyl group;

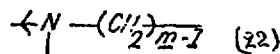
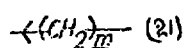
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Y denotes an alkyl, alkenyl, cycloalkyl or cycloalkenyl group with up to 10 carbon atoms, or a vinyl, propenyl, mono-, di- or tri-halo-lower alkyl, aryl, or heterocyclic group, or an aralkyl group with up to 8 carbon atoms;

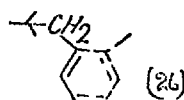
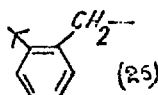
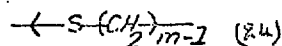
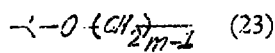
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-(Z)- denotes a divalent group of the general formula:—

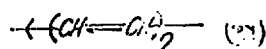
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or



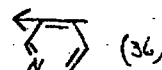
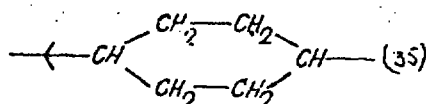
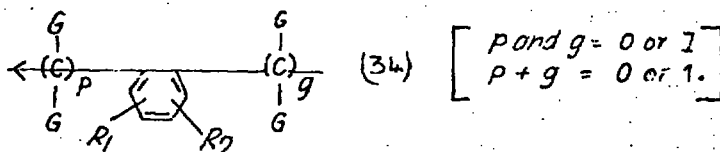
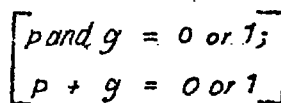
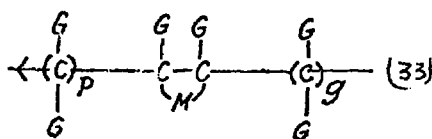
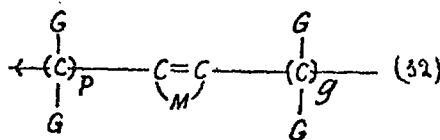
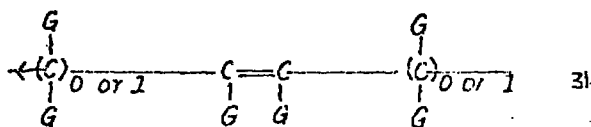
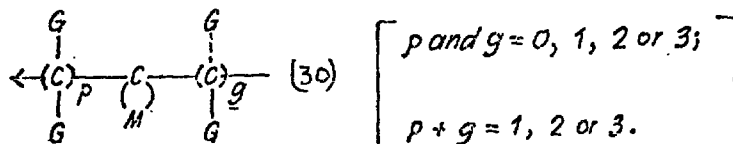
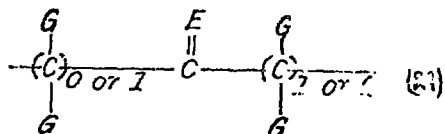
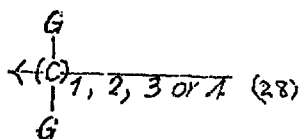
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(in which general formulae (21) to (27) m denotes an integer from 3 to 5, and the arrow in the divalent group Z means that the linkage of the two free valencies of

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$$\text{CO} \xrightarrow{\text{N}_2} \text{N}_2 \quad (3)$$

5



or

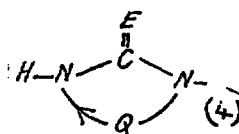


[in which general formulae (28) to (34):

G is a hydrogen atom or a lower alkyl group;

R<sub>1</sub> and R<sub>2</sub> are as defined above;

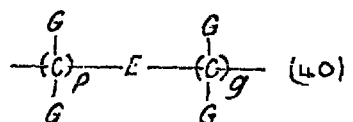
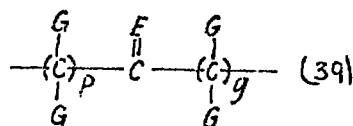
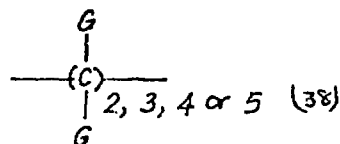
the arrow means that the linkage of the two free valencies of the group Q with the two nitrogen atoms of the group of general formula:—



is not arbitrary but is orientated as indicated by the arrow;

and

M is a group of the general formula:—



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

B denotes a phenyl group or a phenyl or thienyl group substituted by a lower alkyl, lower alkoxy, lower alkylthio group or by a halogen atom; and

C\* is a carbon atom constituting a chirality centre which can be in either of the two possible R— and S— configurations;

R<sub>1</sub>, R<sub>2</sub>, and R<sub>3</sub> denote alkyl radicals having up to 6 carbon atoms; and

W denotes a halogen atom or an azide group.

The process of the invention includes within its scope the production not only of pure stereoisomers in which C\* is in either the R— or the S— configuration, but also mixtures of the stereoisomers in any proportion.

The term "lower alkyl" as used in this specification means straight- and branched-chain alkyl groups having up to 6 carbon atoms. When a part of other groups, such as "di-(lower alkyl)-amino, the term "lower alkyl" refers only to the alkyl part of the particular group.

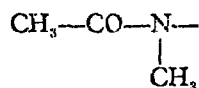
The invention also includes within its scope the following new compounds;

- 1) D-α-(3-Acetyl-3-methyl-ureido)-benzylpenicillin and its sodium salt.
- 2) D-α-(3-Dimethylaminocarbonyl-3-methyl-ureido)-benzylpenicillin and its sodium salt.
- 3) D-α-(Pyrrolidin-2-on-1-yl-carbonylamino)-benzylpenicillin and its sodium salt.
- 4) D-α-(Imidazolidin-2-on-1-yl-carbonylamino)-benzylpenicillin and its sodium salt.

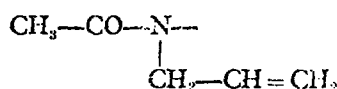
Preferred salts produced by the process of the invention are the pharmaceutically tolerated non-toxic salts of the penicillins of general formula (1). These include salts

of the acid carboxyl group, such as the 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-methylmorpholine and N-ethylmorpholine, 1-phenamine, dehydroabietylamine, N,N'-bis-dehydroabietylthylenediamine, and N-lower alkylpiperidine. Other amines have been used for forming salts of known penicillins, and these may also be used in the present invention.

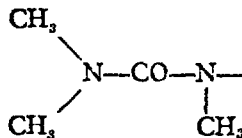
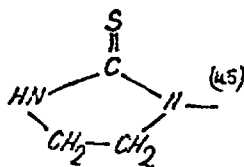
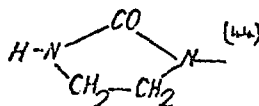
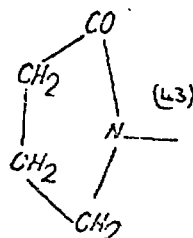
Preferred groups "A" are the following:—



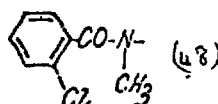
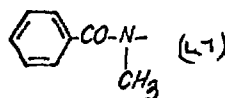
(41);

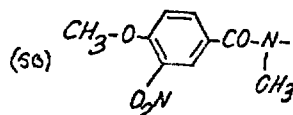
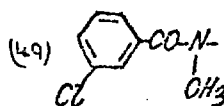


(42);

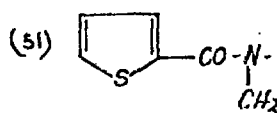


(46);





and



Those stereoisomers in which the chirality centre C\* is in the R— configuration are preferred.

A preferred radical "B" is the phenyl group.

If a compound of the general formulae (52) or (53) is used as the starting material for the synthesis of a penicillin according to the invention, and is reacted with a compound of the general formulae (56), (57) or (58), the reactions can for example be carried out in a mixture of water and one or more organic solvents miscible with water, such as acetone, tetrahydrofuran, dioxane, acetonitrile, dimethylformamide, dimethylsulphoxide or isopropanol. At the same time, the pH of the reaction mixture is for example kept between 6.5 and 8.0 by adding a base or by the use of a buffer solution. The reaction according to the invention can however also be carried out in a different pH range, for example between 4.5 and 9.0 or at pH 2.0—3.0. It is furthermore possible to carry out the reaction in a solvent immiscible with water, for example chloroform or methylene chloride, with the addition of, preferably, triethylamine, diethylamine or N-ethylpiperidine. Furthermore, the reaction can be carried out in a mixture of water and a solvent which is immiscible with water such as, for example, ether, chloroform, methylene chloride, carbon disulphide, isobutyl methyl ketone, acetic acid ethyl ester or benzene, in which case it is desirable to stir the mixture vigorously and to main the pH value between 4.5 and 9.0 or, for example, 2.0 and 3.0, by adding bases or by the use of a buffer solution.

If a compound of the general formula (54) or (55) is used as the starting material for the synthesis, and this substance is reacted with a compound of the general formula (56), (57) or (58), the process must be carried out in a solvent which is anhydrous and free of hydroxyl groups. Such solvents are for example methylene chloride, chloroform, benzene, tetrahydrofuran, acetone and dimethylformamide. In this case, the addition of a base is not necessary, but in individual cases the yield and purity of the products can be improved thereby. Admittedly, the converse effect is also possible. The base which is optionally added must either be a tertiary amine, such as pyridine or triethylamine, or a secondary amine which is difficult to acylate as a result of steric hindrance, such as dicyclohexylamine. The number of usable bases is hence almost unlimited.

As in most chemical reactions, higher or lower temperatures than those indicated in the Examples can be used. If, however, the values given in the Examples are significantly exceeded, side-reaction, which reduce the yield or unfavorably influence the purity of the products, will increasingly occur. On the other hand, excessively lowered reaction temperatures so greatly reduce the reaction speed that reductions in yield can occur. Reaction temperatures in the range of  $-20^{\circ}\text{C}$  to  $+50^{\circ}\text{C}$  are therefore preferred, and a temperature of about  $0^{\circ}\text{C}$  to  $+20^{\circ}\text{C}$  is particularly preferred.

The reactants can be reacted with one another in equimolar amounts. It can however be desirable to use one of the two reactants in excess, in order to facilitate the purification, or preparation in a pure form, of the desired penicillin, and to increase the yield. For example, the compounds of the general formulae (52) or (53) can be employed in an excess of 0.1 to 0.3 mol equivalents, and the decomposition of the reactants of the general formulae (56), (57) or (58) in the aqueous solvent mixture can

thereby be achieved. The excess of the reactants of the general formulae (52) or (53) can be easily removed when working up the reaction mixture, because of their good solubility in aqueous mineral acid. On the other hand, however, the reactants of the general formulae (56), (57) and (58) can also advantageously be employed in an excess of, for example, 0.1 to 1.0 mol equivalents. As a result of this, the reactants, for example of the general formulae (52) or (53), are better utilised, and the decomposition of the reactants of the general formulae (56), (57) or (58) which takes place as a side-reaction in aqueous solvents, is compensated. Since the compounds of the general formulae (56), (57) or (58) which are added in excess rapidly change, in water, into neutral amides, ureas or thioureas which can easily be removed, the purity of the penicillins is thereby hardly impaired.

The amount of the base added is determined *inter alia* by the desired maintenance of a particular pH. Where a pH measurement and adjustment is not carried out, or is impossible or pointless because of the absence of sufficient amounts of water in the diluent, 2 mol equivalents of base are preferably added in the case where a compound of the general formulae (52) or (53) is used, and either no base at all or, preferably, 1 mol equivalent of base is added in the case where a compound of the general formulae (54) or (55) is used.

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

The compounds of the general formula (52) used as the starting material in the present invention can, as regards the configuration at the asymmetrical centre in the side chain ( $C^*$ ), be in the D=R-form or L=S-form. They are described in German Offenlegungsschrift No. 1,156,078, in U.S. Patents Nos. 3,342,677, 3,157,640, 2,985,648 and 3,140,282, and (an anhydrous form) in U.S. Patent No. 3,144,445. All crystal forms and configurations of the compounds of the general formula (52) are suitable for use as the starting material for the reaction according to the invention. The compounds of the general formulae (53), (54) or (55) used as the starting material in the present invention, can, as regards the configuration at the asymmetrical centre in the side chain ( $C^*$ ), also occur in the D=R-form or L=S-form. The configuration of the asymmetrical centres of the 6-aminopenicillanic acid nucleus in the compounds of the general formulae (52), (53), (54) and (55) should be identical with the corresponding asymmetrical centres of the 6-aminopenicillanic acid, which has, for example, been obtained from penicillin-G by fermentative processes.

The production of the compounds of the general formulae (54) and (55), used as the starting material, is described in Netherlands Patent Application No. 68/18057.

The compounds of the general formulae (56) and (57) used as starting materials in the present invention can be produced, if W is halogen, according to processes which are described in German Offenlegungsschrift No. 1 793 287.5, in German Patent No. 1,259,871, in USA Patents Nos. 3,275,618 and 3,337,621, and in British Patent Specification No. 1,226,450.

Furthermore compounds of the general formulae (56) and (57) have been prepared, if W is halogen, from the corresponding amides after metallisation with methyl-lithium and subsequent reaction with phosgene. Such preparations are described in more detail in the Examples.

The production of the compounds of the general formula (58), to be used as the starting material — where W is halogen — is illustrated in Examples No. 86B and 89B/C. It can also be carried out in the same manner as described in the Examples.

The chemotherapeutic activity of the new penicillins was tested *in vivo* and *in vitro*. Table I which follows gives the *in vitro* inhibition values (MIC) in units/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 test tube in the dilution series which is free of turbidity. A complete medium of the following composition was used as the growth medium:

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

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

The number given to each penicillin in Table I and subsequently corresponds to that of the Example of this specification in which its production is illustrated.

MIC in units/ml

TABLE 1

| Bacterial Strains |         |           |         |         |             |          |            |          |                    |          |               |       |                        |  |
|-------------------|---------|-----------|---------|---------|-------------|----------|------------|----------|--------------------|----------|---------------|-------|------------------------|--|
| Penicillin No.    | F. coli |           |         |         | Prot. vulg. |          | Klebsiella |          | Pseudomonas aerug. |          | Staph. aureus |       | Strep. faec. ATCC 9790 |  |
|                   | 14      | A %       | C 165   | 183/58  | 1017        | 3400     | K 10       | 63       | Bonn               | Walter   | 1777 E        | 133   |                        |  |
| Ampicillin        | ~0.8    | >400      | 6.25    | 200     | 400         | >400     | 100—200    | 100—200  | 200                | 200      | 200           | <1.0  | 12.5                   |  |
| 1                 | 1.56    | >400      | 6.25    | 3.12    | 6.25        | 12.5     | 25         | 50       | 12.5               | 25       | 100           | <0.78 | 100                    |  |
| 2                 | 6.25    | >400      | 25      | 12.5    | 25          | 50       | 100        | 50       | 25                 | 50       | 50            | <0.78 | 100                    |  |
| 3                 | 3.12    | >400      | 6.25    | 6.25    | 25          | 25       | 100        | 50       | 12.5               | 25       | 200           | <0.78 | 50                     |  |
| 4                 | 1.56    | 400       | 6.25    | 3.12    | 6.25        | 6.25     | 100        | 100      | 12.5               | 25       | 400           | <0.78 | 100                    |  |
| 5                 | <0.78   | 400       | 1.56    | <0.78   | 1.56        | 3.12     | 50         | 50       | 6.25               | 12.5     | 200           | <0.78 | 50                     |  |
| 6                 | 3.12    | >400      | 25      | 25      | 25          | 100      | 100        | 100      | 25                 | 50       | 50            | 1.56  | 100                    |  |
| 7                 | <0.78   | 400       | 3.12    | 1.56    | 3.12        | 6.25     | 12.5       | 12.5     | 12.5               | 12.5     | 50            | <0.78 | 50                     |  |
| 8                 | 3.12    | >400      | 12.5    | 50      | 50          | 100      | 50         | 50       | 6.25               | 12.5     | 50            | <0.78 | 25                     |  |
| 9                 | 1.56    | 400       | 6.25    | 1.56    | 6.25        | 6.25     | 100        | 100      | 25                 | 50       | 400           | <0.78 | 100                    |  |
| 10                | 3.12    | >400      | 12.5    | 6.25    | 12.5        | 25       | 50         | 25       | 12.5               | 12.5     | 50            | <0.78 | 50                     |  |
| 11                | 1.56    | 400       | 6.25    | 3.12    | 12.5        | 25       | 50         | 25       | 12.5               | 100      |               | <0.78 | 100                    |  |
| 12                | 3.12    | 200       | 6.25    | 3.12    | 12.5        | 12.5     | 25         | 12.5     | 12.5               | 100      |               | <0.78 | 100                    |  |
| 13                | >400    | >400      | >400    | >400    | >400        | >400     | >400       | >400     | >400               | >400     |               | 200   | >400                   |  |
| 14                | 6.25    | 400       | 25      | 12.5    | 50          | 200      | 100        | 50       | 50                 | 400      |               | <0.78 | 100                    |  |
| 15                | 3.12    | 200—400   | 6.25    | 1.56    | 6.25        | 12.5     | 25—50      | 12.5—25  | 12.5               | ~50      |               | 0.78  | 50—100                 |  |
| 16                | 100     | >400      | >400    | >400    | >400        | >400     | >400       | >400     | >400               | >400     |               | 25    | >400                   |  |
| 17                | <0.8    | 100 < 500 | 0.8 < 4 | 0.8 < 4 | 4 < 20      | 0.8 < 4  | 20 < 100   | 4 < 20   | 4 < 20             | 4 < 20   |               | <0.8  | 20 < 100               |  |
| 18                | 0.8 < 4 | 100 < 500 | 4 < 20  | ~4      | 4 < 20      | 20 < 100 | 20 < 100   | 20 < 100 | 4 < 20             | 20 < 100 |               | <0.8  | 20 < 100               |  |
| 25                | 3.12    | 400       | 6.25    | 6.25    | 25          | 6.25     | 25         | 50       | 50                 | 100      |               | <0.78 | 100                    |  |
| 28                | 12.5    | >400      | 25      | 50      | 50          | 50       | 100        | 50       | 25                 | 50       |               | <0.78 | 100                    |  |

TABLE 1 continued

MIC in units/ml

Bacterial Strains

|    |       |         |       |       |      |        |        |        |       |        |
|----|-------|---------|-------|-------|------|--------|--------|--------|-------|--------|
| 17 | <0.8  | 100<500 | 0.8<4 | 0.8<4 | 4<20 | 0.8<4  | 20<100 | 20<100 | <0.8  | 20<100 |
| 18 | 0.8<4 | 100<500 | 4<20  | ~4    | 4<20 | 20<100 | 20<100 | 4<20   | <0.78 | 100    |
| 25 | 3.12  | 400     | 6.25  | 6.25  | 25   | 6.25   | 25     | 50     | <0.78 | 100    |
| 28 | 12.5  | >400    | 25    | 50    | 50   | 50     | 100    | 25     | <0.78 | 100    |

TABLE 1 continued  
MIC in units/ml

| Penicillin No. | Bacterial Strains |         |        |        |                    |        |                   |         |                           |         |                      |
|----------------|-------------------|---------|--------|--------|--------------------|--------|-------------------|---------|---------------------------|---------|----------------------|
|                | <i>E. coli</i>    |         |        |        | <i>Prot. vulg.</i> |        | <i>Klebsiella</i> |         | <i>Pseudomonas aerug.</i> |         | <i>Staph. aureus</i> |
|                | 14                | A 261   | C 165  | 183/58 | 1017               | 3400   | K 10              | 63      | Bonn                      | Walter  |                      |
| 29             | 4<20              | 100<500 | 20<100 | 20<100 | 20<100             | 20<100 | 20<100            | 20<100  | 4<20                      | 20<100  | <0.8                 |
| 30             | 1.56              | 400     | 6.25   | 3.12   | 12.5               | 6.25   | 50                | 25      | 25                        | 50      | <0.78                |
| 31             | 1.56              | 400     | 6.25   | 1.56   | 3.12               | 12.5   | 25                | 12.5    | 25                        | 50      | <0.78                |
| 32             | 6.25              | 400     | 12.5   | 12.5   | 12.5               | 25     | 50                | 25      | 25                        | 50      | 10                   |
| 33             |                   | 100<500 | 0.8<4  |        | 0.8<4              |        |                   | 4<20    | 4<20                      | 4<20    | 20<100               |
| 34 B           |                   | >500    | 4<20   |        | 20<100             |        |                   | 20<100  | 20<100                    | 20<100  | 20<100               |
| 35 B           |                   | >500    | 4<20   |        | 20<100             |        |                   | 20<100  | 20<100                    | 20<100  | 20<100               |
| 36             | 12.5              | >400    | 50     | 100    | 100                | 50     | 200               | 200     | 100                       | 100     | 200                  |
| 38             | 6.25              | >400    | 12.5   | 25     | 50                 | 50     | 200               | 200     | 25                        | 25      | 25                   |
| 39             | 6.25              | >400    | 25     | 6.25   | 25                 | 25     | 400               | 50      | 25                        | 50      |                      |
| 40             | 3.12              | >400    | 6.25   | 6.25   | 12.5               | 25     | 400               | 400     | 12.5                      | 25      | 100                  |
| 41 B           |                   | >500    | 20-100 |        | approx. 500        |        |                   | >500    | 100-500                   | 100-500 | 100-500              |
| 43 R           |                   | >500    | 20-100 |        | 100-500            |        |                   | 100-500 | 100-500                   | 100-500 | approx. 20           |
| 44             |                   | >500    | 4<20   |        | 4<20               |        |                   | 20<100  | 4<20                      | 4<20    | 4<20                 |
| 45             |                   | >500    | 4-20   |        | 100-500            |        | 100-500           |         | 100-500                   |         | 20-100               |
| 47 B           |                   | >500    | 4-20   |        | >500               |        |                   | 100-500 | >500                      | >500    | 20-100               |
| 49             | <0.8              | 20<100  | <0.8   | <0.8   | 0.8-4              | 0.8-4  | ~4                | 4-20    | 0.8-4                     | 0.8-4   | 4-20                 |
| 50             |                   | >500    | 4-20   |        | 20-100             |        |                   | 100-500 | 0.8-4                     | 20-100  | ~20                  |
| 51             |                   | >500    | 4-20   |        | 20-100             |        |                   | 100-500 | 0.8-4                     | 50-100  | 4-20                 |
| 52             | 0.8-4             | 100-500 | 4-20   | 4-20   | 4-20               | 4-20   | 4-20              | 4-20    | 20-100                    | 20-100  | 4-20                 |

TABLE 1 continued  
MIC in units/ml

| Penicillin No. | Bacterial Strains |        |        |        |                    |       |                   |         |                           |               |                      |       |                                     |
|----------------|-------------------|--------|--------|--------|--------------------|-------|-------------------|---------|---------------------------|---------------|----------------------|-------|-------------------------------------|
|                | <i>E. coli</i>    |        |        |        | <i>Prot. vulg.</i> |       | <i>Klebsiella</i> |         | <i>Pseudomonas aerug.</i> |               | <i>Staph. aureus</i> |       | <i>Strep. faec.</i><br>ATCC<br>9790 |
|                | 14                | Δ 261  | C 165  | 183/58 | 1017               | 3400  | K 10              | 63      | Bonn                      | Walter        | 1777E                | 133   |                                     |
| 53             | <0.8              | 20—100 | 0.8—4  | <0.8   | 0.8—4              | 0.8—4 | 4—20              | 4—20    | 4—20                      | 4—20          | 4—20                 | <0.8  | 4—20                                |
| 54             | <0.8              | 20—100 | 0.8—4  | <0.8   | 0.8—4              | 0.8—4 | 4—20              | 4—20    | 4—20                      | 4—20          | 20—100               | <0.8  | 4—20                                |
| 55             |                   |        | 0.8—4  |        | 4—20               |       |                   | 100—500 |                           | 4—20          | 100—500              | <0.8  |                                     |
| 56             |                   |        | 4—20   |        | 20—100             |       |                   | 100—500 |                           | 4—20          | 100—500              | <0.8  |                                     |
| 57             |                   |        | 20—100 |        | 20—100             |       |                   | 100—500 |                           | 20—100        | 100—500              | <0.8  |                                     |
| 58             |                   |        | 4—20   |        | 4—20               |       |                   | 20—100  |                           | approx.<br>20 | 100—500              | <0.8  |                                     |
| 59             | <0.78             | 50     | 1.56   | 1.56   | 3.12               | 3.12  | 6.25              | 12.5    | 12.5                      | 12.5          | 12.5                 | <0.8  | 50                                  |
| 60             | 12.5              | >400   | 50     | 200    | 100                | 200   | 100               | 200     | 200                       | 200           | 100                  | 1.6   | 50                                  |
| 61             | 25                | >400   | 200    | 400    | >400               | >400  | 400               | >400    | >400                      | >400          | 200                  | 1.6   | 100                                 |
| 63             | 6                 | >400   | 50     | 100    | 100                | 200   | 25                | 100     | 100                       | 100           | 100                  | <0.8  | 100                                 |
| 64             | 12.5              | >400   | 50     | 200    | 100                | 400   | 50                | 100     | 200                       | 400           | 400                  | 1.6   | 100                                 |
| 65             | 3.12              | >400   | 25     | 12.5   | 50                 | 100   | 50                | 100     | 50                        | 100           | 25                   | <0.8  | 200                                 |
| 66             | 3.12              | >400   | 12.5   | 25     | 50                 | 50    | 50                | 50      | 50                        | 100           | 25                   | <0.78 | 200                                 |
| 67             | 3.12              | >400   | 25     | 50     | 50                 | 100   | 200               | 100     | 50                        | 100           | 50                   | 3.12  | 200                                 |
| 68             | 12.5              | >400   | 50     | 50     | 100                | 100   | 100               | 200     | 100                       | 200           | 100                  | 1.56  | 200                                 |
| 69             | <0.78             | 50     | 3.12   | 1.56   | 3.12               | 6.25  | 12.5              | 12.5    | 12.5                      | 25            | 12.5                 | <0.78 | 25                                  |
| 70             | <0.78             | 50     | 1.56   | <0.78  | 1.56               | 6.25  | 6.25              | 6.25    | 6.25                      | 12.5          | 12.5                 | <0.78 | 50                                  |
| 71             | 0.78              | 50     | 1.56   | 1.56   | 3.12               | 6.25  | 6.25              | 6.25    | 6.25                      | 12.5          | 6.25                 | <0.78 | 50                                  |
| 72             | 12.5              | >400   | 100    | 100    | 200                | >400  | 25                | 50      | 200                       | 200           |                      | <0.8  | 50                                  |
| 73             | <0.8              | 20—100 | <0.8   | <0.8   | 0.8—4              | 0.8—4 | 0.8—4             | 4—20    | 0.8—4                     | 0.8—4         | 20—100               | <0.8  | 4—20                                |
| 74             | <0.8              | >400   | 0.3—4  | <0.8   | 4—20               | 0.8—4 | 4—20              | 20—100  | 4—20                      | 4—20          | 20—100               | <0.8  | 4—20                                |

TABLE 1 continued  
MIC in units/ml

Bacterial Strains

|    |       |        |       |      |       |       |       |        |       |        |       |      |
|----|-------|--------|-------|------|-------|-------|-------|--------|-------|--------|-------|------|
| 70 | <0.78 | 50     | 1.56  | 1.56 | 3.12  | 6.25  | 6.25  | 6.25   | 12.5  | 6.25   | <0.78 | 50   |
| 71 | 0.78  | 50     | 1.56  | 1.56 | 200   | >400  | 25    | 200    | 200   | <0.8   | <0.8  | 50   |
| 72 | 12.5  | >400   | 100   | 100  | 0.8-4 | 0.8-4 | 0.8-4 | 0.8-4  | 0.8-4 | 20-100 | <1.3  | 4-20 |
| 73 | <0.8  | 20-100 | <0.8  | <0.8 | 4-20  | 0.8-4 | 4-20  | 20-100 | 4-20  | 25-100 | <0.8  | 4-20 |
| 74 | <0.8  | >400   | 0.8-4 | <0.8 | 4-20  | 0.8-4 | 4-20  | 20-100 | 4-20  | 25-100 | <0.8  | 4-20 |

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1,301,961

13

TABLE 1 continued  
MIC in units/ml

| Penicillin No. | Bacterial Strains |       |       |        |             |      |            |      |                    |       |               |      |                        |
|----------------|-------------------|-------|-------|--------|-------------|------|------------|------|--------------------|-------|---------------|------|------------------------|
|                | E. coli           |       |       |        | Prot. vulg. |      | Klebsiella |      | Pseudomonas aerug. |       | Staph. aureus |      | Strep. faec. ATCC 9790 |
|                | 14                | A 261 | C 165 | 183/58 | 1017        | 3400 | K 10       | 63   | Born               | Waite | Staph. aureus |      |                        |
|                |                   |       |       |        |             |      |            |      |                    |       | 1777E         | 133  |                        |
| 76             | 3.1               | >400  | 25    | 25     | 12.5        | 50   | 50         | 200  | 100                | 50    | 200           | 3.1  | 100                    |
| 77             | 12.5              | 400   | 50    | 25     | 25          | 100  | 100        | 400  | 400                | 100   | 100           | <0.8 | 200                    |
| 80             | 6.25              | 200   | 25    | 12.5   | 25          | 100  | 50         | 50   | 25                 | 100   | 12.5          | <0.8 | 50                     |
| 82             | <0.3              | 50    | 3.1   | 1.6    | 3.1         | 6.25 | 12.5       | 25   | 12.5               | 12.5  |               | <0.8 | 12.5                   |
| 83             | <0.8              | 50    | 3.1   | 1.6    | 3.1         | 3.1  | 6.25       | 12.5 | 12.5               | 6.25  |               |      |                        |
| 84             | <0.8              | 50    | 3.1   | 1.6    | 3.1         | 12.5 | 12.5       | 25   | 25                 | 12.5  |               | <0.8 | 25                     |
| 85             | 12.5              | >400  | 50    | 50     | 200         | 400  | 50         | 100  | 100                | 200   |               | <0.3 | 100                    |
| 86             | 1.56              | 400   | 6.25  | 50     | 12          | 25   | 50         | 50   | 6.25               | 12.5  | 200           | <0.8 | 25                     |
| 89 A           | 12.5              | >400  | 50    | 100    | 50          | 200  | 200        | 100  | 25                 | 200   | 100           | <0.8 | 50                     |

The activity spectrum of the penicillins and salts produced according to the invention includes both Gram-negative and Gram-positive bacteria. The particular advantage of the penicillins according to the invention is that they are effective both *in vitro* (Table 1) and in animal experiments (Table 2) against ampicillin-resistant and carbenicillin-resistant *Klebsiella* bacteria and against ampicillin-resistant *Proteus* bacteria. Furthermore, they act on ampicillin-resistant *Pseudomonas* varieties *in vitro* and *in vivo*. The concentrations required for destroying the bacteria are reached in the serum after parenteral administration (Table 3). Table 4 shows the decrease in the number of ampicillin-resistant *Proteus bacteria* present in the blood after intraperitoneal infection and subcutaneous administration of 50,000 units/kg of penicillin. The excellent effect of some of the new penicillins against Gram-positive bacteria is shown in Table 2. The excellent effect is achieved both on a single administration and also on multiple administration. The resorption of the new penicillins often takes place very rapidly after subcutaneous administration (Table 3), and the peak values are often reached within 10 minutes. Elimination is equally rapid in both these cases. The substances according to the invention are stable to acid; as examples, penicillins No. 1, No. 8 and No. 25 may be quoted, which remain microbiologically active at pH 1 for over one hour. Table 5

5

10

15

5

10

15



Number of surviving mice in % (after intraperitoneal infection and subcutaneous therapy) after the indicated number of days.

| Bacterial Strains                     | Penicillin    | Dose*) | 1st | 2nd | 3rd | 5th | day |
|---------------------------------------|---------------|--------|-----|-----|-----|-----|-----|
| <i>E. coli</i> C 165                  | No:—86        | A      | 80  | 80  | 80  | 80  |     |
| <i>E. coli</i> C 165                  | Carbenicillin | A      | 70  | 50  | 50  | 50  |     |
| <i>Prot. vulg.</i> 1017 I             | No:—86        | A      | 70  | 50  | 50  | 50  |     |
|                                       | Carbenicillin | A      | 50  | 50  | 50  | 50  |     |
|                                       | Ampicillin    | A      | 0   | 0   | 0   | 0   |     |
|                                       | No:—89        | B      | 100 | 100 | 100 | 100 |     |
|                                       |               |        |     |     |     |     |     |
| <i>Klebsiella</i> 63                  | No:—86        | B      | 70  | 30  | 0   |     |     |
|                                       | Carbenicillin | B      | 0   |     |     |     |     |
|                                       | Ampicillin    | B      | 0   |     |     |     |     |
|                                       | Cephalothin   | B      | 0   |     |     |     |     |
|                                       | No:—89        | C      | 100 | 100 | 40  | 10  |     |
| <i>Pseudm. aer.</i><br>Walter         | No:—86        | D      | 100 | 20  | 20  | 20  |     |
|                                       | Carbenicillin | D      | 80  | 20  | 20  | 20  |     |
|                                       | Ampicillin    | D      | 0   |     |     |     |     |
|                                       | Cephalothin   | D      | 0   |     |     |     |     |
|                                       |               |        |     |     |     |     |     |
| <i>Pseudomon.</i><br><i>aer.</i> F 41 | No:—86        | E      | 100 |     |     |     |     |
|                                       | Carbenicillin | E      | 0   |     |     |     |     |
| <i>Pseudomon.</i><br><i>aer.</i> F 41 | No:—86        | F      | 100 |     |     |     |     |
|                                       | Carbenicillin | F      | 20  |     |     |     |     |
| <i>Pseudomon.</i><br><i>aer.</i> F 41 | No:—86        | G      | 100 |     |     |     |     |
|                                       | Carbenicillin | G      | 70  |     |     |     |     |
| <i>Pseudomon.</i><br><i>aer.</i> F 41 | No:—86        | H      | 100 |     |     |     |     |
|                                       | Carbenicillin | H      | 70  |     |     |     |     |
| <i>Klebsiella</i> 63                  | No:—86        | A      | 30  |     |     |     |     |

Continuation of TABLE 2

| Bacterial Strains    | Penicillin    | Dose*) | 1st | 2nd | 3rd | 5th day |
|----------------------|---------------|--------|-----|-----|-----|---------|
| <i>Klebsiella</i> 63 | Carbenicillin | A      | 0   |     |     |         |
|                      | No:—86        | B      | 100 |     |     |         |
| <i>Klebsiella</i> 63 | Carbenicillin | B      | 0   |     |     |         |
|                      | No:—86        | C      | 100 |     |     |         |
|                      | Carbenicillin | C      | 0   |     |     |         |

- \*) Dose A = 37,500 units/kg, 30 and 90 minutes after infection  
 Dose B = 75,000 units/kg, 30 and 90 minutes after infection  
 Dose C = 150,000 units/kg, 30 and 90 minutes after infection  
 Dose D = 150,000 units/kg, 0.5, 2, 4 and 6 hours after infection  
 Dose E = 50,000 units/kg, 30 minutes before and 2, 4 and 6 hours after infection  
 Dose F = 75,000 units/kg, 30 minutes before and 2, 4 and 6 hours after infection  
 Dose G = 150,000 units/kg, 30 minutes before and 2, 4 and 6 hours after infection  
 Dose H = 200,000 units/kg, 30 minutes before and 2, 4 and 6 hours after infection.

TABLE 3

Serum level after subcutaneous ("s.c.") administration to white mice, in units/ml of serum, measured from the microbiological activity against *Proteus vulgaris* 1017 (ampicillin-resistant).

| Penicillin No:— | Dose (s.c.)   | Concentration in the serum, number of minutes after administration of the dose |          |          |          |           |
|-----------------|---------------|--------------------------------------------------------------------------------|----------|----------|----------|-----------|
|                 |               | 10 mins.                                                                       | 15 mins. | 20 mins. | 30 mins. | 60 mins.  |
| 1               | 150,000 units |                                                                                | 25 units |          | 20 units | <2 units  |
| 8               | 50,000        | 50 units                                                                       |          | 10 units |          |           |
| 8               | 150,000 units |                                                                                | 42 units |          | 26 units | <10 units |

TABLE 4

Reduction in number of bacteria/ml of blood after subcutaneous administration of Penicillin No. 25.  
Infection took place intraperitoneally with *Proteus vulgaris* 1017,  $8 \times 10^5$ /mouse; ampicillin-resistant.

|                                                                                                                                                    | Number of bacteria after infection, measured after infection: |                 |                            |                 |                 |                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|-----------------|----------------------------|-----------------|-----------------|-----------------|
|                                                                                                                                                    | 30 mins.                                                      | 60 mins.        | 90 mins.                   | 120 mins.       | 150 mins.       | 180 mins.       |
| Control                                                                                                                                            | $3 \times 10^4$                                               | $2 \times 10^4$ | $2 \times 10^4$            | —               | $7 \times 10^4$ | $5 \times 10^4$ |
| Administration of:<br>$1 \times 50,000$ units/kg.<br>subcutaneously,<br>30 minutes after infection.                                                | $9 \times 10^3$                                               | $7 \times 10^3$ | $2 \times 10^3$            | $1 \times 10^3$ | $3 \times 10^3$ | $1 \times 10^3$ |
| Administration of:<br>$1 \times 50,000$ units/kg.<br>subcutaneously, after<br>30 minutes, and a further<br>$50,000$ units/kg. after<br>90 minutes. | $2 \times 10^4$                                               | $8 \times 10^3$ | approx.<br>$5 \times 10^3$ | $2 \times 10^2$ | $<10^1$         | $<10^1$         |

The Table shows that a dose of 50,000 units/kg, administered subcutaneously, already drastically reduces the number of bacteria in the blood; additionally, it shows that the double subcutaneous administration of 50,000 units/kg causes elimination of the bacteria.

TABLE 5

| Penicillin No:— | Acute toxicity (LD <sub>50</sub> ) in white mice after intravenous injection into the vein of the tail, in mg/kg |
|-----------------|------------------------------------------------------------------------------------------------------------------|
| 8               | >4000                                                                                                            |
| 2               | 1500                                                                                                             |
| 28              | ~3000                                                                                                            |
| 25              | ~1200                                                                                                            |
| 36              | 4000                                                                                                             |
| 17              | 1500                                                                                                             |
| Carbenicillin   | 2700                                                                                                             |
| Dicycloxacillin | 900                                                                                                              |

The comparison shows that the penicillins produced by the process of the invention are clearly superior to the commercially available products dicycloxacillin and carbenicillin on intravenous injection of a single dose.

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

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

As stated above, the penicillins and pharmaceutically acceptable salts produced by the process of the present invention may be administered perorally.

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

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

As stated above, the penicillins and pharmaceutically acceptable salts produced by the process of the invention may be administered parenterally. A group of preferred pharmaceutical compositions of the invention are therefore those adapted for parenteral administration. Such administration may be intramuscular, subcutaneous, or intravenous, if appropriate by means of a continuous drip infusion. The diluents and

carriers used are therefore preferably those that adapt the active ingredient for parenteral administration. Examples of such diluents and carriers are solvents and suspending diluents such as water and water-miscible organic solvents, in particular sesame oil, groundnut oil, aqueous propylene glycol, and N,N-dimethyl formamide. Examples of pharmaceutical compositions of the invention are sterile isotonic saline aqueous solutions of the active ingredient, which may be buffered with a pharmaceutically acceptable buffer and are preferably pyrogen-free.

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

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

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

A particularly convenient form for the medicaments in dosage unit form according to the invention is dry ampoules containing predetermined quantities of the active ingredient, which may be used for the *in situ* preparation of parenterally injectable solutions.

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

As stated above it is also preferred to administer the new penicillins and their salts parenterally. Preferred medicaments in dosage unit form according to the invention are therefore those adapted for parenteral injection, such as ampoules containing a measured quantity of a sterile isotonic saline injectable aqueous solution of the new active ingredient, which may be buffered with a pharmaceutically acceptable buffer and are preferably free of pyrogens.

The preferred rate of parenteral and peroral administration for the new penicillins and non-toxic salts of the invention is 25,000 to 1,000,000 units 1 kg. body weight/day. This can be given as a single daily dose or divided, particularly in the case of dosage rates within the upper part of this range, into several doses taken at intervals.

The preferred unit dose for administration of the medicaments of the invention is therefore 25,000 to 1,000,000 units/kg of body weight of active ingredient, which will normally be administered once daily.

The Examples which follow illustrate the invention without restricting it. The  $\alpha$ -aminobenzylpenicillin used in the Examples contained about 14% of water, but anhydrous  $\alpha$ -aminobenzylpenicillin [compare US Patent No. 3,144,445] can be used equally well.

Unless expressly stated otherwise, "ampicillin" denotes the  $\alpha$ -aminobenzylpenicillin having the D(-) - = R-configuration in the side chain.

The  $\beta$ -lactam content was determined iodometrically. All penicillins described here showed an IR spectrum corresponding to their structure.

The NMR spectra were recorded in CD<sub>3</sub>OD solution; the signals indicated in the Examples agree with the particular structure; the position of the signals is quoted in  $\tau$ -values.

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

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

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

#### Example 1

##### Sodium D- $\alpha$ -(3-benzoyl-3-methyl-ureido)-benzylpenicillin:

D- $\alpha$ -Aminobenzylpenicillin (ampicillin) (15 parts by weight) was suspended in 80% strength aqueous tetrahydrofuran (150 parts by volume) and sufficient triethylamine (approx. 7.5 parts by volume) was added dropwise at 20°C, whilst stirring, that a clear solution was just produced and the pH value was between 7.5 and 8.2 (glass electrode). The mixture was now cooled to 0°C and a solution of N-benzoyl-N-methyl-carbamic acid chloride (6.5 parts by weight) in absolute tetrahydrofuran (25 parts by volume) was added dropwise over the course of 30 minutes, whilst cooling with ice, the pH value being kept between 7.5 and 8.0 through simultaneous addition of triethylamine. The mixture was stirred for 30 minutes at 0°C and subsequently further stirred at room temperature until addition of triethylamine was no longer necessary for maintaining the pH value of 7.5. Water (150 parts by volume) was now added and the pH value was adjusted to 6.5 with a little dilute sulphuric acid, after which the tetrahydrofuran was largely removed in a rotary evaporator at room temperature. The aqueous solution which remained was extracted once by shaking with ether, subsequently covered with a 1:1 mixture of ethyl acetate and ether (400 parts by volume) and treated with sufficient dilute sulphuric acid, whilst stirring and cooling with ice, to establish a pH value of 1—2. The organic phase was separated off, twice washed with water (60 parts by volume at a time) and dried at 0°C over MgSO<sub>4</sub> for about one hour, and after filtering, the solution of the penicillin was treated with about 50 parts by volume of a 1 molar solution of sodium 2-ethyl hexanoate in ether containing methanol. The mixture was left to stand at 0°C for some hours, the solvent was subsequently decanted, and the residue was triturated with ether and filtered off. After drying over P<sub>2</sub>O<sub>5</sub> in a vacuum desiccator, the sodium salt of the penicillin was obtained in the form of a non-crystalline solid.

Yield: 14.7 parts by weight (83%).

$\beta$ -Lactam content: 87%.

Calculated: C 55.4 H 4.8 N 10.3 S 5.9

Found: C 56.2 H 7.0 N 9.7 S 5.9

NMR signals at  $\tau$  = 2.4 (10 H), 4.2 (1 H), 4.4 (2 H), 5.7 (1 H), 6.8 (3 H) and 8.5 ppm (6 H).

Effectiveness against *E. coli* 14: 1.56 units/ml (6.25 units/ml)<sup>x</sup>

Effectiveness against *Proteus* 3400: 12.5 units/ml (50 units/ml)<sup>x</sup>

Effectiveness against *Pseudomonas aerug.* Bonn: 12.5 units/ml (25 units/ml)<sup>x</sup>

The figures given in brackets give, for comparison, the particular effectiveness of the corresponding penicillin which carries hydrogen in the 3-position in the side chain (that is to say, which is not a subject of the present invention; compare Netherlands Patent Application No. 69/08909), that is to say sodium D- $\alpha$ -(3-benzoylureido)-benzylpenicillin.

Effectiveness in animal experiments: A and B.

#### Example 2

##### Sodium D- $\alpha$ -(3-benzoyl-3-ethylureido)-benzylpenicillin

This penicillin was prepared in the manner described in Example 1, from 15 parts by weight of ampicillin and 7.0 parts by weight of N-benzoyl-N-ethylcarbamic acid chloride.

Yield (crude product): 79%

$\beta$ -Lactam content: 91%

Calculated: C 53.8 H 5.4 N 9.6 S 5.6

Found: C 53.0 H 5.0 N 9.9 S 5.7

NMR signals at  $\tau$  = 2.5 (5 H), 2.6 (5 H), 4.5 (3 H), 5.8 (1 H), 6.2 (2 H), 8.4 (6 H) and 9.8 ppm (3 H).

Effectiveness against *E. coli* 14: 6.25 units/ml

Effectiveness against *Pseudomonas Aerug.* Bonn: 25 units/ml.

Effectiveness in animal experiments: A and B.

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## Example 3

Sodium D- $\alpha$ -(3-ethoxycarbonyl-3-methylureido)-benzylpenicillin:

If 18 parts by weight of ampicillin were reacted with 6.6 parts by weight of N-ethoxycarbonyl-N-methylcarbamic acid chloride in the manner described in Example 1, the penicillin was obtained in the form of its Na salt, in 72% yield.

$\beta$ -Lactam content: 94%

Calculated: C 49.3 H 5.1 N 11.0 S 6.3

Found: C 48.9 H 5.4 N 10.8 S 6.2

NMR signals at  $\tau$  = 2.6 (5 H), 4.4 (1 H), 4.5 (2 H), 5.8 (3 H), 6.8 (3 H), 8.5 (6 H) and 8.7 ppm (3 H).

Effectiveness against *E. coli* 14: 3.12 units/ml.

Effectiveness against *Pseudomonas Aerug.* Bonn: 12.5 units/ml.

Effectiveness in animal experiments: A and B.

## Example 4

Sodium D- $\alpha$ -(3-hexahydrobenzoyl-3-methylureido)-benzylpenicillin:

On reacting 15 parts by weight of ampicillin with 6.7 parts by weight of N-hexahydrobenzoyl-N-methylcarbamic acid chloride in accordance with the instruction of Example 1, the sodium salt of the penicillin was obtained in 60% yield.

$\beta$ -Lactam content: 89%

Calculated: C 53.5 H 6.0 N 10.0 S 5.8

Found: C 51.9 H 6.2 N 9.6 S 5.8

NMR signals at  $\tau$  = 2.6 (5 H), 4.5 (1 H), 4.55 (2 H), 5.8 (1 H), 6.7 (3 H), 7.3 (1 H), 8.0—9.0 (10 H) and 8.5 ppm (6 H).

Effectiveness against *Proteus* 3400: 6.25 units/ml

Effectiveness against *Pseudomonas Aerug.* Bonn: 12 units/ml.

Effectiveness in animal experiments: A and B.

## Example 5

Sodium D- $\alpha$ -(3-cinnamoyl-3-methylureido)-benzylpenicillin:

The sodium salt of the penicillin was prepared from 15 parts by weight of ampicillin and 7.4 parts by weight of N-cinnamoyl-N-methylcarbamic acid chloride, as in Example 1.

Yield: 72%

$\beta$ -Lactam content: 90%

Calculated: C 55.9 H 5.1 N 9.6 S 5.5

Found: C 54.8 H 5.6 N 9.4 S 5.4

NMR signals at  $\tau$  = 2.0—3.0 (12 H), 4.4 (1 H), 4.5 (1 H), 5.8 (1 H), 6.7 (3 H), 8.4 (3 H) and 8.5 ppm (3 H).

Effectiveness against *E. coli* 14: < 0.78 units/ml.

Effectiveness against *Proteus* 1017: 1.56 units/ml.

Effectiveness against *Pseudomonas Aerug.* Bonn: 6.25 units/ml.

Effectiveness in animal experiments: A and B.

## Example 6

Sodium D- $\alpha$ -(3- $\beta$ -chloropropionyl-3-methylureido)-benzylpenicillin:

19.7 parts by weight of ampicillin were reacted with 7.0 parts by weight of N- $\beta$ -chloropropionyl-N-methylcarbamic acid chloride in accordance with Example 1.

Yield: 80%

$\beta$ -Lactam content: 94%

Calculated: C 47.8 H 4.8 Cl 6.7 N 10.6 S 6.1

Found: C 48.4 H 5.2 Cl 6.0 N 10.5 S 6.5

NMR signals at  $\tau$  = 2.6 (5 H), 4.4 (1 H), 4.5 (2 H), 5.8 (1 H), 6.2 (2 H), 6.8 (3 H), 6.9 (2 H) and 8.5 ppm (6 H).

Effectiveness against *E. coli* 14: 3.12 units/ml

Effectiveness against *Proteus* 1017 25 units/ml

Effectiveness in animal experiments: A and B.

## Example 7

Sodium D- $\alpha$ -(3-(1,2,5,6)-tetrahydrobenzoyl-3-methylureido)-benzylpenicillin:

This penicillin was prepared in the manner described in Example 1, from 15.8

| 22 | 1,301,961                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 22 | 23         |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|------------|
|    | parts by weight of ampicillin and 7.0 parts by weight of N-1,2,5,6-tetrahydrobenzoyl-N-methylcarbamic acid chloride.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |    | by         |
|    | Yield: 55%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |    | de         |
|    | $\beta$ -Lactam content: 85% (according to the IR spectrum)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |    | Yi         |
| 5  | Calculated: C 55.2 H 5.6 N 10.3 S 5.9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 5  | Ca         |
|    | Found: C 54.5 H 6.3 N 10.2 S 5.9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |    | For        |
|    | NMR signals at $\tau$ = 2.3—2.8 (5 H), 4.2—4.6 (5 H), 5.8 (1 H), 6.7 (3 H), 7.1 (1 H) and 7.6—8.8 ppm (12 H).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |    | Na         |
|    | Effectiveness against <i>E. coli</i> 14: <0.78 units/ml.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |    | Eff        |
| 10 | Effectiveness against <i>Proteus</i> 1017: 3.12 units/ml.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 10 | Eff        |
|    | Effectiveness against <i>Pseudomonas Aerug.</i> Bonn: 12.5 units/ml.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |    | Eff        |
|    | Effectiveness in animal experiments: A and B.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |    |            |
|    | Example 8A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |    |            |
|    | Sodium D- $\alpha$ -(3-acetyl-3-methylureido)-benzylpenicillin:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |    |            |
| 15 | This penicillin was prepared in the manner described in Example 1, from 20 parts by weight of ampicillin and 6.0 parts by weight of N-acetyl-N-methyl-carbamic acid chloride.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 15 | ov         |
|    | Yield: 100%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |    | cri        |
|    | $\beta$ -Lactam content: 86%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    | Yie        |
| 20 | Calculated: C 49.2 H 5.1 N 11.5 S 6.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 20 | $\beta$ -L |
|    | Found: C 49.2 H(7.0) N 10.4 S 6.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |    | Cal        |
|    | NMR signals at $\tau$ = 2.6 (5 H), 4.45 (1 H), 4.55 (2 H), 5.8 (1 H), 6.75 (3 H), 7.7 (3 H) and 8.5 ppm (6 H).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |    | For        |
| 25 | Effectiveness against <i>E. coli</i> 14: 3.12 units/ml.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 25 | Na         |
|    | Effectiveness against <i>Pseudomonas Aerug.</i> Bonn: 6.25 units/ml.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |    | Eff        |
|    | Effectiveness against <i>Klebsiella</i> K 10: 50 units/ml.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |    | Eff        |
|    | Effectiveness in animal experiments: A and B.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |    |            |
|    | Example 8B                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |    |            |
| 30 | Crystalline sodium D- $\alpha$ -(3-acetyl-3-methylureido)-benzylpenicillin:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 30 | 16.7       |
|    | The process of preparing sodium D- $\alpha$ -(3-acetyl-3-methylureido)-benzylpenicillin, following Example 1, yields an amorphous product, as is shown by an X-ray diffraction picture. If this substance (3.8 parts by weight) is dissolved in ethanol (15 parts by volume) at room temperature (duration of the solution process, approx. 15 to 20 minutes), acetic acid ethyl ester (60 parts by volume) is subsequently added, and the clear colourless solution is left to stand at room temperature, very fine hair-like crystals (bundles of needles), which are recognisable as such with the naked eye, begin to separate out after 1 to 2 hours, if crystal seeds are not yet present. After some hours the crystals are filtered off, washed with acetic acid ethyl ester and dried thoroughly in a chamber wherein drying is effected by circulating air at 60°C. | 35 | mer        |
| 35 | Yield: 3.0 parts by weight                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 35 | Yiel       |
|    | $\beta$ -Lactam content: 92%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    | $\beta$ -L |
| 40 | Melting point: about 212°C (corrected, decomposition) (Kofler bench).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 40 | Calc       |
|    | NMR signals at $\tau$ = 2.5 (5 H), 4.4 (1 H), 4.55 (2 H), 5.8 (1 H), 6.7 (3 H), 7.7 (3 H) and 8.5 ppm (6 H).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    | Four       |
| 45 | Calculated: (1.9% H <sub>2</sub> O content taken into account)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 45 | NM         |
|    | C 50.1 H 5.0 N 11.7 S 6.7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |            |
| 50 | Found: C 50.1 H 5.8 N 10.8 S 7.0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |    | Eff        |
|    | The IR spectra of the amorphous and crystalline penicillin salt are depicted in Figures 1 and 2.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 50 | Eff        |
|    | It is however also possible to suspend the amorphous penicillin salt in acetic acid ethyl ester and then to add about 20% of ethanol whilst stirring. In that case, also, a clear solution is produced, from which the crystalline penicillin salt separates out.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |    | Eff        |
| 55 | It is furthermore also possible to use other solvent mixtures, for example ethanol/dioxane. If the amorphous salt is dissolved in acetone or warm (approx. 50°C) isopropanol and left to stand, the salt again separates out in a crystalline form.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 55 | Eff        |
|    | Example 9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |            |
|    | Sodium D- $\alpha$ -(3-cyclohexyloxy-carbonyl-3-methylureido)-benzylpenicillin:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |    |            |
| 60 | This penicillin was obtained from 20 parts by weight of ampicillin and 12 parts                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 60 | 15 p       |

|                         |       | 1,301,961                                                                                                                                                                                                                |  | 23 |
|-------------------------|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|----|
| 22                      | 23    |                                                                                                                                                                                                                          |  |    |
| benzoyl-N-              |       | by weight of N-cyclohexyloxycarbonyl-N-methylcarbamic acid chloride, in the manner described in Example 1.                                                                                                               |  |    |
|                         |       | Yield: 49%; $\beta$ -Lactam content: 94%.                                                                                                                                                                                |  |    |
|                         |       | Calculated: C 53.2 H 5.7 N 9.9 S 5.1                                                                                                                                                                                     |  | 5  |
|                         | 5 5   | Found: C 53.1 H 6.5 N 9.7 S 5.5                                                                                                                                                                                          |  |    |
|                         |       | NMR signals at $\tau$ = 2.6 (5 H), 4.4 (1 H), 4.5 (2 H), 5.2 (1 H), 5.8 (1 H), 6.8 (2 H) and 7.9—8.9 (16 H).                                                                                                             |  |    |
|                         |       | Effectiveness against <i>E. coli</i> 14: 1.56 units/ml.                                                                                                                                                                  |  |    |
|                         |       | Effectiveness against <i>Proteus</i> 3400 6.25 units/ml.                                                                                                                                                                 |  | 10 |
|                         | 10 10 | Effectiveness against <i>Pseudomonas aerug.</i> Bonn: 25 units/ml.                                                                                                                                                       |  |    |
|                         |       | Effectiveness in animal experiments: A and B.                                                                                                                                                                            |  |    |
|                         |       | Example 10                                                                                                                                                                                                               |  |    |
|                         |       | Sodium D- $\alpha$ -(3-allyloxycarbonyl-3-methyl-ureido)-benzylpenicillin:                                                                                                                                               |  |    |
| from 20 carbamic        | 15 15 | This penicillin was prepared from 19.2 parts by weight of ampicillin and 7.5 parts by weight of N-allyloxycarbonyl-N-methyl-carbamic acid chloride in the manner described in Example 1.                                 |  | 15 |
|                         |       | Yield: 79%.                                                                                                                                                                                                              |  |    |
|                         |       | $\beta$ -Lactam content: 90%.                                                                                                                                                                                            |  |    |
|                         |       | Calculated: C 50.9 H 5.0 N 10.7 S 6.2                                                                                                                                                                                    |  | 20 |
|                         | 20 20 | Found: C (53.8) H 5.8 N 10.7 S 6.2                                                                                                                                                                                       |  |    |
|                         |       | NMR signals at $\tau$ = 2.6 (5 H), 3.7—4.3 (1 H), 4.4 (1 H), 4.4—4.9 (4 H), 5.2 (2 H), 5.8 (1 H), 6.8 (3 H) and 8.4 ppm (6 H).                                                                                           |  |    |
|                         |       | Effectiveness against <i>Pseudomonas aerug.</i> Bonn: 12.5 units/ml.                                                                                                                                                     |  | 25 |
|                         | 25 25 | Effectiveness in animal experiments: A and B.                                                                                                                                                                            |  |    |
|                         |       | Example 11                                                                                                                                                                                                               |  |    |
|                         |       | Sodium D- $\alpha$ -(3- $\gamma$ -trifluorobutyryl-3-methyl-ureido)-benzylpenicillin:                                                                                                                                    |  |    |
| penicillin, diffraction | 30 30 | This penicillin was obtained in the manner described in Example 1, on reacting 16.7 parts by weight of ampicillin with 8.0 parts by weight of N- $\gamma$ -trifluorobutyryl-N-methylcarbamic acid chloride.              |  | 30 |
| 5 parts by              |       | Yield: 80%.                                                                                                                                                                                                              |  |    |
| 15 to 20                |       | $\beta$ -Lactam content: 91%.                                                                                                                                                                                            |  |    |
| 3, and the              |       | Calculated: C 47.1 H 4.5 N 9.9 S 5.7                                                                                                                                                                                     |  | 35 |
| hair-like               | 35 35 | Found: C 46.6 H 4.9 N 9.6 S 5.8                                                                                                                                                                                          |  |    |
| naked eye,              |       | NMR signals at $\tau$ = 2.6 (5 H), 4.4 (1 H), 4.55 (2 H), 5.8 (1 H), 6.9—7.8 (4 H) and 8.5 ppm (6 H).                                                                                                                    |  |    |
| ent. After              |       | Effectiveness against <i>E. coli</i> 14: 1.56 units/ml.                                                                                                                                                                  |  | 40 |
| and dried               | 40 40 | Effectiveness against <i>Proteus</i> 1017: 12.5 units/ml.                                                                                                                                                                |  |    |
| °C.                     |       | Effectiveness against <i>Pseudomonas aerug.</i> Bonn: 12.5 units/ml.                                                                                                                                                     |  |    |
|                         |       | Effectiveness against <i>Klebsiella</i> 63: 12.5 units/ml.                                                                                                                                                               |  |    |
|                         |       | Effectiveness in animal experiments: A and B.                                                                                                                                                                            |  |    |
|                         |       | Example 12                                                                                                                                                                                                               |  |    |
|                         |       | Sodium D- $\alpha$ -(3-[ <i>m</i> -nitro- <i>p</i> -methyl]-benzoyl-3-methyl-ureido)-benzylpenicillin:                                                                                                                   |  |    |
|                         | 45 45 | This penicillin was obtained in the manner described in Example 1, on reacting 15 parts by weight of ampicillin with 8.5 parts by weight of N- <i>m</i> -nitro- <i>p</i> -methylbenzoyl-N-methyl-carbamic acid chloride. |  | 45 |
|                         |       | Yield: 64%.                                                                                                                                                                                                              |  |    |
|                         |       | $\beta$ -Lactam content: 88%.                                                                                                                                                                                            |  | 50 |
| in Figures              | 50 50 | Calculated: C 50.7 H 4.7 N 11.3 S 5.2                                                                                                                                                                                    |  |    |
| acetic acid             |       | Found: C 50.6 H 5.7 N 11.2 S 5.0                                                                                                                                                                                         |  |    |
| ase, also, a            |       | NMR signals at $\tau$ = 1.9 (1 H), 2.2—2.4 (1 H), 2.4—2.8 (6 H), 4.4 (1 H), 4.5 (2 H), 5.8 (1 H), 6.8 (3 H), 7.4 (3 H) and 8.5 ppm (6 H).                                                                                |  |    |
| s out.                  |       | Effectiveness against <i>Pseudomonas aerug.</i> Bonn: 12.5 units/ml.                                                                                                                                                     |  | 55 |
| le ethanol/             | 55 55 | Effectiveness against <i>Klebsiella</i> 63: 12.5 units/ml.                                                                                                                                                               |  |    |
| 50°C) iso-              |       | Effectiveness in animal experiments: A and B.                                                                                                                                                                            |  |    |
|                         |       | Example 13                                                                                                                                                                                                               |  |    |
|                         |       | Sodium D- $\alpha$ -(3-stearinoyl-3-methyl-ureido)-benzylpenicillin:                                                                                                                                                     |  |    |
| and 12 parts            | 60 60 | This penicillin was prepared from 15 parts by weight of ampicillin and 11.9 parts                                                                                                                                        |  | 60 |

by weight of N-stearinoyl-N-methyl-carbamic acid chloride in the manner described in Example 1.

Yield: 80%

$\beta$ -Lactam content: 80%

5 Calculated: C 61.4 H 8.0 N 8.0 S 4.5

Found: C 61.0 H 8.4 N 7.5 S 4.3

NMR signals at  $\tau$  = 2.6 (5 H), 4.4 (1 H), 4.5 (2 H), 5.8 (1 H), 6.8 (3 H), 7.4 (2 H) and 8.3—9.3 ppm (9 H).

#### Example 14

10 Sodium D- $\alpha$ -(3- $\gamma$ -trichlorobutyryl-3- $\beta$ -chloroethyl-ureido)-benzylpenicillin:

This penicillin was prepared from 15 parts by weight of ampicillin and 10.4 parts by weight of N- $\gamma$ -trichlorobutyryl-N- $\beta$ -chloroethyl-carbamic acid chloride in the manner described in Example 1.

15 Yield: 56%

$\beta$ -Lactam content: 91%

Calculated: C 41.9 H 4.0 Cl 21.5 N 8.5 S 4.8

Found: C 43.2 H 5.1 Cl 20.0 N 8.5 S 4.7

20 NMR signals at  $\tau$  = 2.3—2.8 (5 H), 4.4 (1 H), 4.5 (2 H), 5.8 (1 H), 5.8—7.2 (8 H) and 8.5 ppm (6 H).

Effectiveness against *E. coli* 14: 6.25 units/ml.

Effectiveness against *Klebsiella* 63: 50 units/ml.

Effectiveness in animal experiments: A and B.

#### Example 15

25 Sodium D- $\alpha$ -(3-p-methylbenzoyl-3-methyl-ureido)-benzylpenicillin:

This penicillin was prepared from 18 parts by weight of ampicillin and 11 parts by weight of N-p-methylbenzoyl-N-methyl-carbamic acid chloride in the manner described in Example 1.

Yield: 79%

30  $\beta$ -Lactam content: 89%

Calculated: C 55.4 H 5.2 N 9.9 S 5.7

Found: C 54.6 H 6.7 N 9.9 S 5.8

35 NMR signals at  $\tau$  = 2.3—2.9 (9 H), 4.35 (1 H), 4.5 (2 H), 5.8 (1 H), 6.85 (3 H), 7.65 (3 H) and 8.45 (6 H).

Effectiveness against *E. coli*: 3.12 units/ml.

Effectiveness against *Proteus* 1017: 6.25 units/ml.

Effectiveness against *Klebsiella* 63: 12.5—25 units/ml.

Effectiveness in animal experiments: A and B.

#### Example 16

40 Sodium D- $\alpha$ -(3-acetyl-3-hexadecyl-ureido)-benzylpenicillin:

This penicillin was prepared from 15 parts by weight of ampicillin and 11.4 parts by weight of N-acetyl-N-hexadecyl-carbamic acid chloride in the manner described in Example 1.

45 Yield: 56%

$\beta$ -Lactam content: 75%

Calculated: C 60.7 H 7.9 N 8.1 S 4.6

Found: C 60.3 H 8.0 N 7.6 S 4.9

50 NMR signals at  $\tau$  = 2.6 (5 H), 4.4 (1 H), 4.55 (2 H), 5.8 (1 H), 6.3 (2 H), 7.7 (3 H), 8.45 (6 H), 8.7 (28 H), and 9.1 ppm (3 H).

#### Example 17

55 Sodium D- $\alpha$ -(3-thienoyl-(2)-3-methyl-ureido)-benzylpenicillin:

This penicillin was obtained in 81% yield on reacting 18.1 parts by weight of ampicillin with 8.2 parts by weight of N-2-thienoyl-N-methyl-carbamic acid chloride. (See Example 1).

$\beta$ -Lactam content: 92%

Calculated: C 50.8 H 4.4 N 10.3 S 11.8

Found: C 51.7 H 6.1 N 9.9 S 11.9

60 NMR signals at  $\tau$  = 2.1—3.0 (8 H), 4.4 (1 H), 4.5 (1 H), 4.6 (1 H), 5.0 (1 H), 6.6 (3 H) and 8.5 ppm (6 H).

Effectiveness in animal experiments: A and B.

|                       |    |    |                                                                                                                                                                                          |    |
|-----------------------|----|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
|                       | 24 | 25 | 1,301,961                                                                                                                                                                                | 25 |
| described             |    |    | Example 18                                                                                                                                                                               |    |
|                       |    |    | Sodium D- $\alpha$ -(3-[(5,5-dimethylisoxazol-4-yl)-carbonyl-3-methyl-ureido]-benzylpenicillin:                                                                                          |    |
|                       | 5  | 5  | This penicillin was prepared from 18.1 parts by weight of ampicillin and 8.7 parts by weight of N-4-(3,5-dimethyl)-isoxazolyl-carbonyl-N-methyl-carbamic acid chloride. (See Example 1). | 5  |
|                       |    |    | Yield: 70%                                                                                                                                                                               |    |
|                       |    |    | $\beta$ -Lactam content: 85%                                                                                                                                                             |    |
|                       | 10 | 10 | Calculated: C 51.7 H 4.9 N 12.5 S 5.7                                                                                                                                                    | 10 |
|                       |    |    | Found: C 50.6 H 6.2 N 11.1 S 5.5                                                                                                                                                         |    |
|                       | 10 |    | NMR signals at $\tau$ : 2.6 (5 H), 4.4 (1 H), 4.5 (1 H), 4.6 (1 H), 5.8 (1 H), 6.8 (3 H), 7.6 (3 H), 7.75 (3 H), 8.4 (3 H) and 8.5 ppm (3 H).                                            |    |
| 0.4 parts in the      |    |    | Effectiveness in animal experiments: A and B.                                                                                                                                            |    |
|                       | 15 | 15 | Example 19                                                                                                                                                                               | 15 |
|                       |    |    | If, in the procedure of Examples 1 and 8, the D- $\alpha$ -aminobenzylpenicillin used there is replaced by 0.04 mol of:—                                                                 |    |
|                       |    |    | $\alpha$ -amino- <i>p</i> -methylbenzylpenicillin,                                                                                                                                       |    |
|                       |    |    | $\alpha$ -amino- <i>p</i> -chlorobenzylpenicillin,                                                                                                                                       |    |
|                       | 20 | 20 | $\alpha$ -amino- <i>p</i> -methylsulphenylbenzylpenicillin,                                                                                                                              | 20 |
|                       |    |    | $\alpha$ -amino- <i>p</i> -methoxybenzylpenicillin,                                                                                                                                      |    |
|                       |    |    | $\alpha$ -amino- <i>o</i> -chlorobenzylpenicillin,                                                                                                                                       |    |
|                       |    |    | $\alpha$ -amino- <i>m</i> -iodobenzylpenicillin,                                                                                                                                         |    |
|                       |    |    | $\alpha$ -amino-2,6-dichlorobenzylpenicillin                                                                                                                                             |    |
|                       | 25 | 25 | $\alpha$ -amino-2,6-dimethoxybenzylpenicillin,                                                                                                                                           | 25 |
|                       |    |    | $\alpha$ -amino-2,4-dibromobenzylpenicillin,                                                                                                                                             |    |
|                       | 25 |    | $\alpha$ -amino- <i>m</i> -methylbenzylpenicillin,                                                                                                                                       |    |
|                       |    |    | $\alpha$ -amino-2,6-dimethylbenzylpenicillin,                                                                                                                                            |    |
| 11 parts in manner    |    |    | $\alpha$ -amino-2-chloro-6-fluorobenzylpenicillin,                                                                                                                                       |    |
|                       | 30 |    | $\alpha$ -amino- $\alpha$ -2-thienylmethylpenicillin or                                                                                                                                  | 30 |
|                       |    |    | $\alpha$ -amino- $\alpha$ -3-thienylmethylpenicillin;                                                                                                                                    |    |
|                       | 30 |    | the following penicillins are obtained:                                                                                                                                                  |    |
|                       |    |    | sodium $\alpha$ -(3-benzoyl-3-methyl-ureido)- <i>p</i> -methylbenzylpenicillin,                                                                                                          |    |
|                       |    |    | sodium $\alpha$ -(3-benzoyl-3-methyl-ureido)- <i>p</i> -chlorobenzylpenicillin,                                                                                                          |    |
|                       | 35 |    | sodium $\alpha$ -(3-benzoyl-3-methyl-ureido)- <i>p</i> -methylsulphenylbenzylpenicillin,                                                                                                 | 35 |
|                       |    |    | sodium $\alpha$ -(3-benzoyl-5-methyl-ureido)- <i>p</i> -methoxybenzylpenicillin,                                                                                                         |    |
|                       | 35 |    | sodium $\alpha$ -(3-benzoyl-3-methyl-ureido)- <i>o</i> -chlorobenzylpenicillin,                                                                                                          |    |
|                       |    |    | sodium $\alpha$ -(3-benzoyl-3-methyl-ureido)- <i>m</i> -iodobenzylpenicillin,                                                                                                            |    |
|                       |    |    | sodium $\alpha$ -(3-benzoyl-3-methyl-ureido)-2,6-dichlorobenzylpenicillin,                                                                                                               |    |
|                       | 40 |    | sodium $\alpha$ -(3-benzoyl-3-methyl-ureido)-2,6-dimethoxybenzylpenicillin,                                                                                                              | 40 |
|                       |    |    | sodium $\alpha$ -(3-benzoyl-3-methyl-ureido)-2,4-dibromobenzylpenicillin,                                                                                                                |    |
|                       |    |    | sodium $\alpha$ -(3-benzoyl-3-methyl-ureido)- $\alpha$ -3-thienylmethylpenicillin,                                                                                                       |    |
|                       | 40 |    | sodium $\alpha$ -(3-benzoyl-3-methyl-ureido)- <i>m</i> -methylbenzylpenicillin,                                                                                                          |    |
|                       |    |    | sodium $\alpha$ -(3-benzoyl-3-methyl-ureido)-2,6-dimethylbenzylpenicillin,                                                                                                               |    |
| 11.4 parts described  | 45 |    | sodium $\alpha$ -(3-benzoyl-3-methyl-ureido)-2-chloro-6-fluorobenzylpenicillin,                                                                                                          | 45 |
|                       |    |    | sodium $\alpha$ -(3-benzoyl-5-methyl-ureido)- $\alpha$ -2-thienylmethylpenicillin,                                                                                                       |    |
|                       |    |    | sodium $\alpha$ -(3-acetyl-3-methylureido)- <i>p</i> -methylbenzylpenicillin,                                                                                                            |    |
|                       | 45 |    | sodium $\alpha$ -(3-acetyl-3-methylureido)- <i>p</i> -chlorobenzylpenicillin,                                                                                                            |    |
|                       |    |    | sodium $\alpha$ -(3-acetyl-3-methylureido)- <i>p</i> -methylsulphenylbenzylpenicillin,                                                                                                   |    |
|                       | 50 |    | sodium $\alpha$ -(3-acetyl-3-methylureido)- <i>p</i> -methoxybenzylpenicillin,                                                                                                           | 50 |
|                       |    |    | sodium $\alpha$ -(3-acetyl-3-methylureido)- <i>o</i> -chlorobenzylpenicillin,                                                                                                            |    |
|                       |    |    | sodium $\alpha$ -(3-acetyl-3-methylureido)- <i>m</i> -iodobenzylpenicillin,                                                                                                              |    |
|                       | 50 |    | sodium $\alpha$ -(3-acetyl-3-methylureido)-2,6-dichlorobenzylpenicillin,                                                                                                                 |    |
|                       |    |    | sodium $\alpha$ -(3-acetyl-3-methylureido)-2,6-dimethoxybenzylpenicillin,                                                                                                                |    |
|                       | 55 |    | sodium $\alpha$ -(3-acetyl-3-methylureido)-2,4-dibromobenzylpenicillin,                                                                                                                  | 55 |
|                       |    |    | sodium $\alpha$ -(3-acetyl-3-methylureido)- <i>m</i> -methylbenzylpenicillin,                                                                                                            |    |
|                       |    |    | sodium $\alpha$ -(3-acetyl-3-methylureido)-2,6-dimethylbenzylpenicillin,                                                                                                                 |    |
| weight of d chloride. | 55 |    | sodium $\alpha$ -(3-acetyl-3-methylureido)-2-chloro-6-fluorobenzylpenicillin,                                                                                                            |    |
|                       |    |    | sodium $\alpha$ -(3-acetyl-3-methyl-ureido)- $\alpha$ -2-thienylmethylpenicillin or                                                                                                      |    |
|                       | 60 |    | sodium $\alpha$ -(3-acetyl-3-methyl-ureido)- $\alpha$ -3-thienylmethylpenicillin.                                                                                                        | 60 |
|                       | 60 |    |                                                                                                                                                                                          |    |

## Example 20

If, in the procedure of Example 1, the N-benzoyl-N-methylcarbamic acid chloride used there is replaced by 0.035 mol of:

|                                         |                                                                                                                                                                                                                                                                                                                                                                     |    |    |
|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|----|
| 5                                       | N-acetyl-N-ethyl-carbamic acid chloride,<br>N-acetyl-N-vinyl-carbamic acid chloride,<br>N-acetyl-N-n-propyl-carbamic acid chloride,<br>N-acetyl-N-propenyl-carbamic acid chloride,<br>N-acetyl-N-i-propyl-carbamic acid chloride,<br>N-acetyl-N-n-butyl-carbamic acid chloride,                                                                                     | 5  | 5  |
| 10                                      | N-acetyl-N-t-butyl-carbamic acid chloride,<br>N-acetyl-N-β-methoxyethyl-carbamic acid chloride,<br>N-acetyl-N-β-dimethylaminoethyl-carbamic acid chloride,<br>N-acetyl-N-cyclohexyl-carbamic acid chloride,<br>N-acetyl-N-cyclobutyl-carbamic acid chloride,                                                                                                        | 10 | 10 |
| 15                                      | N-methoxyacetyl-N-methyl-carbamic acid chloride,<br>N-propionyl-N-methyl-carbamic acid chloride,<br>N-methyl-sulphenylacetyl-N-methyl-carbamic acid chloride,<br>N-propionyl-N-ethyl-carbamic acid chloride,<br>N-propionyl-N-vinyl-carbamic acid chloride,                                                                                                         | 15 | 15 |
| 20                                      | N-n-butyryl-N-methyl-carbamic acid chloride,<br>N-methoxycarbonyl-acetyl-N-methyl-carbamic acid chloride,<br>N-i-butyryl-N-methyl-carbamic acid chloride,<br>N-acryloyl-N-methyl-carbamic acid chloride,<br>N-pivaloyl-N-methyl-carbamic acid chloride,                                                                                                             | 20 | 20 |
| 25                                      | N-cyanomethyl-acetyl-N-methyl-carbamic acid chloride,<br>N-acetyl-N-phenyl-carbamic acid chloride or<br>N-propionyl-N-phenyl-carbamic acid chloride;                                                                                                                                                                                                                | 25 | 25 |
| the following penicillins are obtained: |                                                                                                                                                                                                                                                                                                                                                                     |    |    |
| 30                                      | sodium D-α-(3-acetyl-3-ethyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-acetyl-3-vinyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-acetyl-3-n-propyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-acetyl-3-propenyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-acetyl-3-i-propyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-acetyl-3-n-butyl-ureido)-benzylpenicillin, | 30 | 30 |
| 35                                      | sodium D-α-(3-acetyl-3-t-butyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-acetyl-3-β-methoxyethyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-acetyl-3-β-dimethyl-aminoethyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-acetyl-3-cyclohexyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-acetyl-3-cyclobutyl-ureido)-benzylpenicillin,                                 | 35 | 35 |
| 40                                      | sodium D-α-(3-methoxyacetyl-3-methyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-propionyl-3-methyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-methylsulphenyl-acetyl-3-methyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-propionyl-3-ethyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-propionyl-3-vinyl-ureido)-benzylpenicillin,                                   | 40 | 40 |
| 45                                      | sodium D-α-(3-n-butyryl-3-methyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-methoxycarbonyl-acetyl-3-methyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-i-butyryl-3-methyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-acryloyl-3-methyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-pivaloyl-3-methyl-ureido)-benzylpenicillin,                                       | 45 | 45 |
| 50                                      | sodium D-α-(3-cyano-methyl-acetyl-3-methyl-ureido)-benzylpenicillin,<br>sodium D-α-(3-acetyl-3-phenyl-ureido)-benzylpenicillin or<br>sodium D-α-(3-propionyl-3-phenyl-ureido)-benzylpenicillin.                                                                                                                                                                     | 50 | 50 |

## Example 21

Sodium D-α-(3-benzoyl-3-methyl-ureido)-benzylpenicillin:

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |    |    |
|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|----|
| 55 | A solution of 10.6 parts by weight of bis-trimethylsilyl lamioicillin in 50 parts by volume of dry methylene chloride was cooled to -10°C with exclusion of moisture, and treated with a solution of 3.8 parts by weight of N-benzoyl-N-methyl-carbamic acid chloride in 20 parts by volume of absolute methylene chloride, cooled to 0°C. The mixture was left to stand in a refrigerator for 6 hours, the solvent was then stripped off in a rotary evaporator at room temperature, the residue was taken up in 100 parts by volume of a 1:1 mixture of ether and ethyl acetate, and the solution was exhaustively extracted with 2 N sodium bicarbonate solution. The aqueous phase was treated with fresh ether-ethyl acetate mixture and acidified with 2 N HCl to pH=1.5-2.0 (glass | 55 | 55 |
| 60 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 60 | 60 |

id chloride

electrode), whilst cooling with ice; the organic phase was separated off, again washed with water and subsequently dried over  $\text{Na}_2\text{SO}_4$  at  $0^\circ\text{C}$ , and the sodium salt of the penicillin was precipitated and isolated, in the manner described in Example 1.

Yield: 56%

$\beta$ -Lactam content: 74%

Calculated: C 54.1 H 5.0 N 10.1 S 5.8

Found: C 54.6 H 5.6 N 9.5 S 5.7

The IR and NMR spectra are identical with those of the penicillin from Example 1.

16

## Example 22

10

Sodium D- $\alpha$ -(3-benzoyl-3-methyl-ureido)-benzylpenicillin:

10

15 parts by weight of ampicillin were suspended in 150 parts by volume of 80% strength aqueous tetrahydrofuran and sufficient dilute HCl was subsequently added, whilst cooling to  $-5^\circ\text{C}$ , to establish a pH value of 2.5 and partially to dissolve the ampicillin. A solution of 6.5 parts by weight of N-benzoyl-N-methyl-carbamic acid chloride in 25 parts by weight of absolute tetrahydrofuran was now added dropwise over the course of 30 minutes, at  $-5^\circ$  to  $0^\circ\text{C}$ , whilst keeping the pH value at 2.5—3.0 by simultaneous addition of triethylamine. The mixture was stirred for a further 20 minutes until the pH value remained constant at about 3.0 even without the addition of triethylamine. A pH value of 6.5—7.0 was now established by means of triethylamine, 150 parts by volume of water are added, and the tetrahydrofuran was evaporated off in a rotary evaporator at room temperature. The aqueous solution was once extracted with 100 parts by volume of ether, then covered with 200 parts by volume of a 1:1 mixture of ether and ethyl acetate, and brought to pH = 1.5—2.0 by adding 2 N hydrochloric acid whilst cooling with ice, and the penicillin was removed from the water by repeated extraction with ether-ethyl acetate mixture. The combined organic phases were twice washed with 100 parts by volume of water at a time and dried over  $\text{MgSO}_4$ , and the sodium salt of the penicillin was subsequently precipitated and isolated in the manner described in Example 1.

Yield: 60%

$\beta$ -Lactam content: 93.3%

Calculated: C 54.9 H 4.9 N 10.2 S 5.8

Found: C 54.7 H 5.4 N 10.1 S 5.9

The product agrees with that of Example 1 in respect of its IR and NMR spectra.

3

## Example 23

35

Sodium D- $\alpha$ -(3- $\gamma$ -trichlorobutyl-3- $\beta$ -chloroethyl-ureido)-benzylpenicillin:

35

A mixture of 8.0 parts by weight of ampicillin, 100 parts by volume of methylene chloride and 5.5 parts by volume of triethylamine was stirred for 2 hours at room temperature, and then stirred vigorously, for a further 15 minutes, with anhydrous sodium sulphate and filtered. The mixture was cooled to  $0^\circ\text{C}$  and a solution of 6.3 parts by weight of N- $\gamma$ -trichlorobutyl-N- $\beta$ -chloroethyl-carbamic acid chloride in 30 parts by volume of dry methylene chloride was added dropwise over the course of 20 minutes, whilst excluding moisture. Thereafter the mixture was stirred for a further 90 minutes at  $0^\circ\text{C}$  and then concentrated to dryness in a rotary evaporator, in vacuo. The residue was taken up in water, the pH value was adjusted to 7—8 with 2 N NaOH, and the mixture was extracted once with ether. Thereafter working up took place as in Example 1, under acid conditions, and the sodium salt of the penicillin was precipitated and isolated.

Yield: 49%

$\beta$ -Lactam content: 81%

The product agrees with that of Example 14 as regards its IP. and NMR spectrum.

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## Example 24

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Calcium L- $\alpha$ -(3-benzoyl-3-methyl-ureido)-benzylpenicillin:

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This penicillin was prepared as described in Example 1, but instead of the D- $\alpha$ -aminobenzylpenicillin used in Example 1, 0.35 part by weight of L- $\alpha$ -aminobenzylpenicillin was reacted with 0.15 part by weight of N-benzoyl-N-methyl-carbamic acid chloride. The penicillin was isolated as the calcium salt.

Yield: 5%

$\beta$ -Lactam content: 75%

NMR signals at  $\tau = 2.4$ —2.8 (10 H), 4.35—4.65 (3 H), 5.8 (1 H), 6.85 (3 H) and 8.4 ppm (6 H).

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50 parts by moisture, and carbamic acid at  $0^\circ\text{C}$ . The mixture was stripped off and 100 parts by weight of water were added. The mixture was treated with  $-2.0$  (glass

## Example 25

Sodium D- $\alpha$ -(3-[4-methoxy-3-nitrobenzoyl]-3-methyl-ureido)-benzylpenicillin:

5 Sufficient 2 N NaOH was added to a suspension of 17.5 parts by weight of ampicillin in 250 parts by volume of 80% strength aqueous tetrahydrofuran, at 0°C, for  
 10 solution just to occur. A solution of 13.6 parts by weight of N-(4-methoxy-3-nitrobenzoyl)-carbamic acid chloride in 30 parts by volume of absolute tetrahydrofuran was  
 15 now added dropwise over the course of 30 minutes, and the pH value was simultaneously kept between 7.5 and 8.0 by adding 2 N sodium hydroxide solution. The mixture  
 20 was stirred for a further 30 minutes at 0°C and sufficiently long (~60 minutes) at room temperature for the pH value to remain at 7-8 even without addition of sodium  
 25 hydroxide solution. The tetrahydrofuran was now removed in a rotary evaporator, at room temperature, 100 parts by volume of water were added and the mixture was  
 extracted with 100 parts by volume of ether. The aqueous phase was covered with 200  
 parts by volume of a 1:1 mixture of ether and ethyl acetate after which it was  
 acidified to pH=2 with dilute hydrochloric acid, whilst stirring and cooling with  
 ice, and was then extracted twice with 100 parts by volume, at a time, of etherethyl  
 acetate mixture. The combined organic phases were washed with 2 x 50 parts by  
 volume of water and dried over anhydrous MgSO<sub>4</sub>, the drying agent was filtered off,  
 and the filtrate was treated with 50 parts by volume of a molar solution of sodium  
 2-ethylhexanoate in ether containing methanol. Thereafter, the solvent was almost com-  
 pletely removed in vacuo at room temperature, the residue was taken up in methanol,  
 and the sodium salt of the penicillin was precipitated by adding ether. After standing  
 for 30 minutes at 0°C, the supernatant solvent was decanted, and the residue was  
 suspended in ether, filtered and dried over P<sub>2</sub>O<sub>5</sub> in a vacuum desiccator.

Yield: 88%

 $\beta$ -Lactam content: 72%

Calculated: C 51.3 H 4.3 N 11.5 S 5.3

Found: C 51.5 H 5.7 N 10.7 S 5.1

30 NMR signals at  $\tau$  = 1.9 (1 H), 2.2 (1 H), 2.6 (5 H), 2.7 (1 H),  
 4.4 (1 H), 4.5 (2 H), 5.8 (1 H), 6.0 (3 H),  
 6.7 (3 H) and 8.45 ppm (6 H).

Effectiveness against *E. coli* 14: 3.12 units/ml.Effectiveness against *Proteus* 3400: 6.25 units/ml.

Effectiveness in animal experiments: A and B.

## Example 26

If, in the procedure of Example 25, the ampicillin used there is replaced by 0.05 mol of:—

- 40  $\alpha$ -amino-*p*-methylbenzylpenicillin,  
 $\alpha$ -amino-*p*-chlorobenzylpenicillin,  
 $\alpha$ -amino-*p*-methoxybenzylpenicillin,  
 $\alpha$ -amino-*p*-methylsulphenylbenzylpenicillin,  
 $\alpha$ -amino-*o*-chlorobenzylpenicillin,  
 45  $\alpha$ -amino-*m*-iodobenzylpenicillin or  
 $\alpha$ -amino-*m*-methylbenzylpenicillin;

the following penicillins are obtained:

- 50 sodium  $\alpha$ -(3-[3-nitro-4-methoxybenzoyl]-3-methyl-ureido)-*p*-methylbenzylpenicillin,  
 sodium  $\alpha$ -(3-[3-nitro-4-methoxybenzoyl]-3-methylureido)-*p*-chlorobenzylpenicillin,  
 sodium  $\alpha$ -(3-[3-nitro-4-methoxybenzoyl]-3-methylureido)-*p*-methoxybenzylpenicillin,  
 sodium  $\alpha$ -(3-[3-nitro-4-methoxybenzoyl]-3-methylureido)-*p*-methylsulphenylbenzyl-  
 penicillin,  
 sodium  $\alpha$ -(3-[3-nitro-4-methoxybenzoyl]-3-methylureido)-*o*-chlorobenzylpenicillin,  
 sodium  $\alpha$ -(3-[3-nitro-4-methoxybenzoyl]-3-methylureido)-*m*-iodobenzylpenicillin or  
 sodium  $\alpha$ -(3-[3-nitro-4-methoxybenzoyl]-3-methylureido)-*m*-methylbenzylpenicillin.

## Example 27

If, in the procedure according to Example 25, the N-(3-nitro-4-methoxybenzoyl)-N-methyl-carbamic acid chloride used there is replaced by 0.05 mol of:—

- 60 N-(*p*-methoxybenzoyl)-N-methyl-carbamic acid chloride,  
 N-(*p*-methoxycarbonylaminobenzoyl)-N-methyl-carbamic acid chloride,  
 N-(*p*-chlorobenzoyl)-N-ethyl-carbamic acid chloride,  
 N-(*o*-bromobenzoyl)-N-(*n*-propyl)-carbamic acid chloride,  
 N-(*p*-ethoxybenzoyl)-N-(*i*-propyl)-carbamic acid chloride,

of ampicillin, 0°C. for 24 hours. The mixture was simultaneously stirred at room temperature in a sodium vaporator, the mixture was then with 200 ml. of ether. It was then filtered off, washed with ether, and the most common methanol, or standing residue was

N-(*m*-chlorobenzoyl)-N-allyl-carbamic acid chloride,  
N-(2-chloro-5-methoxybenzoyl)-N-(*n*-butyl)-carbamic acid chloride,  
N-(*p*-methylsulphenylbenzoyl)-N-methyl-carbamic acid chloride,  
N-(*p*-nitrobenzoyl)-N-methyl-carbamic acid chloride,  
N-(2,4-dichlorobenzoyl)-N-methyl-carbamic acid chloride,  
N-(2-chloro-4-methoxybenzoyl)-N-methyl-carbamic acid chloride,  
N-(2-chloro-4-ethylsulphenylbenzoyl)-N-methyl-carbamic acid chloride,  
N-(3-chloro-4-methoxybenzoyl)-N-methyl-carbamic acid chloride,  
N-(*m*-cyanobenzoyl)-N-methyl-carbamic acid chloride,  
N-(3,5-dimethylbenzoyl)-N-methyl-carbamic acid chloride,  
N-(*m*-iodobenzoyl)-N-methyl-carbamic acid chloride or  
N-(1-naphthoyl)-N-methyl-carbamic acid chloride;

The sodium salts of the following penicillins are obtained: ---

D- $\alpha$ -(3-*p*-methoxybenzoyl-3-methylureido)-benzylpenicillin,  
D- $\alpha$ -(3-*p*-methoxycarbonylamino-3-methylureido)-benzylpenicillin,  
D- $\alpha$ -(3-*p*-chlorobenzoyl-3-ethylureido)-benzylpenicillin,  
D- $\alpha$ -(3-*o*-bromobenzoyl-3-*n*-propylureido)-benzylpenicillin,  
D- $\alpha$ -(3-*p*-ethoxybenzoyl-3-*i*-propylureido)-benzylpenicillin,  
D- $\alpha$ -(3-*m*-chlorobenzoyl-3-allylureido)-benzylpenicillin,  
D- $\alpha$ -(3-[2-chloro-5-methoxybenzoyl]-3-*n*-butylureido)-benzylpenicillin,  
D- $\alpha$ -(3-*p*-methylsulphenylbenzoyl-3-methylureido)-benzylpenicillin,  
D- $\alpha$ -(3-*p*-nitrobenzoyl-3-methylureido)-benzylpenicillin,  
D- $\alpha$ -(3-[2,4-dichlorobenzoyl]-3-methylureido)-benzylpenicillin,  
D- $\alpha$ -(3-[2-chloro-4-methoxybenzoyl]-3-methylureido)-benzylpenicillin,  
D- $\alpha$ -(3-[2-chloro-4-ethylsulphenylbenzoyl]-3-methylureido)-benzylpenicillin,  
D- $\alpha$ -(3-[3-chloro-4-methoxybenzoyl]-3-methylureido)-benzylpenicillin,  
D- $\alpha$ -(3-*m*-cyanobenzoyl-3-methylureido)-benzylpenicillin,  
D- $\alpha$ -(3-[3,5-dimethylbenzoyl]-3-methylureido)-benzylpenicillin,  
D- $\alpha$ -(3-*m*-iodobenzoyl-3-methylureido)-benzylpenicillin or  
D- $\alpha$ -(3-[*i*-naphthoyl]-3-methylureido)-benzylpenicillin.

#### Example 28

Sodium D- $\alpha$ -(3-acetyl-3-allylureido)-benzylpenicillin:

This penicillin was prepared in the manner described in Example 25, by reacting 17.5 parts by weight of ampicillin with 8.1 parts by weight of N-acetyl-N-allyl-carbamic acid chloride.

Yield: 81%

$\beta$ -Lactam content: 82%

Calculated: C 51.2 H 5.3 N 10.8 S 6.2

Found: C 51.9 H (6.9) N 10.5 S 6.4

NMR signals at  $\tau$  = 2.4—2.8 (5 H), 4.5—5.2 (6 H), 5.6 (2 H), 5.85 (1 H), 7.7 (3 H) and 8.5 ppm (6 H).

Effectiveness against *E. coli* 14: 12.5 units/ml.

Effectiveness against *Pseudomonas Aerug.* Bonn: 25 units/ml.

Effectiveness in animal experiments: A and B.

#### Example 29

Sodium D- $\alpha$ -(3-acetyl-3-benzylureido)-benzylpenicillin:

This penicillin was prepared from 17.5 parts by weight of ampicillin and 10.6 parts by weight of N-acetyl-N-benzyl carbamic acid chloride, in the manner described in Example 25.

Yield: 85%

$\beta$ -Lactam content: 70%

Calculated: C 54.4 H 5.3 N 9.77 S 5.7

Found: C 54.4 H 5.7 N 9.77 S 5.6

NMR signals at  $\tau$  = 2.3—3.0 (10 H), 4.4 (1 H), 4.5 (2 H), 5.0 (2 H), 5.8 (1 H), 7.8 (3 H) and 8.5 ppm (6 H).

Effectiveness in animal experiments: A and B.

#### Example 30

Sodium D- $\alpha$ -(3- $\gamma$ -chlorobutyryl-3-methylureido)-benzylpenicillin: —

This penicillin was prepared from 17.5 parts by weight of ampicillin and 9.9 parts by weight of N- $\gamma$ -chlorobutyryl-N-methylcarbamic acid chloride, in the manner described in Example 25.

Yield: 91%

$\beta$ -Lactam content: 67%

Calculated: C 49.6 H 4.9 Cl 6.6 N 10.5 S 6.0

Found: C 49.8 H 6.1 Cl 6.1 N 10.3 S 6.5

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

Effectiveness in animal experiments: A and B.

#### Example 31

10 Sodium D- $\alpha$ -(3- $\gamma$ -trichlorobutyryl-3-methylureido)-benzylpenicillin:

This penicillin was prepared from 17.5 parts by weight of ampicillin and 13.4 parts by weight of N- $\gamma$ -trichlorobutyryl-N-methyl-carbamic acid chloride, in the manner described in Example 25.

Yield: 77%

15  $\beta$ -Lactam content: 66.5%

Calculated: C 43.9 H 4.0 Cl 17.7 N 9.3 S 5.3

Found: C 44.5 H 5.6 Cl 15.4 N 8.2 S 5.3

15 NMR signals at  $\tau$  = 2.3—2.8 (5 H), 4.4 (1 H), 4.55 (2 H),  
5.8 (1 H), 6.7 (4 H), 6.9 (3 H) and  
8.45 ppm (6 H).

20 Effectiveness in animal experiments: A and B.

#### Example 32

Sodium D- $\alpha$ -(3-benzoyl-3-allylureido)-benzylpenicillin:

25 This penicillin was prepared from 17.5 parts by weight of ampicillin and 11.2 parts by weight of N-benzoyl-N-allylcarbamic acid chloride, in the manner described in Example 25.

Yield: 75%

$\beta$ -Lactam content: 90%

Calculated: C 56.0 H 4.8 N 10.0 S 5.7

30 Found: C 56.1 H 5.6 N 9.7 S 5.8

NMR signals at  $\tau$  = 2.5 (5 H), 2.6 (5 H), 4.3—5.0 (6 H), 5.65 (2 H),  
5.8 (1 H), 8.5 (6 H).

Effectiveness against *E. coli* 14: 6.25 units/ml.

Effectiveness against *Proteus* 1017: 12.5 units/ml.

35 Effectiveness against *Klebsiella* 63: 25 units/ml.

Effectiveness in animal experiments: A and B.

#### Example 33

Sodium D- $\alpha$ -(3-[2-furoyl]-3-methylureido)-benzylpenicillin:

40 This penicillin was prepared from 35 parts by weight of ampicillin and 15 parts by weight of N-2-furoyl-N-methyl-carbamic acid chloride, in the manner described in Example 25.

Yield: 83%

$\beta$ -Lactam content: 85%

Calculated: C 52.7 H 4.4 N 10.7 S 6.1

45 Found: C 52.8 H 5.4 N 9.8 S 6.1

NMR signals at  $\tau$  = 2.3 (1 H), 2.3—2.9 (6 H), 3.4 (1 H), 4.3 (1 H),  
4.5 (2 H), 5.7 (1 H), 6.6 (3 H) and  
8.5 ppm (6 H).

#### Example 34

50 A) N-2-Furoyl-N-*n*-propyl-carbamic acid chloride:

This substance can be prepared according to the data in the literature, but especially according to the following process:

A solution of 7.6 parts by weight of 2-furoiccarboxylic acid-N-*n*-propylamide in a 2:1 mixture of ether and tetrahydrofuran (150 parts by volume), which had shortly before been distilled from  $\text{LiAlH}_4$ , was saturated with dry nitrogen and cooled to  $-30^\circ\text{C}$ . 28.3 parts by volume of a 1.765 M solution of  $\text{CH}_3\text{Li}$  in ether was added dropwise thereto under a nitrogen atmosphere over the course of 30 minutes, whilst excluding moisture and stirring vigorously. The mixture was stirred for a further 15 minutes at  $-30^\circ\text{C}$ . The resulting suspension was added from a cooled dropping funnel, so that it did not rise above  $-10^\circ\text{C}$ , to a mixture, at  $-10^\circ\text{C}$ , of 50 parts by volume of phosgene and 50 parts by volume of absolute tetrahydrofuran,

over the course of one hour. The mixture was allowed to come to room temperature after 15 minutes and stirred for a further 30 minutes, and the excess phosgene and the solvents were then stripped off in vacuo. The LiCl, which very largely remained undissolved, could substantially be separated off by suspending in benzene. The residue which remained after distilling off the benzene could be employed directly for the preparation of the penicillin. It could however also be distilled at 105--112°C and 0.7 mm Hg. Yield 64%. In addition to the desired N-furoyl-N-propyl-carbamic acid chloride, the product also contained a further component, which however proved not to interfere in the subsequent preparation of the penicillin.

B) Sodium D- $\alpha$ -(3-[2-furoyl]-3-*n*-propylureido)-benzylpenicillin:

This penicillin was prepared from 10.5 parts by weight of ampicillin and 6.5 parts by weight of distilled N-2-furoyl-N-*n*-propylcarbamic acid chloride, in the manner described in Example 25.

Yield: 30%

$\beta$ -Lactam content: 90%

NMR signals at  $\tau$  = 2.35 (1 H), 2.6 (5 H), 2.8 (1 H), 3.4 (1 H),  
4.4 (1 H), 4.5 (2 H), 5.8 (1 H), 6.2 (2 H),  
8.1--8.9 (1 H), 8.5 (6 H) and  
9.1 ppm (3 H).

Example 35

A) N-2-Furoyl-N-ethyl-carbamic acid chloride

This substance was prepared from 7.0 parts by weight of 2-furanecarboxylic acid-N-ethylamide,  $\text{CH}_3\text{Li}$  and phosgene, in the manner described in Example 34-A).

Boiling point,  $b_p$  = 90--95°C. Yield: 80% (crude product).

The substance contains a second component, which however proved not to interfere in the preparation of the penicillin.

B) Sodium D- $\alpha$ -(3-[2-furoyl]-3-ethylureido)-benzylpenicillin:

This penicillin was prepared from 12 parts by weight of ampicillin and 7 parts by weight of N-2-furoyl-N-ethyl-carbamic acid chloride, in the manner described in Example 25.

Yield: 29%

$\beta$ -Lactam content: 89%

Calculated: C 52.8 H 4.6 N 10.7

Found: C 52.6 H(6.2) N 9.7

NMR signals at  $\tau$  = 2.3 (1 H), 2.6 (5 H), 2.75 (1 H), 3.4 (1 H),  
4.35 (1 H), 4.5 (2 H), 5.8 (1 H), 6.05 (2 H),  
8.45 (6 H) and 8.7 ppm (3 H).

Example 36

Sodium D- $\alpha$ -(3-dimethylaminocarbonyl-3-methyl-ureido)-benzylpenicillin:

This penicillin was prepared from 17.5 parts by weight of ampicillin and 7.8 parts by weight of N-dimethylaminocarbonyl-N-methyl-carbamic acid chloride, in the manner described in Example 25.

Yield: 74%

$\beta$ -Lactam content: 82%

Calculated: C 49.6 H 5.4 N 13.8 S 6.3

Found: C 49.9 H 6.4 N 13.1 S 6.0

NMR signals at  $\tau$  = 2.6 (5 H), 4.5 (3 H), 5.8 (1 H),  
6.95 (3 H), 7.05 (6 H) and 8.45 ppm (6 H).

Effectiveness in animal experiments: A and B.

Example 37

If the N-dimethylaminocarbonyl-N-methyl-carbamic acid chloride used in Example 36 is replaced by:—

3-dimethylaminocarbonyl-3-ethyl-carbamic acid chloride,

3-dimethylaminocarbonyl-3-propyl-carbamic acid chloride,

3-dimethylaminocarbonyl-3-*i*-propyl-carbamic acid chloride,

3-dimethylaminocarbonyl-3-*n*-butyl-carbamic acid chloride,

3-dimethylaminocarbonyl-3-allyl-carbamic acid chloride,

3-dimethylaminocarbonyl-3-cyclohexyl-carbamic acid chloride,

3-dimethylaminocarbonyl-3-phenyl-carbamic acid chloride,

N-(1-pyrrolidylcarbonyl)-N-methyl-carbamic acid chloride,

in:  
nd 13.4 parts  
the manner

and 11.2 parts  
described in

and 15 parts  
manner described

literature, but

propylamide in  
which had shortly  
and cooled to  
ther was added  
of 30 minutes,  
mixture was  
was added from  
ure, at -10°C,  
trahydrofurane,

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |                 |
|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|-----------------|
|    | N-(1-piperidylcarbonyl)-N-methyl-carbamic acid chloride,<br>N-diethylaminocarbonyl-N-methyl-carbamic acid chloride,<br>N-ethylaminocarbonyl-N-methyl-carbamic acid chloride,<br>N-methylaminocarbonyl-N-methyl-carbamic acid chloride,<br>N-phenylaminocarbonyl-N-methyl-carbamic acid chloride,<br>N-(4-morpholinylcarbonyl)-N-methyl-carbamic acid chloride,<br>N-(1-pyrrolidylcarbonyl)-N-ethyl-carbamic acid chloride,<br>N-(1-piperidylcarbonyl)-N-ethyl-carbamic acid chloride,<br>N-diethylaminocarbonyl-N-ethyl-carbamic acid chloride,<br>N-ethylaminocarbonyl-N-ethyl-carbamic acid chloride,<br>N-methylaminocarbonyl-N-ethyl-carbamic acid chloride,<br>N-phenylaminocarbonyl-N-ethyl-carbamic acid chloride,<br>N-(4-morpholinylcarbonyl)-N-ethyl-carbamic acid chloride,<br>N-(1-pyrrolidylcarbonyl)-N-n-propyl-carbamic acid chloride,<br>N-(1-piperidylcarbonyl)-N-i-propyl-carbamic acid chloride,<br>N-diethylaminocarbonyl-N-n-butyl-carbamic acid chloride or<br>N-dimethylaminocarbonyl-N-cyclohexyl-carbamic acid chloride,<br>the following penicillins are obtained in the form of their sodium salts: —                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |                 |
| 5  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  | 5 <sup>5</sup>  |
| 10 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  | 10 <sup>0</sup> |
| 15 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  | 15 <sup>5</sup> |
| 20 | D-α-(3-dimethylaminocarbonyl-3-ethylureido)-benzylpenicillin,<br>D-α-(3-dimethylaminocarbonyl-3-propylureido)-benzylpenicillin,<br>D-α-(3-dimethylaminocarbonyl-3-i-propylureido)-benzylpenicillin,<br>D-α-(3-dimethylaminocarbonyl-3-n-butylureido)-benzylpenicillin,<br>D-α-(3-dimethylaminocarbonyl-3-allylureido)-benzylpenicillin,<br>D-α-(3-dimethylaminocarbonyl-3-cyclohexylureido)-benzylpenicillin,<br>D-α-(3-dimethylaminocarbonyl-3-phenylureido)-benzylpenicillin,<br>D-α-(3-[1-pyrrolidyl]-carbonyl-3-methylureido)-benzylpenicillin,<br>D-α-(3-[1-piperidyl]-carbonyl-3-methylureido)-benzylpenicillin,<br>D-α-(3-diethylaminocarbonyl-3-methylureido)-benzylpenicillin,<br>D-α-(3-ethylaminocarbonyl-3-methylureido)-benzylpenicillin,<br>D-α-(3-methylaminocarbonyl-3-methylureido)-benzylpenicillin,<br>D-α-(3-phenylaminocarbonyl-3-methylureido)-benzylpenicillin,<br>D-α-(3-[4-morpholinyl]-carbonyl-3-methylureido)-benzylpenicillin,<br>D-α-(3-[1-pyrrolidyl]-carbonyl-3-ethylureido)-benzylpenicillin,<br>D-α-(3-[1-piperidyl]-carbonyl-3-ethylureido)-benzylpenicillin,<br>D-α-(3-diethylaminocarbonyl-3-ethylureido)-benzylpenicillin,<br>D-α-(3-ethylaminocarbonyl-3-ethylureido)-benzylpenicillin,<br>D-α-(3-methylaminocarbonyl-3-ethylureido)-benzylpenicillin,<br>D-α-(3-phenylaminocarbonyl-3-ethylureido)-benzylpenicillin,<br>D-α-(3-[4-morpholinyl]-carbonyl-3-ethylureido)-benzylpenicillin,<br>D-α-(3-[1-pyrrolidyl]-carbonyl-3-n-propylureido)-benzylpenicillin,<br>D-α-(3-[1-piperidyl]-carbonyl-3-i-propylureido)-benzylpenicillin,<br>D-α-(3-diethylaminocarbonyl-3-n-butylureido)-benzylpenicillin or<br>D-α-(3-dimethylaminocarbonyl-3-cyclohexylureido)-benzylpenicillin. |  |                 |
| 25 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  | 25 <sup>5</sup> |
| 30 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  | 30 <sup>0</sup> |
| 35 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  | 35 <sup>0</sup> |
| 40 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  | 40 <sup>0</sup> |
| 45 | Example 38<br>Sodium D-α-(3-methoxycarbonyl-3-methylureido)-benzylpenicillin:<br>This penicillin was prepared from 24.5 parts by weight of ampicillin and 10.2 parts by weight of N-methoxycarbonyl-N-methylcarbamic acid chloride, in the manner described in Example 25.<br>Yield: 84%<br>Lactam content: 84%<br>Calculated: C 47.6 H 5.0 N 11.1 S 6.4<br>Found: C 48.4 H 5.5 N 10.6 S 5.8<br>NMR signals at τ = 2.3—2.9 (5 H), 4.4 (1 H), 4.5 (2 H),<br>5.8 (1 H), 6.2 (3 H), 6.8 (3 H) and<br>8.45 ppm (6 H).<br>Effectiveness against <i>E. coli</i> 14: 6.25 units/ml.<br>Effectiveness against <i>Pseudomonas aerug.</i> Boon: 25 units/ml.<br>Effectiveness in animal experiments: A and B.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |  |                 |
| 50 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  | 50 <sup>5</sup> |
| 55 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  | 55 <sup>5</sup> |
| 60 | Example 39<br>Sodium D-α-(3-i-propoxycarbonyl-3-methylureido)-benzylpenicillin:<br>This penicillin was prepared from 24.4 parts by weight of ampicillin and 12.2 parts by weight of N-i-propoxycarbonyl-N-methyl-carbamic acid chloride, in the manner described in Example 25.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |                 |

Yield: 72%

$\beta$ -Lactam content: 88%

Calculated: C 51.3 H 5.3 N 10.9 S 6.2

Found: C 51.6 H 5.5 N 10.6 S 6.1

5 NMR signals at  $\tau = 2.5-2.8$  (5 H), 4.4 (1 H), 4.5 (2 H), 5.0 (1 H),  
5.8 (1 H), 6.85 (3 H), 8.5 (6 H) and 8.7 ppm (6 H).

Effectiveness against *E. coli* 14: 6.25 units/ml.

Effectiveness against *Proteus* 3400: 25 units/ml.

Effectiveness in animal experiments: A and B.

10

#### Example 40

Sodium D- $\alpha$ -(3-*n*-butoxycarbonyl-5-methylureido)-benzylpenicillin:

This penicillin was prepared from 24.5 parts by weight of ampicillin and 13.6 parts by weight of N-*n*-butoxycarbonyl-N-methyl-carbamic acid chloride, in the manner described in Example 25.

15

Yield: 63%

$\beta$ -Lactam content: 78%

Calculated: C 52.2 H 5.5 N 10.6 S 6.0

Found: C 52.2 H 5.5 N 10.7 S 6.0

20 NMR signals at  $\tau = 2.3-2.8$  (5 H), 4.45 (1 H), 4.55 (2 H),  
5.8 (3 H), 6.85 (3 H) and 8.1-9.3 ppm  
(13 H)

Effectiveness against *E. coli* 14: 3.12 units/ml.

Effectiveness against *Proteus* 1017: 12.5 units/ml.

Effectiveness against *Pseudomonas aerug.* Bonn: 12.5 units/ml.

25

Effectiveness in animal experiments: A and B.

#### Example 41

A) N-Benzoyl-N-phenyl-carbamic acid chloride:

30

This substance was obtained from 19.7 parts by weight of benzoylanilide by reaction with  $\text{CH}_3\text{Li}$  and phosgene, in the manner described in Example 34-A). Instead of distilling, the product was recrystallized from benzene-petroleum ether.

Yield: 90%. Melting point 64-66°C

35

B) Sodium D- $\alpha$ -(3-benzoyl-3-phenylureido)-benzylpenicillin:

The triethylamine salt was prepared from 11.5 parts by weight of ampicillin in methylene chloride, as described in Example 23. Instead of anhydrous sodium sulphate, 4 parts by weight of powdered Zeolite VS 10-2 molecular sieve, added from the start, were used. Reaction with 7.8 parts by weight of N-benzoyl-N-phenylcarbamic acid chloride, as described in Example 23, though with the addition of a further 2.0 parts by weight of triethylamine to the reaction solution, yielded this penicillin.

40

Yield: 72%

$\beta$ -Lactam content: 88%

Calculated: C 57.9 H 4.8 N 9.0 S 5.4

Found: C 57.7 H 5.4 N 9.0 S 6.3

45 NMR signals at  $\tau = 2.4-2.9$  (15 H), 4.35 (1 H), 4.5 (2 H),  
5.8 (1 H), 8.4 and 8.5 ppm (6 H).

Effectiveness in animal experiments: B.

50

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lin and 10.2  
in the manner

#### Example 42

D- $\alpha$ -(3-[3-Nitro-4-methoxybenzoyl]-3-methylureido)-benzylpenicillin:

55

This penicillin was prepared from 7.0 parts by weight of ampicillin and 5.5 parts by weight of N-(3-nitro-4-methoxybenzoyl)-N-methylcarbamic acid chloride, in the manner described in Examples 23 and 41-B).

Yield: 77%

$\beta$ -Lactam content: 89%

Calculated: C 48.5 H 4.7 N 10.9 S 5.0

Found: C 48.4 H 5.4 N 10.8 S 5.4

60

The substance agrees with that of Example 25 as regards its IR and NMR spectrum.

#### Example 43

A) 1-Chlorocarbonyl-hexahydroazepin-2-one:

65

The substance was prepared from 6.8 parts by weight of  $\epsilon$ -caprolactam and  $\text{CH}_3\text{Li}$  and phosgene, in the manner described in Example 34-A).

Boiling point  $d_{4.2} = 80-85^\circ\text{C}$ . Yield: 37% of pure material.

70

lin:  
lin and 12.2  
ride, in the

B) Sodium D- $\alpha$ -(hexahydroazepin-2-on-1-yl-carbonyl-amino)-benzylpenicillin:

This penicillin was prepared from 8.1 parts by weight of ampicillin and 4 parts by weight of 1-chlorocarbonylhexahydroazepin-2-one, in the manner described in Examples 23 and 41-B).

5

Yield: 40%

$\beta$ -Lactam content: 90%

NMR signals at  $\tau$  = 2.6 (5 H), 4.3—4.6 (3 H), 5.8 (1 H), 6.2—6.6 (2 H), 7.5—8.0 (2 H) and 8.0—8.9 ppm (12 H).

10

Example 44

Sodium D- $\alpha$ -(pyrrolid-2-on-1-yl-carbonylamino)-benzylpenicillin:

This substance was prepared from 35 parts by weight of ampicillin and 15 parts by weight of 1-chlorocarbonylpyrrolidone, in the manner described in Example 25.

Yield: 83%

15

$\beta$ -Lactam content: 70%

NMR signals at  $\tau$  = 2.6 (5 H), 4.4 (1 H), 4.55 (2 H), 5.8 (1 H), 6.25 (2 H), 7.4 (2 H), 8.0 (2 H) and 8.5 ppm (6 H).

20

Example 45

Sodium D- $\alpha$ -(3-formyl-3-methylureido)-benzylpenicillin:

This penicillin was prepared from 35 parts by weight of ampicillin and 12.2 parts by weight of N-formyl-N-methylcarbamic acid chloride, in the manner described in Examples 23 and 41-B).

Yield: 25%

25

$\beta$ -Lactam content: 83%

Example 46

If the N-formyl-N-methylcarbamic acid chloride used in Example 45 is replaced by:—

30

N-formyl-N-ethylcarbamic acid chloride,

N-formyl-N-propylcarbamic acid chloride,

N-formyl-N-*i*-propylcarbamic acid chloride,

N-formyl-N-*n*-butylcarbamic acid chloride,

N-formyl-N-allylcarbamic acid chloride,

N-formyl-N-benzylcarbamic acid chloride,

35

N-formyl-N-phenylcarbamic acid chloride,

N-formyl-N-cyclopropylcarbamic acid chloride,

N-formyl-N-cyclobutylcarbamic acid chloride,

N-formyl-N-cyclopentylcarbamic acid chloride or

N-formyl-N-cyclohexylcarbamic acid chloride;

40

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

sodium D- $\alpha$ -(3-formyl-3-ethylureido)-benzylpenicillin,

sodium D- $\alpha$ -(3-formyl-3-propylureido)-benzylpenicillin,

sodium D- $\alpha$ -(3-formyl-3-*i*-propylureido)-benzylpenicillin,

sodium D- $\alpha$ -(3-formyl-3-*n*-butylureido)-benzylpenicillin,

45

sodium D- $\alpha$ -(3-formyl-3-allylureido)-benzylpenicillin,

sodium D- $\alpha$ -(3-formyl-3-benzylureido)-benzylpenicillin,

sodium D- $\alpha$ -(3-formyl-3-phenylureido)-benzylpenicillin,

sodium D- $\alpha$ -(3-formyl-3-cyclopropylureido)-benzylpenicillin,

sodium D- $\alpha$ -(3-formyl-3-cyclobutylureido)-benzylpenicillin,

50

sodium D- $\alpha$ -(3-formyl-3-cyclopentylureido)-benzylpenicillin and

sodium D- $\alpha$ -(3-formyl-3-cyclohexylureido)-benzylpenicillin.

Example 47

A) N-2-Furoyl-N-phenylcarbamic acid chloride:

The substance was prepared from 9.4 parts by weight of 2-furoylanilide by reaction with  $\text{CH}_3\text{Li}$  and phosgene, in the manner described in Example 43-A).

55

Crude yield: 95%

The product was reacted, without further purification, to give the penicillin of Example 46-B).

ampicillin:  
in and 4 parts  
as described in

B) Sodium D- $\alpha$ -(3-[2-furoyl]-3-phenylureido)-benzylpenicillin:

This penicillin was prepared from 16.2 parts by weight of ampicillin and 11.5 parts by weight of N-2-furoyl-N-phenylcarbamic acid chloride, in the manner described in Example 25.

Yield: 50%

$\beta$ -Lactam content: 91%

NMR signals at  $\tau$  = 2.4 (1 H), 2.5 (1 H), 3.7 (1 H), 4.3—4.7 (3 H), 5.8 (1 H) and 8.45 ppm (6 H).

Example 48

If, instead of the N-2-furoyl-N-phenylcarbamic acid chloride used in Example 47, 0.03 mol of:—

N-(2,5-dimethyl-fur-3-oyl)-N-methylcarbamic acid chloride,

N-(5-bromo-fur-3-oyl)-N-methylcarbamic acid chloride,

N-(5-methoxymethyl-fur-2-oyl)-N-methylcarbamic acid chloride or

N-3,5-dimethylisothiazol-3-yl-carbonyl)-N-methylcarbamic acid chloride

are reacted with ampicillin, the sodium salts of the following penicillins are obtained:

D- $\alpha$ -(3-[2,5-dimethyl-fur-3-yl]-3-methylureido)-benzylpenicillin,

D- $\alpha$ -(3-[5-bromo-fur-3-yl]-3-methylureido)-benzylpenicillin,

D- $\alpha$ -(3-[5-methoxymethyl-fur-2-yl]-3-methylureido)-benzylpenicillin or

D- $\alpha$ -(3-[3,5-dimethylisothiazol-3-yl-carbonyl]-3-methylureido)-benzylpenicillin.

Example 49

Sodium D- $\alpha$ -(3-*o*-chlorobenzoyl-3-methylureido)-benzylpenicillin:

16.2 parts by weight of N-*o*-chlorobenzoyl-N-methylcarbamic acid chloride and 5 parts by weight of triethylamine were added at  $-10^{\circ}\text{C}$  to a solution of the triethylamine salt of 28 parts by weight of ampicillin in 300 parts by volume of methylene chloride, the mixture was stirred, with exclusion of moisture, for 30 minutes at this temperature, and subsequently for a further 2 hours at  $0^{\circ}\text{C}$ , and was then poured into ice water, and the pH was adjusted to 6.5. Thereafter, the organic phase was separated off, and the aqueous phase was covered with ether/ethyl acetate mixture and adjusted to pH = 1.5—2.0 with dilute hydrochloric acid, whilst cooling with ice. After having separated off the organic phase and again having extracted the water with ether/ethyl acetate mixture, the combined organic solutions were dried over  $\text{MgSO}_4$  and filtered, and about 70 parts by volume of a 1 molar solution of sodium 2-ethylhexanoate in ether containing methanol were added to the filtrate. The mixture was evaporated almost to dryness in vacuo, the residue was dissolved in methanol, and the product was precipitated as a non-crystalline, white solid substance by adding ether.

Yield: 26%

$\beta$ -Lactam content: 81%

Calculated: C 51.3 H 4.5 Cl 6.1 N 9.6

Found: C 51.4 H 5.9 Cl 5.6 N 9.0

NMR signals at  $\tau$  = 2.3—2.8 (9 H), 4.3 (1 H), 4.5 (2 H), 5.8 (1 H), 6.95 (3 H) and 8.5 ppm (6 H).

Effectiveness in animal experiments: A and B

Effectiveness in animal experiments against *Pseudomonas aeruginosa* Walter: better than carbenicillin.

Example 50

Sodium D- $\alpha$ -(3-[3-nitro-4-methoxy-benzoyl]-3-ethylureido)-benzylpenicillin:

This penicillin was prepared from 14.8 parts by weight of ampicillin and 12.2 parts by weight of N-(3-nitro-4-methoxy-benzoyl)-N-ethyl-carbamic acid chloride, as described in Example 49.

Yield: 24%

$\beta$ -Lactam content: 86%

Calculated: C 49.2 H 4.9 N 10.6 S 4.9

Found: C 49.2 H 5.3 N 10.1 S 5.5

NMR signals at  $\tau$  = 2.0 (1 H), 2.3 (1 H), 2.4—2.9 (6 H), 4.5 (3 H), 5.9 (1 H), 6.1 (3 H), 6.2 (2 H), 8.3—9.0 ppm (9 H).

Effectiveness in animal experiments: A and B

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and 12.2 parts  
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aroylanilide by  
as 43-A).

the penicillin of

Example 51

Sodium D- $\alpha$ -(3-[3-nitro-4-methoxybenzoyl]-3-*n*-propyl-ureido)-benzylpenicillin:

5 This penicillin was prepared from 21 parts by weight of ampicillin and 18 parts by weight of N-(3-nitro-4-methoxybenzoyl)-N-*n*-propyl-carbamic acid chloride, in the manner described in Example 49.  
Yield: 16%  
 $\beta$ -Lactam content: 90%  
10 NMR signals at  $\tau$  = 2.0 (1 H), 2.3 (1 H), 2.5—3.0 (6 H), 4.45 (1 H), 4.55 (2 H), 5.8 (1 H), 6.05 (3 H), 6.1—6.6 (2 H) and 8.45—9.1 ppm (11 H).  
Effectiveness in animal experiments: A and B.

Example 52

Sodium D- $\alpha$ -(3-methylaminocarbonyl-3-methyl-ureido)-benzylpenicillin:

15 This penicillin was prepared from 30 parts by weight of ampicillin and 10.5 parts by weight of N-methylaminocarbonyl-N-methyl-carbamic acid chloride, in the manner described in Example 49.  
Yield: 92%  
20  $\beta$ -Lactam content: 93%  
Calculated: C 48.6 H 5.1 N 14.1 S 6.5  
Found: C 49.0 H 6.3 N 12.6 S 6.9  
NMR signals at  $\tau$  = 2.6 (5 H), 4.45 (1 H), 4.5 (2 H), 5.8 (1 H), 6.8 (3 H), 7.2 (3 H) and 8.4 ppm (6 H).  
25 Effectiveness in animal experiments: B.

Example 53

Sodium D- $\alpha$ -(3-[2,5-dichlorobenzoyl]-3-methyl-ureido)-benzylpenicillin:

30 This penicillin was prepared from 28 parts by weight of ampicillin and 18.7 parts by weight of N-(2,5-dichlorobenzoyl)-N-methylcarbamic acid chloride, in the manner described in Example 49.  
Yield: 32%  
35  $\beta$ -Lactam content: 85%  
Calculated: C 47.6 H 4.2 Cl 11.1 N 8.8  
Found: C 48.0 H(6.0) Cl 9.7 N 8.6  
NMR signals at  $\tau$  = 2.3—2.8 (8 H), 4.35 (1 H), 4.5 (2 H), 5.8 (1 H), 6.9 (3 H), 8.4 (3 H) and 8.5 ppm (3 H).

Example 54

Sodium D- $\alpha$ -(3-*p*-chlorobenzoyl-3-methyl-ureido)-benzylpenicillin:

40 This penicillin was prepared from 28 parts by weight of ampicillin and 16 parts by weight of N-*p*-chlorobenzoyl-N-methylcarbamic acid chloride, in the manner described in Example 49.  
Yield: 16%  
45  $\beta$ -Lactam content: 82%  
Calculated: C 51.3 H 4.5 Cl 6.1 N 9.5 S 5.5  
Found: C 51.9 H 5.6 Cl 5.4 N 9.1 S 5.5  
NMR signals at  $\tau$  = 2.3—2.8 (9 H), 4.35 (1 H), 4.5 (2 H), 5.8 (1 H), 6.95 (3 H), 8.4 (3 H) and 8.5 ppm (3 H).  
50 Effectiveness in animal experiments: B.

Example 55

Sodium D- $\alpha$ -(3-propionyl-3-methyl-ureido)-benzylpenicillin:

55 6.0 parts by weight of N-propionyl-N-methyl-carbamic acid chloride in 25 parts by volume of absolute tetrahydrofuran were added dropwise, at 0°C, to a solution of 18 parts by weight of ampicillin in 180 parts by volume of 80% strength aqueous tetrahydrofuran (pH = 8.2 adjusted with triethylamine), whilst keeping the pH at 7—8 by adding triethylamine. Thereafter the mixture was further stirred at 0°C until no more triethylamine had to be added to maintain the pH at 7 (about 15 minutes).  
60 Water was now added, the tetrahydrofuran was stripped off in vacuo, the residue was extracted once with ether/ethyl acetate mixture, and the aqueous phase was covered

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with fresh ether/ethyl acetate mixture. Thereafter a pH of 1.5—2.0 was established by adding dilute hydrochloric acid at 0°C, whereupon the mixture was worked up as in Example 49, and the penicillin was precipitated as the sodium salt.

Yield: 85%

$\beta$ -Lactam content: 91%

Calculated: C 51.1 H 5.3 N 11.3 S 6.5

Found: C 51.2 H 6.5 N 11.1 S 7.5

NMR signals at  $\tau$  = 2.3—2.8 (5 H), 4.4 (1 H), 4.5 (2 H), 5.8 (1 H), 6.8 (1 H), 7.4 (2 H), 8.4 (3 H), 8.5 (3 H) and 8.8 ppm (3 H).

Effectiveness in animal experiments: B.

#### Example 56

##### Sodium D- $\alpha$ -(3-acetyl-3-ethyl-ureido)-benzylpenicillin:

This penicillin was prepared from 18 parts by weight of ampicillin and 6 parts by weight of N-acetyl-N-ethyl-carbamic acid chloride in the manner described in Example 55.

Yield: 62%

$\beta$ -Lactam content: 89%

Calculated: C 50.6 H 5.4 N 11.2 S 6.5

Found: C 50.7 H 6.3 N 10.8 S 6.9

NMR signals at  $\tau$  = 2.4—2.8 (5 H), 4.4 (1 H), 4.5 (2 H), 5.8 (1 H), 6.25 (2 H), 7.7 (3 H), 8.45 (6 H) and 8.8 ppm (3 H).

Effectiveness in animal experiments: B.

#### Example 57

##### Sodium D- $\alpha$ -(3-acetyl-3-n-propyl-ureido)-benzylpenicillin:

This penicillin was prepared from 28 parts by weight of ampicillin and 10 parts by weight of N-acetyl-N-n-propylcarbamic acid chloride, in the manner described in Example 55.

Yield: 67%

$\beta$ -Lactam content: 89.

Calculated: C 53.0 H 5.4 N 11.2 S 6.4

Found: C 52.5 H(6.6) N 10.5 S 6.4

NMR signals at  $\tau$  = 2.3—2.8 (5 H), 4.4 (1 H), 4.5 (2 H), 5.8 (1 H), 6.3 (2 H), 7.65 (3 H), 8.2—8.7 (8 H), and 9.1 ppm (3 H).

#### Example 58

##### Sodium D- $\alpha$ -(3-*i*-butyryl-3-methylureido)-benzylpenicillin:

This penicillin was prepared from 28 parts by weight of ampicillin and 10 parts by weight of N-*i*-butyryl-N-methyl-carbamic acid chloride, in the manner described in Example 55.

Yield: 33%

$\beta$ -Lactam content: 91%

Calculated: C 51.1 H 5.6 N 10.8

Found: C 50.8 H 6.4 N 10.9

NMR signals at  $\tau$  = 2.4—2.8 (5 H), 4.45 (1 H), 4.55 (2 H), 5.85 (1 H), 6.7 (3 H), 7.1 (1 H), 8.5 (6 H) and 8.9 ppm (6 H).

Effectiveness in animal experiments: 8.

#### Example 59

##### Sodium D- $\alpha$ -(3-*m*-chlorobenzoyl-3-methylureido)-benzylpenicillin:

This penicillin was prepared from 19.7 parts by weight of ampicillin and 10 parts by weight of N-*m*-chlorobenzoyl-N-methyl-carbamic acid chloride, in the manner described in Example 55.

Yield: 62%

$\beta$ -Lactam content: 86%

Calculated: C 51.5 H 4.4 Cl 6.1 N 9.6 S 5.6

Found: C 52.1 H(6.0) Cl 5.6 N 9.4 S 5.5

NMR signals at  $\tau$  = 2.4—2.8 (9 H), 4.35 (1 H), 4.5 (2 H), 5.8 (1 H), 6.85 (3 H) and 8.45 ppm (6 H).

## Example 60

Sodium  $\alpha$ -(3-acetyl-3-methylureido)-4-methylbenzylpenicillin:

This penicillin was prepared from 2.1 parts by weight of  $\alpha$ -amino-4-methylbenzylpenicillin and 1.2 parts by weight of N-acetyl-N-methyl-carbamic acid chloride, in the manner described in Example 55.

Yield: 45%

 $\beta$ -Lactam content: (determined by IR spectroscopy): 75%,NMR signals at  $\tau$  = 2.65 (2 H), 2.8 (2 H), 4.4—4.6 (3 H),

5.8 (1 H), 6.75 (3 H), 7.7 (6 H) and

8.25 to 8.55 ppm (6 H).

## Example 61

Sodium R,S- $\alpha$ -(3-dimethylaminocarbonyl-3-methyl-ureido)-4-methylbenzylpenicillin:

This penicillin was prepared from 1.8 parts by weight of R,S- $\alpha$ -amino-4-methylbenzylpenicillin and 1.6 parts by weight of N-dimethylaminocarbonyl-N-methyl-carbamic acid chloride, as described in Example 25.

Yield: 39%

 $\beta$ -Lactam content: (determined by IR spectroscopy): 65%,NMR signals at  $\tau$  = 2.5—2.9 (4 H), 4.4—4.7 (3 H), 5.8 (1 H),

6.9 (3 H), 7.05 (6 H), 7.7 (3 H) and 8.4 ppm (6 H).

## Example 62

Sodium R,S- $\alpha$ -(3-dimethylaminocarbonyl-3-methyl-ureido)-4-chlorobenzylpenicillin:

This penicillin was prepared from 2.7 parts by weight of R,S- $\alpha$ -amino-4-chlorobenzylpenicillin and 2.0 parts by weight of N-dimethylaminocarbonyl-N-methyl-carbamic acid chloride, as described in Example 55.

Yield: 43%

 $\beta$ -Lactam content: (determined by IR spectroscopy): 55—60%.NMR signals at  $\tau$  = 2.6 (4 H), 4.5 (3 H), 5.7 (1 H), 6.95 (3 H),

7.05 (6 H) and 8.3 to 8.5 ppm (6 H).

## Example 63

Sodium R,S- $\alpha$ -(3-acetyl-3-methyl-ureido)-4-chlorobenzylpenicillin:

This penicillin was prepared from 1.8 parts by weight of D,L- $\alpha$ -amino-4-chlorobenzylpenicillin and 1.0 part by weight of N-acetyl-N-methyl-carbamic acid chloride, as described in Example 55.

Yield: 80%

 $\beta$ -Lactam content: (determined by IR spectroscopy): 55—60%NMR signals at  $\tau$  = 2.4—2.8 (4 H), 4.3—4.6 (3 H), 5.8 (1 H),

6.7 (3 H), 7.65 (3 H) and 8.3—8.5 ppm (6 H).

## Example 64

Sodium D,L- $\alpha$ -(3-acetyl-3-methyl-ureido)- $\alpha$ -thienyl(2)-methylpenicillin:

This penicillin was prepared from 3.5 parts by weight of D,L- $\alpha$ -amino- $\alpha$ -thienyl(2)-methylpenicillin and 1.7 parts by weight of N-acetyl-N-methyl-carbamic acid chloride, as described in Example 55.

Yield: 42%

 $\beta$ -Lactam content: (determined by IR spectroscopy): 80%NMR signals at  $\tau$  = 2.5—3.2 (3 H), 4.1—4.6 (3 H), 5.8 (1 H),

6.8 (3 H), 7.7 (3 H) and 8.3—8.6 ppm (6 H).

## Example 65

Sodium D- $\alpha$ -(3-[1-piperidyl]-carbonyl-3-methylureido)-benzylpenicillin:

This penicillin was prepared from 30 parts by weight of ampicillin and 13.5 parts by weight of N-(1-piperidylcarbonyl)-N-methyl-carbamic acid chloride, in the manner described in Example 1.

Yield (crude product): 66%

 $\beta$ -Lactam content: 97%

Calculated: C 53.4 H 5.6 N 12.9 S 5.9

Found: C 53.1 H 6.5 N 12.3 S 6.3

NMR signals at  $\tau$  = 2.6 (5 H), 4.5 (3 H), 5.8 (1 H), 6.6 (4 H),

6.9 (3 H) and 8.4 ppm (12 H).

Effectiveness against *E. coli* 14: 3.12 units/ml.  
Effectiveness against *Klebsiella* K 10: 50 units/ml.

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ride,

5

5

## Example 66

Sodium D- $\alpha$ -(3-[1-pyrrolidyl]-carbonyl-3-methylureido)-benzylpenicillin:

This penicillin was prepared from 30 parts by weight of ampicillin and 12.6 parts by weight of N-(1-pyrrolidylcarbonyl)-N-methylcarbamic acid chloride, in the manner described in Example 1.

Yield (crude product): 72%

$\beta$ -Lactam content: 96%

Calculated: N 13.3 S 6.1

Found: N 13.2 S 6.1

NMR signals at  $\tau$  = 2.6 (5 H), 4.5 (3 H), 5.8 (1 H), 6.5—6.8 (4 H), 6.9 (3 H), 8.0—8.3 (4 H) and 8.5 ppm (6 H).

Effectiveness against *E. coli* 14: 3.12 units/ml.

Effectiveness against *Proteus* 3400: 50 units/ml.

Effectiveness in animal experiments: A.

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hyl-  
nyl-

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## Example 67

Sodium D- $\alpha$ -(3-[4-morpholinyl]-carbonyl-3-methylureido)-benzylpenicillin:

This penicillin was prepared from 30 parts by weight of ampicillin and 13.6 parts by weight of N-(4-morpholinylcarbonyl)-N-methylcarbamic acid chloride, in the manner described in Example 1.

Yield (crude product): 80%

$\beta$ -Lactam content: 93%

Calculated: N 12.9 S 5.9

Found: N 11.8 S 5.9

NMR signals at  $\tau$  = 2.6 (5 H), 4.5 (3 H), 5.9 (1 H), 6.3—6.8 (8 H), 6.9 (3 H) and 8.5 ppm (6 H).

Effectiveness against *Proteus* 1017: 50 units/ml.

Effectiveness in animal experiments: A.

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## Example 68

Sodium D- $\alpha$ -(3-diethylaminocarbonyl-3-methylureido)-benzylpenicillin:

This penicillin was prepared from 30 parts by weight of ampicillin and 12.7 parts by weight of N-diethylaminocarbonyl-N-methylcarbamic acid chloride, in the manner described in Example 1.

Yield (crude product): 46%

$\beta$ -Lactam content: 97%

Calculated: N 13.3 S 6.1

Found: N 12.9 S 6.0

NMR signals at  $\tau$  = 2.6 (5 H), 4.5 (3 H), 5.8 (1 H), 6.5—7.0 (7 H), 8.4 (6 H) and 8.7—9.0 ppm (6 H).

Effectiveness against *E. coli* 14: 12.5 units/ml.

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## Example 69

Sodium D- $\alpha$ -(3-[2-nitro-4-chlorobenzoyl]-3-methylureido)-benzylpenicillin:

This penicillin was prepared from 21 parts by weight of ampicillin and 12.8 parts by weight of N-(2-nitro-4-chlorobenzoyl)-N-methylcarbamic acid chloride, in the manner described in Example 1.

Yield (crude product): 81%

$\beta$ -Lactam content: 95%

Calculated: N 11.4 S 5.2

Found: N 10.6 S 5.1

NMR signals at  $\tau$  = 1.7 (1 H), 2.1—2.5 (2 H), 2.6 (5 H), 4.3—4.6 (3 H), 5.8 (1 H), 6.9 (3 H) and 8.4 ppm (6 H).

Effectiveness against *Proteus* 1017: 3.12 units/ml.

Effectiveness against *Pseudomonas aeruginosa*: 12.5 units/ml.

Effectiveness against *Klebsiella* K 10: 12.5 units/ml.

Effectiveness in animal experiments: A and B.

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## Example 70

Sodium D- $\alpha$ -(3-[2-bromobenzoyl]-3-methylureido)-benzylpenicillin:

This penicillin was prepared from 30 parts by weight of ampicillin and 18.3 parts by weight of N-(2-bromobenzoyl)-N-methyl-carbamic acid chloride, in the manner described in Example 1.

Yield (crude product): 64%

 $\beta$ -Lactam content: 95%NMR signals at  $\tau$  = 2.2—2.7 (9 H), 4.3—4.6 (3 H), 5.8 (1 H), 7.0 (3 H) and 8.4 ppm (6 H).Effectiveness against *Proteus* 1017: 1.56 units/ml.Effectiveness against *Pseudomonas aerug* Bonn: 6.25 units/ml.

Effectiveness in animal experiments: A and B.

## Example 71

Sodium D- $\alpha$ -(3-[2-methylbenzoyl]-3-methylureido)-benzylpenicillin:

This penicillin was prepared from 30 parts by weight of ampicillin and 14.4 parts by weight of N-(2-methylbenzoyl)-N-methyl-carbamic acid chloride, in the manner described in Example 1.

Yield (crude product): 66%

 $\beta$ -Lactam content: 93%NMR signals at  $\tau$  = 2.4—2.8 (9 H), 4.3—4.6 (3 H), 5.8 (1 H), 7.0 (3 H), 7.7 (3 H) and 8.5 ppm (6 H).Effectiveness against *Proteus* 1017: 3.12 units/ml.Effectiveness against *Pseudomonas aerug*. Bonn: 6.25 units/ml.

Effectiveness in animal experiments: A and B.

## Example 72

Sodium D- $\alpha$ -(3-acetyl-3-phenyl-ureido)-benzylpenicillin:

This penicillin was prepared from 10 parts by weight of N-acetyl-N-phenyl-carbamic acid chloride and 19 parts by weight of ampicillin, in the manner described in Example 55.

Yield: 86%

 $\beta$ -Lactam content: 85%

Calculated: C 53.1 H 5.0 N 9.9 S 5.7

Found: C 53.6 H 5.5 N 9.8 S 5.7

NMR signals at  $\tau$  = 2.4—2.8 (10 H), 4.4 (1 H), 4.55 (2 H), 5.8 (1 H), 8.1 (3 H), 8.4 (3 H) and 8.5 ppm (3 H).

Effectiveness in animal experiments: B.

## Example 73

Sodium D- $\alpha$ -(3-*m*-nitrocinnamoyl-3-methyl-ureido)-benzylpenicillin:

This penicillin was prepared from 18.9 parts by weight of N-(*m*-nitrocinnamoyl)-N-methyl-carbamic acid chloride and 28 parts by weight of ampicillin, in the manner described in Example 55.

Yield: 78%

 $\beta$ -Lactam content: 88%

Calculated: C 47.9 H 5.4 N 10.2 S 4.8

Found: C 47.5 H 5.0 N 10.4 S 5.4

NMR signals at  $\tau$  = 1.6 (1 H), 1.7—2.9 (8 H), 4.4 (1 H), 4.5 (2 H), 5.8 (1 H), 6.6 (3 H) and 8.5 ppm (6 H).

Effectiveness in animal experiments: A and B.

## Example 74

Sodium D- $\alpha$ -(3-[4-nitrophenacetyl]-3-methyl-ureido)-benzylpenicillin:

This penicillin was prepared from 16.3 parts by weight of N-*p*-nitrophenacetyl-N-methyl-carbamic acid chloride and 28 parts by weight of ampicillin, in the manner described in Example 55.

Yield: 92%

 $\beta$ -Lactam content: 84%Calc  
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Calculated: C 51.1 H 4.6 N 11.5 S 5.3

Found: C 51.3 H 5.4 N 11.2 S 5.7

NMR signals at  $\tau$  = 1.8 (2 H), 2.5 (2 H), 2.6 (5 H),  
4.4 (1 H), 4.55 (2 H), 5.8 (1 H),  
5.85 (2 H), 6.7 (3 H), 8.4 (3 H), and  
8.5 ppm (3 H).

Effectiveness in animal experiments: A and B.

#### Example 75

##### D- $\alpha$ -(Imidazolidin-2-on-1-yl-carbonylamino)-benzylpenicillin:

This penicillin was prepared from 5.4 parts by weight of N-chlorocarbonyl-imidazolidin-2-one and 12.7 parts by weight of ampicillin in the manner described in Example 1. After acidification, the product was obtained as the free penicillin acid, which is sparingly soluble in ethyl acetate, and which was filtered off, washed with water and dried over  $P_2O_5$  in vacuo.

Yield: 72%

$\beta$ -Lactam content: 93%

Calculated: C 50.1 H 5.0 N 14.6 S 6.7

Found: C 50.1 H 5.6 N 13.8 S 6.8

NMR signals at  $\tau$  = 0.9 (2 H), 2.35 (1 H), 2.6 (5 H), 4.25 (1 H),  
4.55 (2 H), 5.7 (1 H), 6.0—7.0 (4 H),  
8.4 (3 H) and 8.55 ppm (3 H)

Solvent: DMSO- $d_6$ .

#### Example 76

##### Sodium D- $\alpha$ -(piperidin-2-on-1-yl-carbonylamino)-benzylpenicillin:

This penicillin was prepared from 9 parts by weight of 1-chlorocarbonyl-2-chloro-1,4,5,6-tetrahydropyridine and 21 parts by weight of ampicillin in the manner described in Example 55.

Yield: 85%

$\beta$ -Lactam content: 89%

NMR signals at  $\tau$  = 2.4—2.8 (5 H), 4.4 (1 H), 4.45 (1 H),  
4.55 (1 H), 5.8 (1 H), 6.15—6.5 (2 H),  
7.6—8.0 (2 H) and 8.0—8.6 ppm (10 H).

Effectiveness in animal experiments: A and B.

#### Example 77

##### Sodium $\alpha$ -(3-*o*-chlorobenzoyl-3-methyl-urcido)- $\alpha$ -thienyl(2)-methylpenicillin:

This penicillin was prepared from 1.9 parts by weight of N-*o*-chlorobenzoyl-N-methylcarbamic acid chloride and 1.5 parts by weight of  $\alpha$ -amino- $\alpha$ -thienyl(2)-methylpenicillin in the manner described in Example 55.

Yield: 35%

$\beta$ -Lactam content: 55—60% (estimated from the IR spectrum).

NMR signals at  $\tau$  = 2.4—3.1 (7 H), 4.3—4.5 (3 H), 5.8 (1 H),  
6.9 (3 H) and 8.2—8.6 ppm (6 H).

Effectiveness in animal experiments: B.

#### Example 78

##### Sodium D- $\alpha$ -(3-methyl-1,3-diazacyclohexan-2-on-1-yl-carbonylamino)-benzylpenicillin:

This penicillin was prepared from 12.4 parts by weight of 1-chloro-carbonyl-2-oxo-3-methyl-1,3-diazacyclohexane and 17.5 parts by weight of ampicillin, in the manner described in Example 55.

Yield: 46%

$\beta$ -Lactam content: 90%

Calculated: C 50.1 H 5.3 N 13.3 S 6.1

Found: C 50.4 H 6.2 N 13.1 S 6.4

NMR signals at  $\tau$  = 2.3—2.8 (5 H), 4.3—4.6 (3 H), 5.8 (1 H),  
6.25 (2 H), 6.4—6.8 (2 H), 7.0 (3 H),  
8.0 (2 H), 8.4 (3 H) and 8.5 ppm (3 H).

## Example 79

Sodium D- $\alpha$ -(3-*o*-fluorobenzoyl-3-methyl-ureido)-benzylpenicillin:

This penicillin was prepared from 9.05 parts by weight of N-*o*-fluorobenzoyl-N-methyl-carbamic acid chloride and 17.5 parts by weight of ampicillin, in the manner described in Example 55.

Yield: 88%

 $\beta$ -Lactam content: 92%

Calculated: C 54.6 H 4.4 N 10.2 S 5.8

Found: C 54.2 H(5.6) N 10.1 S 5.8

NMR signals at  $\tau$  = 2.4—2.9 (9 H), 4.35 (1 H), 4.5 (2 H), 5.8 (1 H), 6.8 (3 H) and 8.5 ppm (6 H).

## Example 80

Sodium D- $\alpha$ -(3-*o*-chlorobenzoyl-3-ethyl-ureido)-benzylpenicillin:

This penicillin was prepared from 10.7 parts by weight of N-*o*-chlorobenzoyl-N-ethyl-carbamic acid chloride and 17.5 parts by weight of ampicillin, in the manner described in Example 55.

Yield: 90%

 $\beta$ -Lactam content: 93%

Calculated: C 52.5 H 4.6 Cl 6.0 N 9.4 S 5.4

Found: C 52.3 H 5.4 Cl 5.6 N 9.2 S 5.4

NMR signals at  $\tau$  = 2.3—2.8 (9 H), 4.35 (1 H), 4.5 (2 H), 5.8 (1 H), 6.4 (2 H), 8.4 (3 H), 8.5 (3 H) and 9.0 ppm (3 H).

## Example 81

Sodium D- $\alpha$ -(3-*o*-chlorobenzoyl-3-*n*-propyl-ureido)-benzylpenicillin:

This penicillin was prepared from 11.0 parts by weight of N-*o*-chlorobenzoyl-N-*n*-propyl-carbamic acid chloride and 17.5 parts by weight of ampicillin, in the manner described in Example 55.

Yield: 82%

 $\beta$ -Lactam content: 92%

Calculated: C 53.3 Cl 5.8 N 9.2 H 4.8 S 5.3

Found: C 53.7 Cl 5.4 N 9.2 H(6.2) S 5.6

NMR signals at  $\tau$  = 2.3—2.8 (9 H), 4.4 (1 H), 4.5 (2 H), 5.8 (1 H), 6.3—6.7 (2 H), 8.2—8.7 (2 H), 8.4 (3 H), 8.5 (3 H) and 9.3 ppm (3 H).

## Example 82

Sodium D- $\alpha$ -(3-*o*-nitrobenzoyl-3-methyl-ureido)-benzylpenicillin:

This penicillin was prepared from 12.1 parts by weight of N-*o*-nitrobenzoyl-N-methyl-carbamic acid chloride and 21 parts by weight of ampicillin, in the manner described in Example 55.

Yield: 94%

 $\beta$ -Lactam content: 92%

Calculated: C 51.1 H 4.3 N 11.9 S 5.5

Found: C 50.9 H 5.3 N 11.1 S 5.6

NMR signals at  $\tau$  = 1.75 (1 H), 2.05—2.8 (8 H), 4.35 (1 H), 4.5 (2 H), 5.8 (1 H), 6.95 (3 H), 8.4 (3 H) and 8.5 (3 H).

Effectiveness in animal experiments: B.

## Example 83

Sodium D- $\alpha$ -(3-*o,o'*-dichlorobenzoyl-3-methyl-ureido)-benzylpenicillin:

This penicillin was prepared from 13.3 parts by weight of N-*o,o'*-dichlorobenzoyl-N-methyl-carbamic acid chloride and 21 parts by weight of ampicillin, in the manner described in Example 55.

Yield: 91%

 $\beta$ -Lactam content: 91%

Calculated: C 48.6 H 4.0 Cl 11.5 N 9.1 S 5.2

Found: C 48.9 H 4.5 Cl 11.1 N 8.9 S 5.3

NMR signals at  $\tau$  = 2.3—2.8 (8 H), 4.3 (1 H), 4.5 (2 H), 5.75 (1 H), 6.9 (3 H), 8.4 (3 H) and 8.5 ppm (3 H).

Effectiveness in animal experiments: B.

|                | 42 | 43 | 1,301,961                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 43 |
|----------------|----|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
|                |    |    | Example 84                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |
|                |    |    | Sodium D- $\alpha$ -(3-[2,4-dichlorobenzoyl]-3-methyl-ureido)-benzylpenicillin:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |    |
| zoyl-<br>inner | 5  | 5  | This penicillin was prepared from 13.3 parts by weight of N-(2,4-dichlorobenzoyl)-N-methyl-carbamic acid chloride and 21 parts by weight of ampicillin, in the manner described in Example 55.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 5  |
|                |    |    | Yield: 84%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |
|                |    |    | $\beta$ -Lactam content: 92%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |    |
|                | 10 | 10 | Calculated: C 48.6 H 4.0 Cl 11.5 N 9.1 S 5.2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |    |
|                |    |    | Found: C 48.7 H 4.6 Cl 10.9 N 9.0 S 5.8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 10 |
|                |    |    | NMR signals $\tau$ = 2.4 (1 H), 2.4—2.8 (7 H), 4.35 (1 H), 4.5 (2 H), 5.8 (1 H), 6.9 (3 H), 8.4 (3 H) and 8.5 ppm (3 H).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |    |
|                |    |    | Effectiveness in animal experiments: A and B.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |    |
| l-N-<br>inner  | 15 | 15 | Example 85                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 15 |
|                |    |    | Sodium D- $\alpha$ -(3-propionyl-3-phenyl-ureido)-benzylpenicillin:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |    |
|                |    |    | This penicillin was prepared from 15.5 parts by weight of N-propionyl-N-phenyl-carbamic acid chloride and 27.5 parts by weight of ampicillin, in the manner described in Example 55.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |    |
|                | 20 | 20 | Yield: 78%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 20 |
|                |    |    | $\beta$ -Lactam content: 87%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |    |
|                |    |    | Calculated: C 55.3 H 5.1 N 9.9 S 5.7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |    |
|                |    |    | Found: C 55.1 H 5.1 N 9.8 S 6.0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |    |
|                |    |    | NMR signals at $\tau$ = 2.2—3.0 (10 H), 4.4 (1 H), 4.5 (2 H), 5.75 (1 H), 7.9 (2 H), 8.4 (3 H), 8.5 (3 H) and 9.0 ppm (3 H).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 25 |
| l-N-<br>inner  | 25 | 25 | Effectiveness in animal experiments: B.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |    |
|                |    |    | Example 86                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |
|                | 30 | 30 | A. D- $\alpha$ -(Imidazolidin-2-on-1-yl-carbonylamino)-benzylpenicillin:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 30 |
|                |    |    | 14 parts by weight of D- $\alpha$ -aminobenzylpenicillin (ampicillin) were suspended in 80% strength aqueous tetrahydrofuran (130 parts by volume) and sufficient triethylamine (approx. 6.5 parts by volume) was added dropwise, whilst stirring, at 20°C, that a clear solution was just produced and the pH value was between 7.5 and 8.2 (glass electrode). The mixture was now cooled to 0°C and a solution of 5.4 parts by weight of N-chlorocarbonyl-imidazolidin-2-one in 25 parts by volume of absolute tetrahydrofuran was added dropwise over the course of 30 minutes, whilst cooling with ice and stirring vigorously, the pH value being kept between 7.5 and 8.0 by simultaneous addition of triethylamine. The mixture was further stirred for 30 minutes at 0°C and subsequently at room temperature until no further addition of triethylamine was necessary to maintain the pH value of 7.5. 130 parts by volume of water were now added and the tetrahydrofuran was largely removed in a rotary evaporator at room temperature. The aqueous solution which remained was once extracted by shaking with ether, covered with 300 parts by volume of ethyl acetate, cooled to 0°C and treated with sufficient dilute hydrochloric acid, whilst stirring and cooling with ice, to establish a pH value of 1.5 to 2.0. The organic phase was separated off, the aqueous suspension was again extracted with about 300 parts by volume of ethyl acetate, and the organic extracts were combined. | 35 |
| N-<br>ner      | 40 | 40 | The penicillin, which is rather sparingly soluble in ethyl acetate and which was suspended in the aqueous phase, was filtered off, carefully washed with ice water until free of acid, and dried in vacuo at about 1 mm Hg over P <sub>2</sub> O <sub>5</sub> . The substance is crystalline; long needles are visible under the microscope.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 40 |
|                | 45 | 45 | Yield: 71%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 45 |
|                |    |    | $\beta$ -Lactam content: 93%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |    |
|                | 50 | 50 | Calculated: C 50.1 H 5.0 N 14.6 S 6.7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 50 |
|                |    |    | Found: C 50.1 H 5.6 N 13.8 S 6.8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |    |
|                | 55 | 55 | NMR signals (dimethylsulphoxide-d <sub>6</sub> as the solvent) at $\tau$ = 0.9 (2 H), 2.35 (1 H), 2.6 (5 H), 4.25 (1 H), 4.55 (2 H), 5.7 (1 H), 6.0—7.0 (4 H), 8.4 (3 H) and 8.55 ppm (3 H).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 55 |
| en-<br>the     |    |    | IR bands at 3380, 3230, 1784, 1728, 1687, 1639, 1520, 1375, 1219 and 735 cm <sup>-1</sup> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |    |
|                | 60 | 60 | According to separation in a paper chromatogram and subsequent development with <i>B. subtilis</i> , the product only contains one antibiotically active component.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 60 |
|                |    |    | A further 0.45 part by weight (2.6% of theory) of the penicillin, in the form of its sodium salt, could be isolated from the ethyl acetate extract after addition of about                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |

2 parts by volume of a 1 molar solution of sodium 2-ethyl-hexanoate in ether containing methanol.

The free acid of the penicillin can be easily converted into the chemotherapeutically usable salts by conventional processes. (See Example 92A).

#### 5 B. 1-Chlorocarbonyl-imidazolidi-2-one

4 parts by weight of phosgene in 10 parts by volume of absolute tetrahydrofuran were added dropwise, over the course of 15 minutes, to a vigorously stirred solution of 3.5 parts by weight of imidazolidone (2) [manufactured according to Fischer and Koch, Ann, 232, page 224 (1886)] in 50 parts by volume of absolute tetrahydrofuran. Thereafter the reaction mixture was stirred for 3 hours at 10°C and a stream of dry 10 3.5 parts by weight of imidazolidone(2) [manufactured according to Fischer and remnants of phosgene. The mixture was now evaporated to dryness on a rotary evaporator in vacuo, and the solid residue was dried over concentrated sulphuric acid and at about 12 mm Hg.

Yield: 93%. Melting point = 150°C after recrystallisation from acetone-pentane.

Calculated: C 32.3 H 3.4 N 18.8 Cl 23.9

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

NMR signals at  $\tau = 5.7$  to 6.1 (2H) and 6.3 to 6.7 (2H), (acetone- $d_6$  as the solvent), symmetrical  $A_2B_2$ -system.

20 IR bands at 3230, 1790, 1700, 1270 and 1150  $\text{cm}^{-1}$ .

#### Example 87

If, in the procedure of Example 86, the D- $\alpha$ -aminobenzylpenicillin used therein is replaced by:—

25 0.04 mol of  $\alpha$ -amino-*p*-methylbenzylpenicillin,

$\alpha$ -amino-*p*-chlorobenzylpenicillin,

$\alpha$ -amino-*p*-methylthiobenzylpenicillin,

$\alpha$ -amino- $\alpha$ -(2)thienylmethylpenicillin or

$\alpha$ -amino- $\alpha$ -(3)thienylmethylpenicillin,

the following penicillins are obtained:

30  $\alpha$ -(imidazolidin-2-on-1-yl-carbonylamino)-*p*-methylbenzylpenicillin,

$\alpha$ -(imidazolidin-2-on-1-yl-carbonylamino)-*p*-chlorobenzylpenicillin,

$\alpha$ -(imidazolidin-2-on-1-yl-carbonylamino)-*p*-methylthiobenzylpenicillin,

$\alpha$ -(imidazolidin-2-on-1-yl-carbonylamino)- $\alpha$ -(2)-thienylmethylpenicillin or

$\alpha$ -(imidazolidin-2-on-1-yl-carbonylamino)- $\alpha$ -(3)thienylmethylpenicillin.

#### Example 88

35 If, in the procedure of Example 86, the 1-chlorocarbonylimidazolidone used therein is replaced by 0.035 mol of:—

1-chlorocarbonyl-1,3-diazacyclohexan-2-one,

1-chlorocarbonyl-1,3-diazacycloheptan-2-one,

40 1-chlorocarbonyl-5-methyl-imidazolidone(2),

1-chlorocarbonyl-4-methyl-imidazolidone(2),

1-chlorocarbonyl-5,5-dimethyl-imidazolidone(2),

1-chlorocarbonyl-4,4-dimethyl-imidazolidone(2),

1-chlorocarbonyl-4,5-cis-dimethyl-imidazolidone(2),

45 1-chlorocarbonyl-4,5-trans-dimethyl-imidazolidone,

1-chlorocarbonyl-benzimidazolone,

1-chlorocarbonyl-6-methyl-benzimidazolone,

1-chlorocarbonyl-5-methyl-benzimidazolone,

1-chlorocarbonyl-4-methyl-benzimidazolone,

50 1-chlorocarbonyl-7-methylbenzimidazolone,

1-chlorocarbonyl-5-nitrobenzimidazolone,

1-chlorocarbonyl-6-nitrobenzimidazolone,

1-chlorocarbonyl-hexahydrobenzimidazolone(2),

1-chlorocarbonyl-6-aza-benzimidazolone,

55 1-chlorocarbonyl-5-aza-benzimidazolone,

1-chlorocarbonyl-5-carbethoxy-benzimidazolone,

1-chlorocarbonyl-6-carbethoxy-benzimidazolone or

$\Delta$ -chlorocarbonyl-2,4-diazabicyclo[3,2,2]-nonan-3-one,

the following penicillins are obtained:—

60 D- $\alpha$ -(1,3-diazacyclohexan-2-on-1-yl-carbonylamino)-benzylpenicillin,

D- $\alpha$ -(1,3-diazacycloheptan-2-on-1-yl-carbonylamino)-benzylpenicillin,

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|------|----|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
|      | 44 |    | 1,301,961                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 45 |
| ing  |    |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |    |
| ally |    |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |    |
|      | 5  | 5  | D- $\alpha$ -(5-methyl-imidazolidin-2-on-1-yl-carbonylamino)-benzylpenicillin,<br>D- $\alpha$ -(4-methylimidazolidin-2-on-1-yl-carbonylamino)-benzylpenicillin,<br>D- $\alpha$ -(5,5-dimethylimidazolidin-2-on-1-yl-carbonylamino)-benzylpenicillin,<br>D- $\alpha$ -(4,4-dimethylimidazolidin-2-on-1-yl-carbonylamino)-benzylpenicillin,<br>D- $\alpha$ -(4,5-cis-dimethylimidazolidin-2-on-1-yl-carbonylamino)-benzylpenicillin,<br>D- $\alpha$ -(4,5-trans-dimethylimidazolidin-2-on-1-yl-carbonylamino)-benzylpenicillin,<br>D- $\alpha$ -(benzimidazolin-2-on-1-yl-carbonylamino)-benzylpenicillin,<br>D- $\alpha$ -(6-methylbenzimidazolin-2-on-1-yl-carbonylamino)-benzylpenicillin,<br>D- $\alpha$ -(5-methylbenzimidazolin-2-on-1-yl-carbonylamino)-benzylpenicillin,<br>D- $\alpha$ -(4-methylbenzimidazolin-2-on-1-yl-carbonylamino)-benzylpenicillin,<br>D- $\alpha$ -(7-methylbenzimidazolin-2-on-1-yl-carbonylamino)-benzylpenicillin,<br>D- $\alpha$ -(5-nitrobenzimidazolin-2-on-1-yl-carbonylamino)-benzylpenicillin,<br>D- $\alpha$ -(6-nitrobenzimidazolin-2-on-1-yl-carbonylamino)-benzylpenicillin,<br>D- $\alpha$ -(hexahydrobenzimidazolin-2-on-1-yl-carbonylamino)-benzylpenicillin,<br>D- $\alpha$ -(6-azabenzimidazolin-2-on-1-yl-carbonylamino)-benzylpenicillin,<br>D- $\alpha$ -(5-azabenzimidazolin-2-on-1-yl-carbonylamino)-benzylpenicillin,<br>D- $\alpha$ -(5-carbethoxybenzimidazolin-2-on-1-yl-carbonylamino)-benzylpenicillin,<br>D- $\alpha$ -(6-carbethoxybenzimidazolin-2-on-1-yl-carbonylamino)-benzylpenicillin or<br>D- $\alpha$ -(2,4-diazabicyclo[3,2,2]nonan-3-on-2-yl-carbonylamino)-benzylpenicillin.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 5  |
|      | 10 | 10 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 10 |
|      | 15 | 15 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 15 |
|      | 20 | 20 | Example 89                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 20 |
| ein  |    |    | A. Sodium D- $\alpha$ -(imidazolidine-2-thion-1-yl-carbonylamino)-benzylpenicillin:<br>8.5 parts by weight of 1-chlorocarbonyl-imidazolidine-2-thione were reacted with<br>17.5 parts by weight of D- $\alpha$ -aminobenzylpenicillin in 170 parts by volume of 80%<br>strength aqueous tetrahydrofuran, at 0°C and pH 7.5 to 8.0 (glass electrode), whilst<br>stirring. Triethylamine was added gradually to maintain the pH value. The mixture<br>was further stirred at room temperature until no further addition of triethylamine was<br>necessary to maintain the pH at 7.5. Thereafter, 150 parts by volume of water were<br>added, a pH of 6.5 was established by means of a little dilute hydrochloric acid, and<br>the tetrahydrofuran was stripped off in a rotary evaporator at room temperature.<br>The mixture was now extracted once with ether, the aqueous phase was covered with<br>300 parts by volume of ethyl acetate, the whole was cooled to 0°C, and dilute hydro-<br>chloric acid was introduced, whilst stirring and cooling with ice, until a pH value of<br>1.5 to 2.0 was reached. The organic phase was separated off, the aqueous solution<br>was again extracted with 300 parts by volume of ethyl acetate, and the organic solutions<br>were combined and subsequently dried with MgSO <sub>4</sub> . On adding about 40 parts by<br>volume of a 1 molar solution of sodium 2-ethylhexanoate in ether containing methanol,<br>the sodium salt of the penicillin precipitated. The bulk of the ethyl acetate was stripped<br>from the suspension in vacuo, and the residue was dissolved in methanol and added<br>dropwise to a mixture of 300 parts by volume of ether and 30 parts by volume of<br>methanol. The ether/methanol mixture was decanted from the precipitated product<br>after it had stood for a short time, and the product was again repeatedly worked with<br>ether, filtered off and dried over P <sub>2</sub> O <sub>5</sub> in a vacuum desiccator.<br>Effectiveness against <i>Psdm. aerug.</i> Bonn: 25 units/ml.<br>Effectiveness against <i>Proteus</i> 3400: 50 units/ml.<br>Yield: 40%<br>$\beta$ -Lactam content: 90% (estimated on the basis of the $\beta$ -lactam band of the IR<br>spectrum).<br>NMR signals (methanol-d <sub>4</sub> as the solvent) at $\tau$ = 2.3 to 2.8 (5H), 4.4 (1 H), 4.55 (2 H),<br>5.85 (1 H), 6.0 to 6.5 (4 H), 8.4 (3 H) and 8.5 ppm (3 H).<br>IR bands at 3320, 1760, 1720, 1665, 1602, 1520, 1365, and 1255 cm <sup>-1</sup> . | 25 |
|      | 30 | 30 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 30 |
|      | 35 | 35 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 35 |
| ein  |    |    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |    |
|      | 40 | 40 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 40 |
|      | 45 | 45 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 45 |
|      | 50 | 50 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 50 |
|      | 55 | 55 | B. 1-Trimethylsilyl-imidazolidine-2-thione:<br>30.6 parts by weight of imidazolidine-2-thione were boiled overnight with 54.4<br>parts by weight of trimethylchlorosilane and 51.5 parts by weight of triethylamine in<br>absolute tetrahydrofuran. The warm suspension was freed of the precipitated triethyl-<br>amine hydrochloride by filtration, and the filtrate was evaporated and dried in a vacuum<br>desiccator.<br>Melting point: approx. 130°C.<br>Yield: 97%<br>Calculated: N 14.4 S 16.5<br>Found: N 15.3 S 16.9<br>Strong Si-C stretching vibration in the IR spectrum at 850 cm <sup>-1</sup> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 55 |
|      | 60 | 60 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 60 |

C. 1-Chlorocarbonyl-imidazolidine-2-thione:

50 parts by weight of 1-trimethylsilyl-imidazolidine-2-thione in 150 parts by volume of methylene chloride were treated with 35 parts by weight of phosgene in 50 parts by volume of methylene chloride over the course of 2 hours at 0°C. The mixture was stirred for 24 hours at 0°C, the methylene chloride was subsequently stripped off, and the residue was dried in a high vacuum. Semi-solid mass, incompletely soluble in acetone.

Crude yield: 97%.

IR bands at 1830, 1590 and 1240  $\text{cm}^{-1}$ .

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Example 90

If, following the procedure desired in Example 89A, 17.5 parts by weight of ampicillin are reacted with 0.05 mol of:—

- 1-chlorocarbonyl-1,3-diazacyclohexane-2-thione,  
1-chlorocarbonyl-4-methylimidazolidine-2-thione,  
1-chlorocarbonyl-5-methylimidazolidine-2-thione,  
1-chlorocarbonyl-4,4-dimethylimidazolidine-2-thione,  
1-chlorocarbonyl-5,5-dimethylimidazolidine-2-thione or  
1-chlorocarbonyl-4,5-dimethylimidazolidine-2-thione,

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

- D- $\alpha$ -(1,3-diazacyclohexane-2-thion-1-yl-carbonylamino)-benzylpenicillin,  
D- $\alpha$ -(4-methylimidazolidine-2-thion-1-yl-carbonylamino)-benzylpenicillin,  
D- $\alpha$ -(5-methylimidazolidine-2-thion-1-yl-carbonylamino)-benzylpenicillin,  
D- $\alpha$ -(4,4-dimethylimidazolidine-2-thion-1-yl-carbonylamino)-benzylpenicillin,  
D- $\alpha$ -(5,5-dimethylimidazolidine-2-thion-1-yl-carbonylamino)-benzylpenicillin or  
D- $\alpha$ -(4,5-dimethylimidazolidine-2-thion-1-yl-carbonylamino)-benzylpenicillin.

Example 91

If, in the procedure of Example 89A the D- $\alpha$ -aminobenzylpenicillin used there is replaced by 0.05 mol of

- $\alpha$ -amino-*p*-methylbenzylpenicillin,  
 $\alpha$ -amino-*p*-chlorobenzylpenicillin,  
 $\alpha$ -amino-*p*-methylthiobenzylpenicillin,  
 $\alpha$ -amino- $\alpha$ -(2)-thienylmethylpenicillin or  
 $\alpha$ -amino- $\alpha$ -(3)-thienylmethylpenicillin,

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

- $\alpha$ -(imidazolidine-2-thion-1-yl-carbonylamino)-*p*-methylbenzylpenicillin,  
 $\alpha$ -(imidazolidine-2-thion-1-yl-carbonylamino)-*p*-chlorobenzylpenicillin,  
 $\alpha$ -(imidazolidine-2-thion-1-yl-carbonylamino)-*p*-methylthiobenzylpenicillin,  
 $\alpha$ -(imidazolidine-2-thion-1-yl-carbonylamino)- $\alpha$ -(2)thienylmethylpenicillin or  
 $\alpha$ -(imidazolidine-2-thion-1-yl-carbonylamino)- $\alpha$ -(3)thienylmethylpenicillin.

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Example 92

A. Sodium D- $\alpha$ -(imidazolidin-2-on-1-yl-carbonylamino)-benzylpenicillin.

5.5 parts by weight of D- $\alpha$ -(imidazolidin-2-on-1-yl-carbonylamino)-benzylpenicillin, which was obtained, moist with water, according to the instructions of Example 86, were dissolved in 13 parts by volume of dimethylacetamide whilst cooling with ice, and subsequently treated with 10 parts by volume of a 1 molar solution of sodium 2-ethylhexanoate in ether containing methanol. The resulting clear solution was added dropwise over the course of a few minutes to a mixture, cooled to  $-20^{\circ}\text{C}$ , of 200 parts by volume of ether and 20 parts by volume of methanol, whereupon the sodium salt of the penicillin separated out as a finely granular precipitate, which was filtered off and thoroughly washed with anhydrous ether.

Yield: 81% relative to 1-chlorocarbonyl-imidazolidin-2-one employed.

$\beta$ -Lactam content: 90% (determined on the basis of the intensity of the  $\beta$ -lactam carbonyl band of the IR spectrum).

IR bands at 3290, 1770, 1715, 1647, 1538 and 1276  $\text{cm}^{-1}$ .

(IR spectrum in Nujol).

B. Crystalline sodium D- $\alpha$ -(imidazolidin-2-on-1-yl-carbonylamino)-benzylpenicillin:

0.4 part by weight of the product from Example 92A was dissolved in 0.5 part by volume of water to give a clear solution. 1.3 parts by volume of ethanol were added and the mixture slowly diluted with 3.0 parts by volume of ethyl acetate, whilst shaking. 0.2 part by weight of sodium D- $\alpha$ -(imidazolidin-2-on-1-yl-carbonylamino)-

benzylpenicillin crystallised overnight from the initially clear solution, in the form of bundles of fine needles.

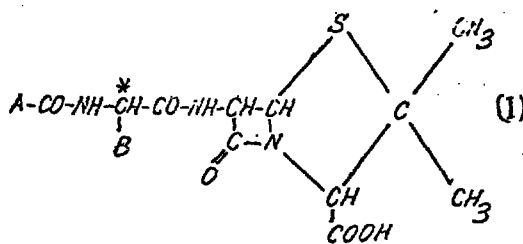
Decomposition range: 200—220°C.

IR bands at 3370, 3225, 1775, 1728, 1688, 1640 and 1275  $\text{cm}^{-1}$ .

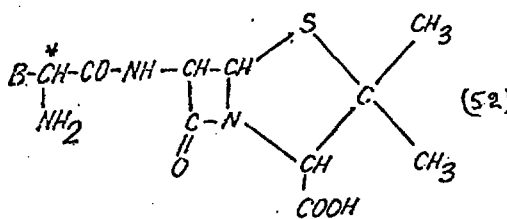
Figures 3, 4 and 5 show, for comparison purposes, the IR spectra of D- $\alpha$ -(imidazolidin-2-on-1-yl-carbonylamino)-benzylpenicillin as the free acid and as the amorphous and crystalline sodium salt.

# WHAT WE CLAIM IS:—

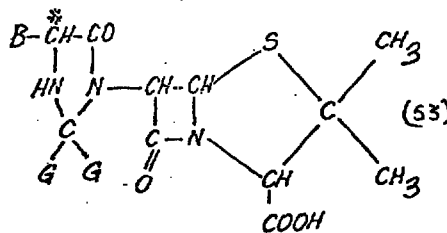
1. A process for the production of penicillins of the following general formula and their salts:—



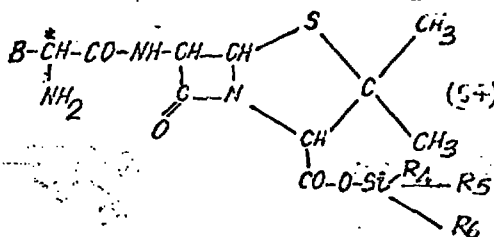
in which process a compound of the general formula:



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



or a compound of the general formula:—





\* C L M S \*

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47

benzylpenicillin crystallised overnight from the initially clear solution, in the form of bundles of fine needles.

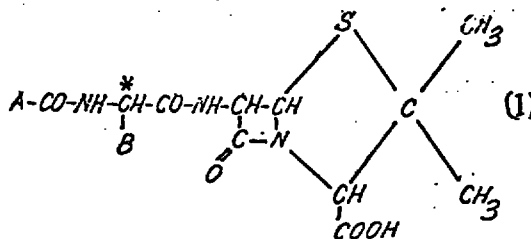
Decomposition range: 200—220°C.

IR bands at 3370, 3225, 1775, 1728, 1688, 1640 and 1275  $\text{cm}^{-1}$ .

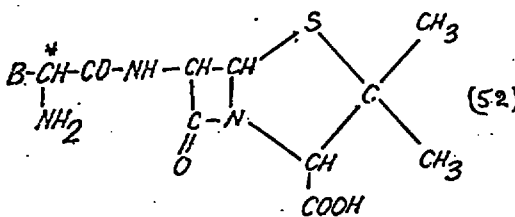
Figures 3, 4 and 5 show, for comparison purposes, the IR spectra of D- $\alpha$ -(imidazolidin-2-on-1-yl-carbonylamino)-benzylpenicillin as the free acid and as the amorphous and crystalline sodium salt.

WHAT WE CLAIM IS:—

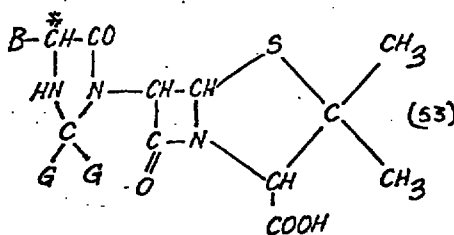
1. A process for the production of penicillins of the following general formula and their salts:—



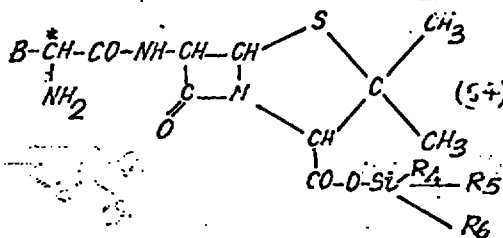
in which process a compound of the general formula:

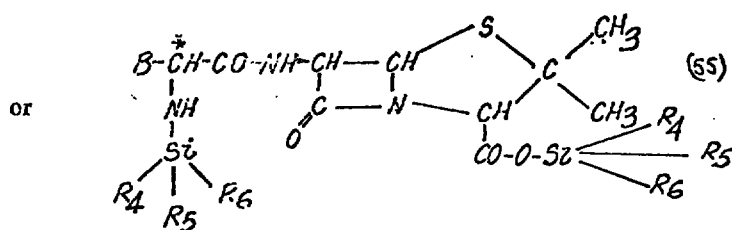


or a condensation product of such a compound with a carbonyl compound, the said condensation product being of the general formula:—

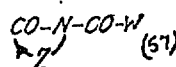
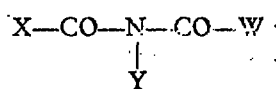


or a compound of the general formula:—

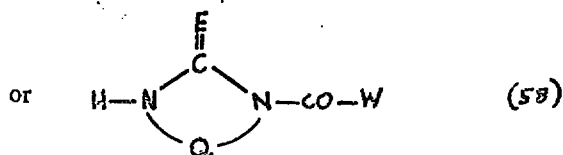




is reacted at a temperature of  $-20$  to  $50^\circ\text{C}$  with a compound of the general formula:—



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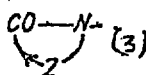
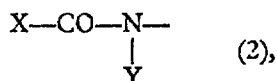
in a solvent and in the presence of a base when a compound of general formula (52) or (53) is used, and in an anhydrous solvent free of hydroxyl groups with or without the presence of a base when a compound of general formula (54) or (55) is used;

and, where necessary, the penicillin produced is converted to its desired salt or vice versa;

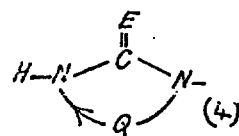
10

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[in which general formulae A denotes a group of the general formula:—



or



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

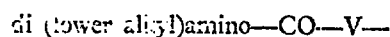
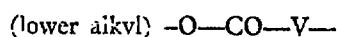
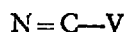
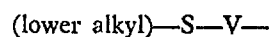
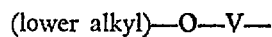
X denotes a hydrogen atom or an alkyl, alkenyl, cycloalkyl, or cycloalkenyl group with up to 10 carbon atoms, or a vinyl, arylvinyl, mono-, di-, or tri-halo-lower alkyl, mono-lower alkylamino, di-lower alkylamino, monoarylamino, or aryl-(lower alkyl)-amino group, or an alkoxy or aralkoxy group with up to 8 carbon atoms, or cycloalkoxy group with up to 7 carbon atoms, or an aryloxy group, or a group of the general formula:—

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(5);

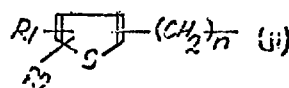
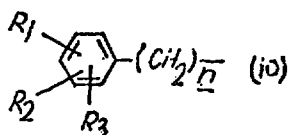
(6);

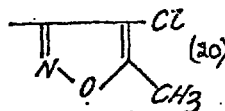
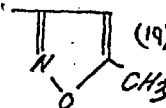
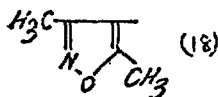
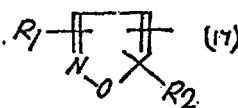
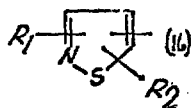
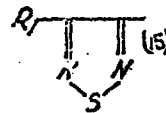
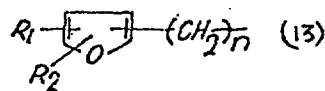
(7);

(8);

25

25





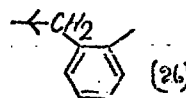
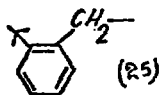
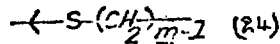
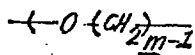
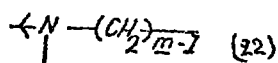
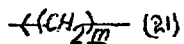
(in which general formulae (5) to (20):

V denotes a divalent organic radical with one to three carbon atoms;

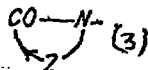
n is 0, 1 or 2; and

R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub>, which may be the same or different, are each a hydrogen, chlorine, bromine, iodine or fluorine atom or a nitro, nitrile, di-lower alkylamino, di-lower-alkylaminocarbonyl, lower alkanoylamino, lower alkoxy, lower alkanoyloxy, lower alkyl, lower alkoxy, sulphonyl, or trifluoromethyl group;

Y denotes an alkyl, alkenyl, cycloalkyl or cycloalkenyl group with up to 10 carbon atoms, or a vinyl, propenyl, mono-, di or tri-halo-lower alkyl, aryl or heterocyclic group, or an aralkyl group with up to 8 carbon atoms;

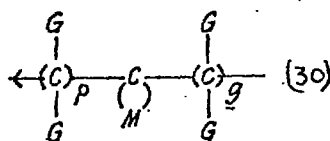
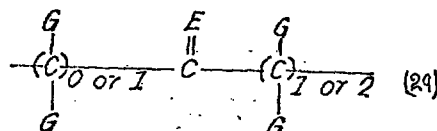
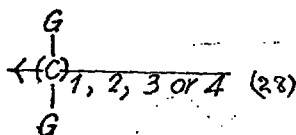


51:

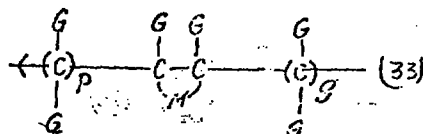
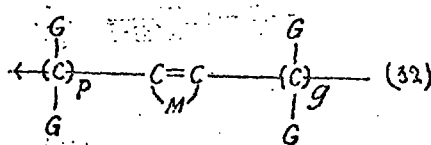
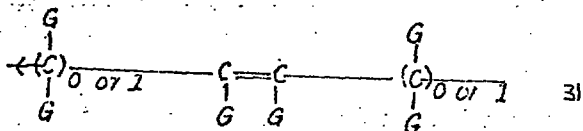


5

10



$p$  and  $g = 0, 1, 2$  or  $3$ ;  
 $p + g = 1, 2$  or  $3$ .



$p \text{ and } g = 0 \text{ or } 1;$   
 $p + g = 0 \text{ or } 1$

in v  
G is  
R<sub>1</sub> :  
the  
two  
as i  
M i

 $\{i\}$ 

in  
gr  
gr



\* C L M S \*

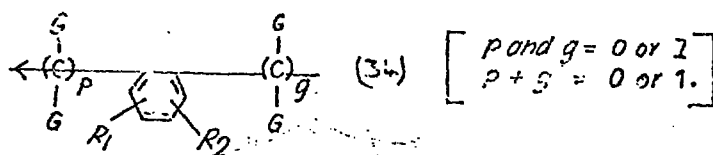
50

51

1,301,961

51

d the  
of the

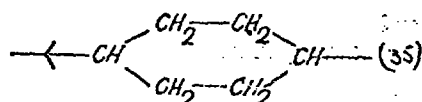


5

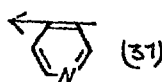
alkyl,

10

and



or



in which general formulae (28) to (34):

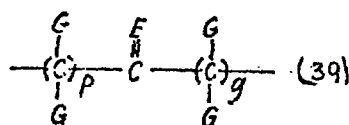
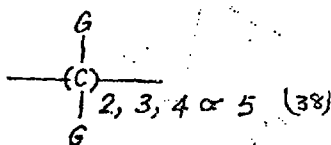
G is a hydrogen atom or a lower alkyl group;

R<sub>1</sub> and R<sub>2</sub> are as defined in claim 1;

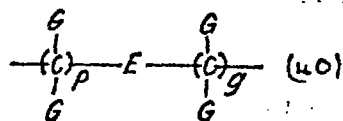
the arrow means that the linkage of the two free valencies of the group Q with the two nitrogen atoms of the group of general formula (4) is not arbitrary but is orientated as indicated by the arrow; and

M is a group of the general formula: —

15



or

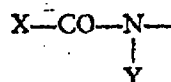


$$\left[ \begin{array}{l} p \text{ and } q = 0, 1 \text{ or } 2 \\ p + q = 2 \text{ or } 3 \end{array} \right];$$

[in which E and G are as defined above].

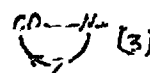
3. The process of claim 1 in which A denotes a group of the general formula: —

15



(2)

or



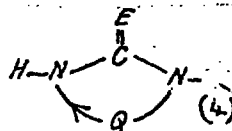
15

in which X, Y, and Z are as defined in claim 1 and B is a phenyl group, a thienyl group, or a phenyl group substituted by a lower alkyl, lower alkoxy, or lower alkylthio group or by a halogen atom.

(34)

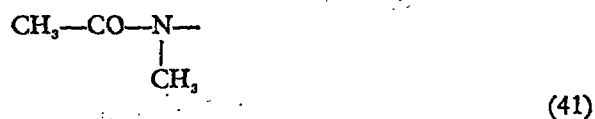


4. The process of claim 1 or 2 in which A denotes a group of the general formula:—

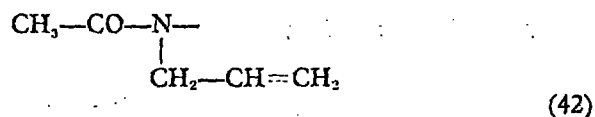


in which E and Q are as defined in claim 1 or 2.

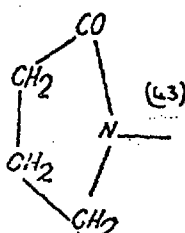
5. The process of claim 1 or 3 in which the group A is:



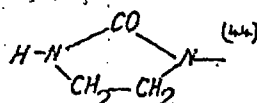
6. The process of claim 1 or 3 in which the group A is:



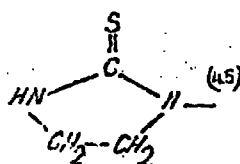
7. The process of claim 1 or 3 in which the group A is:



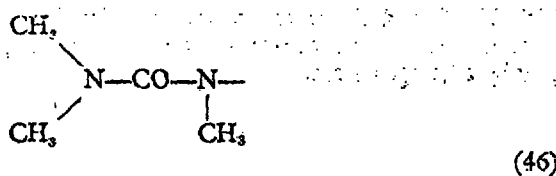
8. The process of claim 2 in which the group A is:



9. The process of claim 2 in which the group A is:

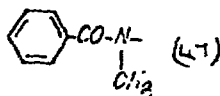


10. The process of claim 1 or 3 in which the group A is:

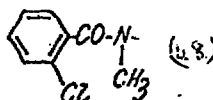




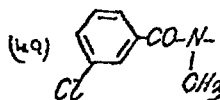
11. The process of claim 1 or 3 in which the group A is:



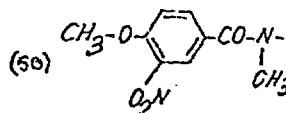
12. The process of claim 1 or 3 in which the group A is:



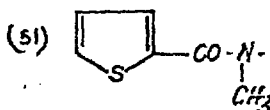
13. The process of claim 1 or 3 in which the group A is: —



14. The process of claim 1 or 3 in which the group A is:



15. The process of claim 1 or 3 in which the group A is: —



16. The process of any preceding claim in which B is a phenyl group.

17. The process of any preceding claim in which C\* is in the R-configuration.

18. The process of any preceding claim in which a compound of general formula (52) in the form of its condensation product with acetone is used, the said condensation product having the general formula (53) in which G is a methyl group.

19. The process of any preceding claim in which a compound of general formula (52) or (53) is used and the solvent is a mixture of water and a water-miscible organic solvent maintained at a pH of 6.5 to 8.0

20. The process of any preceding claim in which a compound of general formula (52) or (53) is used, and about 2 mol equivalents of base are present.

21. The process of any preceding claim in which a compound of general formula (52) or (53) is used and is present in an excess of 0.1 to 0.3 mol equivalents.

22. The process of any of claims 1 to 17 in which a compound of general formula (54) or (55) is used in the presence of a tertiary or secondary organic amine.

23. The process of claim 21 in which up to one mol equivalent of base is present.

24. The process of any of claims 17—20, 22 or 23 in which the compound of general formula (56), (57), or (58) is present in an excess of 0.1—1.0 molar equivalents.

25. The process of any preceding claim in which the reaction is carried out at a temperature of 0—20°C.

26. The process of any of claims 17 to 25 as dependent on claim 3 in which a compound of general formula (52), (54) or (55) is reacted with a compound of general