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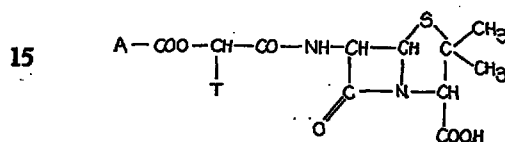


(54) 6-AMINOPENICILLANIC ACID DERIVATIVES AND A PROCESS FOR THE MANUFACTURE THEREOF

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESellschaft, a Swiss Company of 124-184 Grenzacherstrasse, Basle, Switzerland, 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 6-aminopenicillanic acid derivatives and a process for the manufacture thereof.

The 6-aminopenicillanic acid derivatives provided by the present invention are compounds of the general formula



(I)

wherein T represents a C₂₋₅ alkyl or alkenyl group or the cyclopropylmethyl, cyclobutylmethyl or cyclopentyl group and A represents a furyl, tetrahydrofuryl, pyrrolyl, pyrrolidinyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-thiadiazolyl, pyridyl, imidazolyl, pyrazolyl, 1-oxidopyridyl, tetrahydropyranyl, pyrimidinyl, pyrazinyl, benzofuranyl, indolyl, quinolyl or isoquinolyl group and wherein the groups A can be substituted by halogen, oxo, hydroxy, amino, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ alkoxy-carbonyl and/or C₁₋₃ alkanoylamino, and pharmaceutically utilisable salts thereof and hydrates of solid salts.

The preferred halogen substituents in formula I hereinbefore are fluorine, chlorine and bromine. The C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₃ alkoxy-carbonyl and C₁₋₃ alkanoylamino groups are those in which the alkyl portion contains 1-3 C-atoms. An alkyl or alkenyl group denoted by T can be straight-chain or

branched-chain. Examples of such groups are ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl, 3-methylbutyl and neopentyl, and vinyl, allyl, methallyl, butenyl and pentenyl.

Preferred 6-aminopenicillanic acid derivatives provided by the invention are those in which A represents a 3-pyridyl, 2-methyl-4-pyridyl, 3-isoxazolyl, 4-oxazolyl, 2-oxo-2-pyrrolidinyl, pyrazinyl, tetrahydro-2-furyl, 2-acetamido-4-thiazolyl, 1,5-dimethyl-3-pyrazolyl, tetrahydro-4-pyranyl, 1,2,3-thiadiazol-4-yl, 2-furyl or 4-pyridyl group.

Further preferred 6-aminopenicillanic acid derivatives provided by the invention are those in which T represents an alkyl or alkenyl group containing 4 or 5 C-atoms. Still further preferred 6-aminopenicillanic acid derivatives are those which are set out in the Table given hereinafter. Especially preferred is the compound of formula I in which A represents the 2-furyl group and T represents the 2-methylpropyl group, i.e. [1-(2-furoyloxy)-3-methylbutyl]-penicillin, especially the R-form, and pharmaceutically utilisable salts thereof.

As will be evident from the foregoing, the invention also includes the pharmaceutically utilisable salts of the compounds of formula I. For the preparation of such salts there can be used those bases which have hitherto been used for the preparation of pharmaceutically utilisable salts of other penicillins. Examples of pharmaceutically utilisable salts are alkali metal salts such as the sodium and potassium salt, the ammonium salt, alkaline earth metal salts such as the calcium salt, as well as salts with organic bases such as amines, for example N-ethylpiperidine, procaine, dibenzylamine, N,N'-dibenzyl ether-ethylenediamine or with mono-, di- or tri-alkylamines.

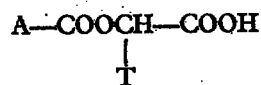
The salts of the compounds of formula I can also be hydrated. The hydration can be effected in the course of the manufacturing process or can occur gradually as a result of hygroscopic properties of an initially an-

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hydrous salt of a compound of formula I.

The compounds of formula I and their salts can exist as optically pure isomers and as diastereomeric mixtures.

- 5 According to the process provided by the present invention, the 6-aminopenicillanic acid derivatives aforesaid (that is to say, the compounds of formula I and pharmaceutically utilisable salts thereof and hydrates of said salts) are manufactured by reacting 6-aminopenicillanic acid, the carboxyl group of which is present in protected form, with an acid of the general formula



(II)

- 15 wherein A and T have the significance given earlier, or with an N-acylating functional derivative thereof, cleaving off the protecting group and if desired, converting the resulting product into a pharmaceutically utilisable salt.

20 The protection of the carboxyl group of 6-aminopenicillanic acid can be effected, for example, by conversion into a readily cleavable ester, for example the benzyl ester or a silyl ester (e.g. the trimethylsilyl ester) or by salt formation with an inorganic base or a tertiary organic base such as triethylamine.

25 Examples of N-acylating functional derivatives of acids of formula II include, for example, halides (that is to say, chlorides, bromides and fluorides), azides, anhydrides (particularly mixed anhydrides with strong acids), reactive esters (e.g. N-hydroxysuccinimide esters) and amides (e.g. imidazolides).

- 30 The reaction of 6-aminopenicillanic acid, the carboxyl group of which is present in protected form, with an acid of formula II or a N-acylating functional derivative thereof can be carried out according to methods which are usual in peptide chemistry. Thus, for example, an acid of formula II can be condensed with one of the aforementioned esters of 6-aminopenicillanic acid in the presence of a carbodiimide (e.g. dicyclohexylcarbodiimide) in an inert solvent (e.g. ethyl acetate, acetonitrile, dioxane, chloroform, methylene chloride, benzene or dimethylformamide) and the ester group can subsequently be cleaved off. An oxazolium salt (e.g. N-ethyl-5-phenylisoxazolium-3'-sulphonate) can be used as the condensation agent in place of a carbodiimide.

35 According to another embodiment of the present process, a salt of 6-aminopenicillanic acid (e.g. a trialkylammonium salt) can be reacted with an N-acylating functional derivative of an acid of formula II as mentioned earlier in an inert solvent (e.g. one of those mentioned earlier).

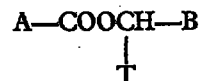
- 40 The reaction of 6-aminopenicillanic acid

the carboxyl group of which is present in protected form, with an acid of formula II or an N-acylating functional derivative thereof can conveniently be carried out at a temperature between about +5° C. and -40° C., for example, at about 0° C.

After completion of the reaction, the protecting group is cleaved off. Where the protecting group is the benzyl group (benzyl ester), this can be cleaved off by catalytic hydrogenation; for example, in the presence of a noble metal catalyst such as palladium-on-carbon. Where the protecting group is a silyl group (silyl ester), this can be cleaved off in a particularly ready manner by treating the reaction product with water. Where the carboxyl group of the 6-aminopenicillanic acid is protected by salt formation (e.g. with triethylamine), the cleaving off of this protecting group can be carried out by treatment with acid at a relatively lower temperature (e.g. at about 0° C. to about 10° C.). Examples of acids which can be used are hydrochloric acid, sulphuric acid, phosphoric acid or citric acid.

The acid starting materials of formula II can be used in the present process in optically pure form or in the form of racemates. It is preferred to use the R-enantiomers.

The acid starting materials of formula II, which are described and claimed in our co-pending Application No. 3848/73 (Serial No. 1,334,036), can be prepared by converting the group B in a compound of the general formula



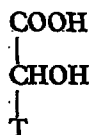
(III)

wherein A and T have the significance given earlier and B represents a protected carboxyl group, into the free carboxyl group.

The protected carboxyl group denoted by B in formula III can be a readily cleavable ester group, for example, the benzyl or the tert.butyl ester group. The conversion of the protected carboxyl group denoted by B into the free carboxyl group can be carried out by catalytic hydrogenation in the presence of a noble metal catalyst (e.g. palladium-on-carbon) in the case of the benzyl ester or by treatment with acid (e.g. with a mineral acid such as hydrochloric acid or with trifluoroacetic acid) in the case of the tert.butyl ester.

The subsequent conversion of a resulting acid of formula II into an N-acylating functional derivative thereof (e.g. a halide, azide, anhydride, ester or amide) can be carried out according to methods known per se.

The compounds of formula III can be obtained in a manner known per se by protecting the carboxyl group in a compound of the general formula



(IV)

wherein T has the significance given earlier, for example, by formation of the benzyl or the tert.butyl ester, and reacting the resulting product with a compound of the general formula



(V)

wherein A has the significance given earlier, for example, in the presence of benzene-sulphonyl chloride.

The 6-aminopenicillanic acid derivatives provided by the present invention possess antibiotic, especially bactericidal, activity. They possess a broad spectrum of activity against gram-positive and gram-negative micro-organisms. As advantageous properties there can, moreover, be mentioned their stability towards gastric acid. They can be used as therapeutics and disinfectants. Unit dosages of 200—1000 mg can be administered to adults. Oral administration of the present 6-aminopenicillanic acid derivatives is particularly preferred.

The antimicrobial activity of the 6-aminopenicillanic acid derivatives provided by the present invention can be seen from the following Table.

TABLE

Compounds from Example No.	Minimal inhibitory concentration [$\mu\text{g}/\text{ml}$]		Mouse CD_{50} [mg/kg] (oral)	
	Staphylococcus aureus FDA	Escherichia coli 1346	Staphylococcus aureus (Schoch)	Escherichia coli 1346
1	0.073	73	0.7	16
2	0.156	19	1.1	18
3	0.312	0.625	2.0	37
14	0.312	10	7.2	93
15	1.25	19	3.1	27
16	0.625	78	2.9	42
17	1.25	10	2.4	47
18	1.25	10	1.6	55
21	0.312	2.5	1.1	47
25	0.625	1.25	1.4	41
26	0.312	5	0.8	27
27	0.312	2.5	2.8	52
37	0.312	19	4.8	23

The minimal inhibitory concentration in vitro was determined in double dilution series in nutrient bouillon.

Pharmaceutical preparations can contain the 6-aminopenicillanic acid derivatives provided by the present invention in association with a compatible pharmaceutical carrier which may be an organic or inorganic inert carrier material suitable for enteral, especially oral, percutaneous or parenteral application. Ex-

amples of such carrier materials are water, gelatine, gum arabic, lactose, starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, petroleum jelly etc. The pharmaceutical preparations can be made up in solid form (e.g. as tablets, dragées, dry ampoules or capsules), in semi-solid form (e.g. as salves) or in liquid form (e.g. as solutions, suspensions or emulsions). They may be sterilized and/or may contain adjuvants such

as preserving, stabilising, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They can also contain other therapeutically valuable substances.

- 5 The following Examples illustrate the process provided by the invention:

EXAMPLE 1.

A mixture of 22.6 g of R-2-(2-furoyloxy)-isocaproic acid, 80 ml of absolute benzene and
10 36 ml of thionyl chloride is warmed for 2.5 hours, evaporated and dried. There are obtained 24.5 g of R- α -(2-furoyloxy)-isocaproic acid chloride. This is dissolved in 70 ml of methylene chloride and the solution is
15 added dropwise at 0° C. with stirring to a solution of 21.6 g of aminopenicillanic acid in a mixture of 150 ml of methylene chloride and 23 ml of triethylamine. The reaction mixture is kept for 20 hours at 0° C. and then
20 evaporated under reduced pressure at 20° C. The residue is dissolved in 150 ml of ice-water and extracted twice with 50 ml of ether each time. The aqueous phase is adjusted to pH 2 at 0° C. with 3-N sulphuric acid
25 and extracted three times with 80 ml of ethyl acetate each time. The ethyl acetate solutions are washed three times with 20 ml of ice-cold 5% sodium chloride solution each time, dried with magnesium sulphate and
30 evaporated under reduced pressure at 20° C. The residue is dissolved in 300 ml of absolute ether and the solution is filtered and treated with stirring with 50 ml of 2-M sodium-2-ethylcaproate solution in ethyl acetate. The [(R) - 1 - (2-furoyloxy) - 3-methylbutyl]penicillin sodium which is precipitated is filtered off by suction, washed
35 with absolute ether and low-boiling petroleum ether and, after drying, recrystallized from water/isopropanol to give a product of melting point 182°—183° C. (with decomposition); $[\alpha]_D^{25} = +221.5^\circ$ ($c = 2.0$ in water).

The (R) - 2 - (2-furoyloxy) - isocaproic acid which was used as the starting material
45 can be prepared in the manner described hereinafter:

55.5 g of benzyl - (R) - 2 - (2-furoyloxy)-isocaproate are hydrogenated in 400 ml of alcohol after the addition of 5 g of
50 palladium-on-charcoal (5%) until the theoretical amount of hydrogen has been taken up. The catalyst is filtered off by suction and the filtrate is evaporated under reduced pressure at 40° C. The oil is dissolved in 250
55 ml of 8% sodium bicarbonate solution and the solution which results is washed twice with 80 ml of ether each time. The bicarbonate solution is adjusted to pH 2 with concentrated hydrochloric acid and extracted
60 three times with 100 ml of ethyl acetate each time. The ethyl acetate solutions are washed twice with 50 ml of water each time, dried with magnesium sulphate and evaporated

under reduced pressure at 45° C. The residual oil is dried for 2 hours at 0.4 Torr
65 and 40° C. to give (R)-2-(2-furoyloxy)-isocaproic acid; $[\alpha]_D^{25} = +7.0^\circ$ ($c = 4.0$ in alcohol).

The benzyl - (R) - 2 - (2-furoyloxy)-isocaproate which was used can be prepared
70 in the manner described hereinafter:

264 g of (R)-2-hydroxy-isocaproic acid are dissolved in 1.8 litres of absolute dioxan in a three-necked flask which is fitted with a stirrer, a thermometer and a reflux condenser
75 with a calcium chloride tube. The solution is treated successively with 285 ml of triethylamine and 236 ml of benzyl chloride and heated at an internal temperature of 100° C. for 20 hours with stirring in an oil-bath. After cooling, the resulting triethylamine hydrochloride is filtered off and washed with
80 500 ml of ethyl acetate. The filtrate is evaporated under reduced pressure at 50° C. The residual oil is dissolved in 800 ml of ethyl acetate and washed twice with 150 ml of 3-N hydrochloric acid each time, twice with 100 ml of 5% sodium chloride solution each time, twice with 150 ml of
85 10% potassium bicarbonate solution each time and twice with 100 ml of 5% sodium chloride solution each time. After each of these washings, it is rinsed with 200 ml of ethyl acetate. The ethyl acetate solutions are dried over magnesium sulphate and evaporated under reduced pressure at 50° C. The
90 crude product which is thus obtained is distilled at 0.3 Torr (112°—115° C.). There is obtained benzyl - (R) - 2 - hydroxy - isocaproate; $[\alpha]_D^{25} = +18.0^\circ$ ($c = 1$ in methanol); $n_D^{25} = 1.498$.

27 ml of benzenesulphonyl chloride are added dropwise at 25° C. with stirring within
105 20 minutes to a solution of 23.6 g of furan-2-carboxylic acid in 100 ml of pyridine. The mixture is subsequently stirred for 30 minutes at 25° C. 44.4 g of benzyl-(R)-2-hydroxy-isocaproate are then added dropwise with stirring. The solution is either warmed to
110 60° C. for 2 hours or stirred at 25° C. for 20 hours.

The pyridine is distilled off under reduced pressure at 30°—50° C. The residue is dissolved in 600 ml of 3-N hydrochloric acid with the addition of ice and extracted twice
115 with 250 ml of ethyl acetate each time. The ethyl acetate solutions are washed once with 100 ml of 3-N hydrochloric acid, twice with 100 ml of water each time, twice with 100 ml of 5% sodium bicarbonate solution each time and twice with 100 ml of water each time and dried with magnesium sulphate. The ethyl acetate is distilled off under reduced pressure at 40° C. and the oil is dried for
120 60 minutes under reduced pressure at 60° C. There is obtained benzyl-(R)-2-furoyloxy-isocaproate; $[\alpha]_D^{25} = +9.0^\circ$ ($c = 4.0$ in alcohol).

EXAMPLE 2.

A mixture of 23.7 g of (R)-2-(isonicotinoyloxy)-isocaproic acid, 80 ml of absolute benzene and 36 ml of thionyl chloride is warmed for 2 hours, evaporated and evaporated three times under reduced pressure at 45° C. with 30 ml of absolute benzene each time and dried. There are obtained 25.6 g of (R) - 2 - (isonicotinoyloxy) - isocaproic acid chloride hydrochloride. This is dissolved in 80 ml of chloroform and added dropwise at 0° C. with stirring to a solution of 21.6 g of 6-aminopenicillanic acid in a mixture of 150 ml of chloroform and 42 ml of triethylamine. The reaction mixture is kept for 20 hours at 0° C. and then evaporated under reduced pressure at 20° C. The residue is dissolved in 200 ml of ice-water and extracted twice with 70 ml of ethyl acetate each time. The aqueous phase is adjusted to pH 2.5 at 0° C. with citric acid and extracted three times with 100 ml of ethyl acetate each time. The ethyl acetate solutions are washed three times with 30 ml of ice-cold 5% sodium chloride solution each time, dried with magnesium sulphate and evaporated under reduced pressure at 20° C. The residue is dissolved in 100 ml of ethyl acetate and the solution is treated with stirring with 50 ml of 2-M sodium-2-ethylcaproate solution in ethyl acetate and with 200 ml of absolute ether. The [(R) - 1 - (isonicotinoyloxy)-3-methylbutyl]penicillin sodium which is precipitated is filtered off by suction, washed with absolute ether and low-boiling petroleum ether and, after drying, recrystallized from water/isopropanol to give a product of melting point 197°—198° C. (with decomposition); $[\alpha]_D^{25} = +227^\circ$ (c=1.0 in water).

The (R) - 2 - (isonicotinoyloxy) - isocaproic acid [melting point 138°—139° C.; $[\alpha]_D^{25} = +22.3^\circ$ (c=3 in ethanol)] which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

EXAMPLE 3.

9.2 g of 6-aminopenicillanic acid are stirred at 0° C. for one hour in 100 ml of absolute chloroform with 12.0 ml of triethylamine. Meanwhile, a solution of 10.4 g of (R)-2-[(S)-pyroglutamoyloxy]-isocaproic acid and 6.0 ml of triethylamine in 100 ml of absolute chloroform at -10° C. is treated with 5.2 g of pivaloyl chloride and stirred for 20 minutes at -10° C. It is then cooled to -40° C., the above 6-aminopenicillanic acid solution is added and the mixture is subsequently kept for 16 hours at 0° C. It is then evaporated under reduced pressure at a bath temperature of 20° C., taken up in water and extracted twice with ethyl acetate. After washing the ethyl acetate with water and

saturated sodium chloride solution and drying it over sodium sulphate, it is concentrated in vacuum at a bath temperature of 20° C. to 80 ml and stirred into 800 ml of petroleum ether. After decantation, this procedure is repeated, chloroform being used in place of ethyl acetate. The decantation residue is taken up in 100 ml of acetone and treated with 20 ml of 2-M sodium-2-ethylcaproate in ethyl acetate, precipitated with petroleum ether and decanted. From methanol/isopropyl ether there crystallizes (R) - 3 - methyl - 1 - [(S)-pyroglutamoyloxybutyl]penicillin sodium of melting point 180° C. (with decomposition); $[\alpha]_D^{25} = +187.0^\circ$ (c=1.0 in water).

The (R) - 2 - [(S) - pyroglutamoyloxy]-isocaproic acid which was used as the starting material can be prepared in the manner described hereinafter:

14.2 g of (S)-pyroglutamic acid are suspended in 60 ml of dimethylformamide and brought into solution with 15.4 ml of triethylamine. There are then added at -60° C. with stirring within 20 minutes 52 ml of a 5.2 molar solution of phosgene in toluene and, after a further 5 minutes, with strong stirring, a solution of 22.2 g of benzyl-(R)-2-hydroxy-isocaproate in 80 ml of pyridine, which has been previously cooled to -40° to -50° C. It is then left for 16 hours at 2°—4° C. and evaporated under reduced pressure with a receiver cooled with dry-ice. The residue is taken up in ether and washed three times each with 1-N hydrochloric acid, water, 10% potassium bicarbonate and water, dried over sodium sulphate and evaporated under reduced pressure. The residue which contains benzyl - (R) - 2 - [(S) - pyroglutamoyloxy]-isocaproate is hydrogenated in glacial acetic acid/water (95.5) with 5% palladium-on-charcoal until no more hydrogen is taken up. It is then filtered off from the catalyst and evaporated under reduced pressure. After crystallization of the residue from ethyl acetate/petroleum ether, there are obtained 11 g of (R)-2-[(S)-pyroglutamoyloxy]-isocaproic acid of melting point 148°—150° C. (after transformation at 80° C.); $[\alpha]_D^{25} = +20.4^\circ$ (c=1.0 in methanol).

Example 4.

In a manner analogous to that described in Example 1, with (R)-2-(5-bromo-2-furoyloxy)-isocaproic acid there is obtained [(RS)-1-(5-bromo - 2 - furoyl)oxy] - 3 - methylbutyl]penicillin sodium of melting point 205°—206° C. (with decomposition); $[\alpha]_D^{25} = +189^\circ$ (c=1 in water).

The (R) - 2 - (5 - bromo - 2 - furoyloxy)-isocaproic acid which was used as the starting material can be prepared via its tert.butyl ester in a manner analogous to that described for the preparation of the starting material in Example 14.

Example 5.

In a manner analogous to that described in Example 1, with (R)-2-(2,6-dimethoxyisonicotinoyloxy)-isocaproic acid there is obtained [(R)-1-(2,6-dimethoxyisonicotinoyloxy)-3-methylbutyl]penicillin sodium melting point from 170° C. (with decomposition); $[\alpha]_D^{25} = +157^\circ$ ($c=2$ in water).

The compound [melting point 79°—81° C.; $[\alpha]_D^{25} = 12.2^\circ$ ($c=2$ in ether)] which was used as the starting material can be prepared via the corresponding benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 6.

In a manner analogous to that described in Example 1, with (R)-2-(5-methyl-2-furoyloxy)-isocaproic acid there is obtained [(R)-3-methyl-1-[(5-methyl-2-furoyl)oxy]butyl]-penicillin sodium of melting point 204° C. (with decomposition); $[\alpha]_D^{25} = +211.3^\circ$ ($c=1$ in water).

The (R)-2-(5-methyl-2-furoyloxy)-isocaproic acid which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 7.

In a manner analogous to that described in Example 1, with (R)-2-(2-benzofuroyl-oxy)-isocaproic acid there is obtained [(R)-1-[2-benzofuroyloxy]-3-methylbutyl]-penicillin sodium of melting point 197° C.; $[\alpha]_D^{25} = +183.3^\circ$ ($c=1$ in water).

The (R)-2-(2-benzofuroyloxy)-isocaproic acid used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 8.

In a manner analogous to that described in Example 1, with (R)-2-(3-methyl-5-isoxazolyl-carbonyloxy)-isocaproic acid there is obtained [(R)-1-[(3-methyl-5-isoxazolyl)-carbonyloxy]-3-methylbutyl]penicillin sodium of melting point 185° C. (with decomposition); $[\alpha]_D^{25} = +214.3^\circ$ ($c=2$ in water).

The (R)-2-(3-methyl-5-isoxazolyl-carbonyloxy)-isocaproic acid [melting point 59°—62° C.; $[\alpha]_D^{25} = +13^\circ$ ($c=2$ in ethanol)] which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 9.

In a manner analogous to that described in Example 1, with (RS)-2-(3-furoyloxy)-iso-

caproic acid there is obtained [(RS)-1-(3-furoyloxy)-3-methylbutyl]penicillin sodium of melting point 208° C. (with decomposition); $[\alpha]_D^{25} = +210.6^\circ$ ($c=0.5$ in water).

The (RS)-2-(3-furoyloxy)-isocaproic acid [melting point 85°—87° C.] which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 10.

In a manner analogous to that described in Example 1, with (S)-2-(2-furoyloxy)-isocaproic acid there is obtained [(S)-1-(2-furoyloxy)-3-methylbutyl]penicillin sodium of melting point from 150° C. (with decomposition); $[\alpha]_D^{25} = +216^\circ$ ($c=2$ in water).

The (S)-2-(2-furoyloxy)-isocaproic acid [$[\alpha]_D^{25} = -7^\circ$ ($c=4$ in ethanol)] which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 11.

In a manner analogous to that described in Example 1, with (R)-2-[(1,2,3,6-tetrahydro-2,6-dioxo-4-pyrimidinyl)-carbonyloxy]-isocaproic acid there is obtained [(R)-3-methyl-1-[(1,2,3,6-tetrahydro-2,6-dioxo-4-pyrimidinyl)carbonyloxy]butyl]penicillin sodium of melting point from 220° C. (with decomposition); $[\alpha]_D^{25} = +162.5^\circ$ ($c=1$ in water).

The (R)-2-[(1,2,3,6-tetrahydro-2,6-dioxo-4-pyrimidinyl)carbonyloxy]-isocaproic acid [melting point 94°—96° C.; $[\alpha]_D^{25} = +15.5^\circ$ ($c=2$ in methanol)] which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 12.

In a manner analogous to that described in Example 1, with (R)-2-(1-methyl-4-imidazolylcarbonyloxy)-isocaproic acid there is obtained [(R)-3-methyl-1-[(1-methylimidazol-4-yl)carbonyloxy]butyl]penicillin sodium of melting point 150° C. (with decomposition); $[\alpha]_D^{25} = +182.8^\circ$ ($c=1$ in ethanol).

The (R)-2-(1-methyl-4-imidazolylcarbonyloxy)-isocaproic acid which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 13.

In a manner analogous to that described in Example 1, with (R)-2-(4-isquinolylcarbonyloxy)-isocaproic acid there is

obtained [(R) - 1 - [(4 - isoquinolylcarbonyl)oxy] - 3 - methylbutyl]penicillin sodium of melting point 136° C.; $[\alpha]_D^{25} = +192.7^\circ$ (c=1 in ethanol).

- 5 The (R) - 2 - (4 - isoquinolylcarbonyloxy) - isocaproic acid which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material
- 10 in Example 1.

Example 14.

In a manner analogous to that described in Example 1, with (R) - 2 - (1,2,3-thiadiazol - 4 - yl - carbonyloxy) - isocaproic acid there is obtained [(R) - 3 - methyl - 1 - [(1,2,3 - thiadiazol - 4 - ylcarbonyl)oxy] - butyl]penicillin sodium of melting point 210° C. (with decomposition); $[\alpha]_D^{25} = +240.2^\circ$ (c=1 in water).

- 20 The (R) - 2 - (1,2,3 - thiadiazol - 4 - yl - carbonyloxy) - isocaproic acid which was used as the starting material can be prepared in the manner described hereinafter:

13.0 g of 1,2,3-thiadiazol-4-carboxylic acid are suspended in 100 ml of pyridine and treated dropwise at 25°—35° C. within 20 minutes with 12.8 ml of benzenesulphonyl chloride. The mixture is stirred at room temperature for a further half an hour and a clear solution results. 17.9 g of tert.butyl-(R)- α -hydroxyisovalerate are subsequently added within 20 minutes with further stirring, the temperature rising to ca 40° C. After stirring for two hours at 60° C., the mixture is evaporated under reduced pressure, suspended in 200 ml of ethyl acetate and filtered off. The precipitate is washed twice with ethyl acetate and the combined filtrates are washed three times rapidly with ice-cold dilute hydrochloric acid, once with ice-water and three times with 10% potassium bicarbonate solution, dried over sodium sulphate and evaporated under reduced pressure. The residue which contains tert.butyl-(R)-2-(1,2,3 - thiadiazol - 4 - yl - carbonyloxy) - isocaproate is irrigated with 100 ml of trifluoroacetic acid and evaporated after half an hour under reduced pressure, taken up in ether and exhaustively extracted with 10% potassium bicarbonate. The combined bicarbonate extracts are acidified to Congo red and extracted three times with ethyl acetate. After washing, drying and evaporation of the solvent, there remain 19 g of a crystallizing oil. Recrystallization from isopropanol yields 12 g of (R) - 2 - (1,2,3 - thiadiazol - 4 - yl - carbonyloxy) - isocaproic acid of melting point 104°—105° C.; $[\alpha]_D^{25} = +20.0^\circ$ (c=1 in methanol).

- 60 Example 15.

In a manner analogous to that described in Example 1, with (R) - 2 - (tetrahydropyran - 4 - ylcarbonyloxy) - isocaproic

acid there is obtained [(R) - 3 - methyl - 1 - {[(tetrahydropyran - 4 - yl)carbonyl] - oxy}butyl]penicillin sodium of melting point 183° C. (with decomposition); $[\alpha]_D^{25} = +218.5^\circ$ (c=1 in water).

The (R) - 2 - (tetrahydropyran - 4 - ylcarbonyloxy) - isocaproic acid which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 22.

Example 16.

In a manner analogous to that described in Example 1, with (R) - 2 - (1,5-dimethyl - 3 - pyrazolylcarbonyloxy) - isocaproic acid there is obtained [(R) - 1 - {[(1,5 - dimethylpyrazol - 3 - yl)carbonyl] - oxy} - 3 - methylbutyl]penicillin sodium of melting point 205° C. (with decomposition); $[\alpha]_D^{25} = +196.7^\circ$ (c=1 in water).

The compound which was used as the starting material can be prepared in the manner described hereinafter:

19.2 g of 1,5-dimethylpyrazole-3-carboxylic acid are heated at reflux for 20 minutes with 80 ml of thionyl chloride and subsequently freed under reduced pressure from excess thionyl chloride. The mixture is evaporated a further twice under reduced pressure with toluene, then taken up in 100 ml of toluene and added dropwise at 0° C. with stirring to 22.4 g of tert.butyl-(R)- α -hydroxyisocaproate in 80 ml of pyridine. After stirring for two hours at room temperature, the mixture is evaporated under reduced pressure, taken up in ether and washed three times each with water and 10% potassium bicarbonate. After drying and evaporating off the solvent, there remains 25.5 g of a residue of melting point 69°—71° C. which crystallizes under petroleum ether. This residue which contains tert.butyl - (R) - 2 - (1,4 - dimethylpyrazol - 3 - ylcarbonyloxy) - isocaproate is left to stand at room temperature for 30 minutes with 50 ml of trichloroacetic acid and, after evaporation in vacuum, is dissolved in ether and exhaustively extracted with 10% potassium bicarbonate. After acidification of the bicarbonate extracts to Congo red, it is extracted with ether and the ether is evaporated under reduced pressure after washing and drying. The residue which remains is recrystallized from ethyl acetate to yield 16 g of (R) - 2 - (1,5 - dimethylpyrazol - 3 - ylcarbonyloxy) - isocaproic acid of melting point 155°—161° C.; $[\alpha]_D^{25} = +13.1^\circ$ (c=1.0 in methanol).

Example 17.

In a manner analogous to that described in Example 3, with (R) - 2 - (2 - acetamido - 4 - thiazolylcarbonyloxy) - isocaproic acid there is obtained [(R) - 1 - {[(2 - acetamido - 4 - thiazolyl)carbonyl]oxy} - 3 -

methylbutyl]penicillin sodium of melting point 220° C. (with decomposition); $[\alpha]_D^{25} = +151.5^\circ$ ($c=1$ in water).

The compound which was used as the starting material can be prepared in the manner described hereinafter:

A suspension of 14.4 g of 2-acetamido-4-thiazolecarboxylic acid in 200 ml of dimethylformamide is brought into solution with 11.9 ml of triethylamine. It is treated slowly at -60° C. with strong stirring with 38.1 ml of a 2.86 molar solution of phosgene in toluene and then a solution of 14.6 g of tert.butyl-(R)-2-hydroxyisocaproate in 50 ml of pyridine which has been previously cooled to ca -50° C., is added in one portion. After the mixture has reached room temperature, it is evaporated under reduced pressure and the residue is taken up in ether and washed three times each with water and 10% potassium bicarbonate solution, dried and once more evaporated under reduced pressure. There remain 26 g of a crystalline mass which contains tert.butyl - (R) - 2 - (2 - acetamido-4 - thiazolecarbonyloxy) - isocaproate. This mass is allowed to stand for 30 minutes at room temperature with 100 ml of trifluoroacetic acid. After removal of the solvent under reduced pressure, the residue is taken up in ether and exhaustively extracted with 10% potassium bicarbonate solution. After acidification of the aqueous solution to pH 3, it is extracted three times with ethyl acetate and the extract, after washing with water and drying over sodium sulphate, is evaporated under reduced pressure. The (R) - 2 - (2 - acetamido - 4 - thiazolecarbonyloxy) - isocaproic acid remains as a non-crystallizing resin.

Example 18.

In a manner analogous to that described in Example 1, with (R) - 2 - [(RS)-tetrahydro - 2 - furoyloxy] - isocaproic acid there is obtained [(R) - 3 - methyl - 1 - [(RS) - tetrahydro - 2 - furoyloxy]butyl]penicillin sodium of melting point 170°—185° C. (with decomposition); $[\alpha]_D^{25} = +200^\circ$ ($c=1$ in water).

The (R) - 2 - [(RS) - tetrahydro - 2 - furoyloxy] - isocaproic acid $[\alpha]_D^{25} = -7^\circ$ ($c=4$ in ethanol) which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 19.

In a manner analogous to that described in Example 1, with (RS)-2-(2-furoyloxy)-valeric acid there is obtained (RS)-1-(2-furoyloxy)-butyl penicillin sodium of melting point 165°—170° C. (with decomposition); $[\alpha]_D^{25} = +209^\circ$ ($c=1$ in water).

The (RS) - 2 - (2 - furoyloxy) - valeric

acid [melting point 53°—56° C.] which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 35.

Example 20.

In a manner analogous to that described in Example 1, with (RS) - 2 - (1,6 - dihydro - 6 - oxonicotinoyloxy) - isocaproic acid there is obtained [(RS) - 1 - [(1,6-dihydro - 6 - oxonicotinoyloxy) - 3 - methylbutyl]penicillin sodium of melting point 200° C. (with decomposition); $[\alpha]_D^{25} = +191^\circ$ ($c=1$ in water).

The (RS) - 2 - (1,6 - dihydro - 6 - oxonicotinoyloxy) - isocaproic acid [melting point 167°—170° C.] which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 35.

Example 21.

In a manner analogous to that described in Example 3, with (R) - 2 - (pyrazinylcarbonyloxy) - isocaproic acid there is obtained [(R) - 3 - methyl - 1 - [(pyrazinylcarbonyloxy)butyl]penicillin potassium of melting point 150° C. (with decomposition); $[\alpha]_D^{25} = +186.5^\circ$ ($c=1$ in water).

The (R) - 2 - (pyrazinylcarbonyloxy) - isocaproic acid which was used as the starting material can be prepared via its tert.butyl ester in a manner analogous to that described for the preparation of the starting material in Example 17.

Example 22.

In a manner analogous to that described in Example 1, with (R) - 2 - (nicotinoyloxy) - isocaproic acid N-oxide there is obtained [(R) - 3 - methyl - 1 - [(1 - oxidonicotinoyloxy)butyl]penicillin sodium of melting point 175° C. (with decomposition); $[\alpha]_D^{25} = +168.3^\circ$ ($c=1$ in water).

The (R) - 2 - (nicotinoyloxy) - isocaproic acid N-oxide which was used as the starting material can be prepared in the manner described hereinafter:

17.8 g of nicotinoyl chloride hydrochloride are dissolved in 150 ml of pyridine and 50 ml of dimethylformamide and the solution is treated slowly with stirring at maximally 15° C. with 22.2 g of benzyl-(R)- α -hydroxyisovalerate (prepared from (R)-2-hydroxyisovaleric acid and benzyl chloride in a manner analogous to that described for the preparation of the corresponding compound in Example 1). After stirring for two hours at room temperature, the mixture is evaporated under reduced pressure. The residue is taken up in ether, washed three times with water and extracted six times with ice-cold 3-N hydrochloric acid. The hydrochloride phases

are immediately allowed to run into saturated sodium bicarbonate solution and the base which is thus released is extracted three times with ether. After washing and drying, it is evaporated under reduced pressure and there are obtained 27 g of a resin which contains benzyl - (R) - 2 - (nicotinoyloxy) - isocaproate. This is hydrogenated in 200 ml of ethanol with 2 g of 5% palladium-on-charcoal until 2 equivalents of hydrogen have been taken up. After filtration and evaporation, the residue is taken up in 10% potassium bicarbonate, washed twice with ether and adjusted to pH 3 with citric acid. After extraction with ether, washing, drying and evaporation of the extract, there is obtained a crystallizing oil. Recrystallization from ethyl acetate/petroleum ether yields 14 g of (R) - 2 - (nicotinoyloxy) - isocaproic acid of melting point 101°—103° C.; $[\alpha]_D^{25} = +18.8^\circ$ (c=1.0 in methanol).

The N-oxide is obtained from 26.4 g of the acid in 70 ml of glacial acetic acid by treating it for three hours at 70°—80° C. with 11 ml of 30% hydrogen peroxide. After the addition of a further 8 ml of 30% hydrogen peroxide, the mixture is left overnight at the same temperature. It is then cautiously evaporated under reduced pressure and evaporated off twice with 50 ml of water each time, care being taken to ensure that the mixture is never evaporated to dryness. The residue is taken up in chloroform, washed four times with water, dried and evaporated under reduced pressure. Recrystallization from ethyl acetate yields 19 g of (R) - 2 - nicotinoyloxy-isocaproic acid N-oxide of melting point 132°—134° C.; $[\alpha]_D^{25} = +20.8^\circ$ (c=1.0 in methanol).

Example 23.

In a manner analogous to that described in Example 3, with (R) - 2 - (4 - chloropicolinoyloxy) - isocaproic acid there is obtained [(R) - 1 - [(4 - chloropicolinoyl) - oxy] - 3 - methylbutyl]penicillin sodium of melting point 140° C. (with decomposition); $[\alpha]_D^{25} = +146.7^\circ$ (c=1 in water).

The (R) - 2 - (4 - chloropicolinoyloxy) - isocaproic acid (melting point 120°—122° C.) which was used as the starting material can be prepared via its tert.butyl ester in a manner analogous to that described for the preparation of the starting material in Example 17.

Example 24.

In a manner analogous to that described in Example 1, with (R) - 2 - (2,6 - dichloroisonicotinoyloxy) - isocaproic acid there is obtained [(R) - 1 - [(2,6 - dichloroisonicotinoyl)oxy] - 3 - methylbutyl]penicillin sodium of melting point from 162° C. (with decomposition); $[\alpha]_D^{25} = +164.6^\circ$ (c=2 in water).

The (R) - 2 - (2,6 - dichloroisonicotinoyloxy) - isocaproic acid [melting point 79°—81° C. (with decomposition)] which was used as the starting material can be prepared via its tert.butyl ester in a manner analogous to that described for the preparation of the starting material in Example 16.

Example 25.

In a manner analogous to that described in Example 1, with (R) - 2 - (4 - oxazolyrcarbonyloxy) - isocaproic acid there is obtained [(R) - 1 - [(4 - oxazolyrcarbonyl)oxy] - 3 - methylbutyl]penicillin sodium of melting point 173° C. (with decomposition); $[\alpha]_D^{25} = +150.8^\circ$ (c=1 in ethanol).

The (R) - 2 - (4 - oxazolyrcarbonyloxy) - isocaproic acid which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 26.

In a manner analogous to that described in Example 1, with (R) - 2 - (2 - methylisonicotinoyloxy) - isocaproic acid there is obtained [(R) - 3 - methyl - 1 - [(2 - methylisonicotinoyl)oxy]butyl]penicillin sodium of melting point 195°—200° C. (with decomposition); $[\alpha]_D^{25} = +188^\circ$ (c=1 in water).

The (R) - 2 - (2 - methylisonicotinoyloxy) - isocaproic acid which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 22.

Example 27.

In a manner analogous to that described in Example 1, with (R) - 2 - (3 - isoxazolyrcarbonyloxy) - isocaproic acid there is obtained [(R) - 1 - [(3 - isoxazolyrcarbonyl)oxy] - 3 - methylbutyl]penicillin sodium of melting point 188° C. (with decomposition); $[\alpha]_D^{25} = +209.6^\circ$ (c=1 in ethanol).

The (R) - 2 - (3 - isoxazolyrcarbonyloxy) - isocaproic acid which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 28.

In a manner analogous to that described in Example 1, with (R) - 2 - (3 - indolyrcarbonyloxy) - isocaproic acid there is obtained [(R) - 1 - [(3 - indolyrcarbonyl)oxy] - 3 - methylbutyl]penicillin sodium of melting point 175° C. (with decomposition); $[\alpha]_D^{25} = +131.2^\circ$ (c=1 in ethanol).

The (R) - 2 - (3 - indolyrcarbonyloxy) - isocaproic acid which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described

for the preparation of the starting material in Example 1.

Example 29.

In a manner analogous to that described in Example 2, with (S) - 2 - (isonicotinoyloxy)-isocaproic acid chloride hydrochloride there is obtained [(S) - 1 - (isonicotinoyloxy) - 3 - methylbutyl]penicillin sodium of melting point 177° C. (with decomposition); $[\alpha]_D^{25} = +225^\circ$ (c=2 in water).

The compound which was used as the starting material can be prepared by treating (S) - 2 - (isonicotinoyloxy) - isocaproic acid with thionyl chloride. The (S) - 2 - (isonicotinoyloxy)-isocaproic acid [melting point 138°—139° C.; $[\alpha]_D^{25} = +22.3^\circ$ (c=2 in ethanol)] can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 30.

In a manner analogous to that described in Example 2, with (RS) - 2 - (2,6 - dimethylisonicotinoyloxy) - isocaproic acid chloride hydrochloride there is obtained [(RS) - 1 - [(2,6 - dimethylisonicotinoyloxy) - 3 - methylbutyl]penicillin sodium; $[\alpha]_D^{25} = +159^\circ$ (c=2 in water).

The compound which was used as the starting material can be prepared by treating (RS) - 2 - (2,6 - dimethylisonicotinoyloxy)-isocaproic acid with thionyl chloride. The (RS) - 2 - (2,6 - dimethylisonicotinoyloxy)-isocaproic acid (melting point 95°—96° C.) can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 35.

Example 31.

In a manner analogous to that described in Example 1, with (R) - 2 - (cinchoninoyloxy)-isocaproic acid there is obtained [(R) - 1 - (cinchoninoyloxy) - 3 - methylbutyl]penicillin sodium of melting point 143° C. (with decomposition); $[\alpha]_D^{25} = +208.7^\circ$ (c=1 in ethanol).

The (R) - 2 - (cinchoninoyloxy) - isocaproic acid which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 32.

In a manner analogous to that described in Example 1, with (R) - 2 - (7 - chlorocinchoninoyloxy) - isocaproic acid there is obtained [(R) - 1 - [(7 - chlorocinchoninoyloxy) - 3 - methylbutyl]penicillin sodium of melting point 135° C. (with decomposition); $[\alpha]_D^{25} = +196.4^\circ$ (c=1 in ethanol).

The (R) - 2 - (7 - chlorocinchoninoyloxy)-isocaproic acid which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 33.

In a manner analogous to that described in Example 1, with (R) - 2 - (2 - chloronicotinoyloxy) - isocaproic acid there is obtained [(R) - 1 - [(2 - chloronicotinoyloxy) - 3 - methylbutyl]penicillin potassium of melting point 120° C. (with decomposition); $[\alpha]_D^{25} = +167.3^\circ$ (c=1 in water).

The (R) - 2 - (2 - chloronicotinoyloxy)-isocaproic acid [melting point 64°—67° C.; $[\alpha]_D^{25} = +17.5^\circ$ (c=1 in methanol)] which was used as the starting material can be prepared via tert.butyl ester in a manner analogous to that described for the preparation of the starting material in Example 16.

Example 34.

In a manner analogous to that described in Example 1, with (R)-2-(quinaldoyloxy)-isocaproic acid there is obtained [(R)-3-methyl - 1 - (quinaldoyloxy) - butyl]penicillin sodium of melting point 170° C. (with decomposition); $[\alpha]_D^{25} = +119.3^\circ$ (c=1 in ethanol).

The (R) - 2 - (quinaldoyloxy) - isocaproic acid which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 22.

Example 35.

In a manner analogous to that described in Example 1, with (RS) - 2 - (isonicotinoyloxy) - isocaproic acid there is obtained [(RS) - 1 - (isonicotinoyloxy) - 3 - methylbutyl]penicillin sodium; $[\alpha]_D^{25} = +197.5^\circ$ (c=2 in water).

The compound which was used as the starting material can be prepared in the manner described hereinafter:

29.5 g of benzyl-(RS)- α -bromo-isocaproate are added dropwise at 60° C. with stirring within 15 minutes to a solution of 12.8 g of isonicotinic acid in a mixture of 60 ml of dimethylformamide and 14.8 ml of triethylamine. The reaction mixture is stirred for 5 hours at 90° C. The triethylamine hydrobromide is filtered off by suction and the filtrate is evaporated under reduced pressure at 60° C. The residue is dissolved in 100 ml of ethyl acetate and filtered and the filtrate is washed three times with 15 ml of 1-N potassium bicarbonate solution each time and twice with 20 ml of water each time. The ethyl acetate solution is dried with magnesium sulphate and evaporated under reduced pressure at 45° C. The benzyl-(RS)-

2 - (isonicotinoyloxy) - isocaproate is obtained as an oil.

For purification, this ester is dissolved in 10 ml of ethyl acetate and the solution which results is mixed with a solution of 19 g of p-toluenesulphonic acid in 35 ml of ethyl acetate and crystallized for 2 hours at 0° C. The benzyl - (RS) - 2 - (isonicotinoyloxy) - isocaproate p - toluenesulphonate is filtered off by suction, washed with 100 ml of ether and dried under reduced pressure at 60° C. to give a compound of melting point 136° C. The p-toluenesulphonate is dissolved in 30 ml of water and the solution is adjusted to pH 9 with potassium carbonate and extracted twice with 50 ml of ethyl acetate each time. The ethyl acetate solution is washed twice with 10 ml of water each time, dried with magnesium sulphate and evaporated under reduced pressure at 40° C. Crystallization of the resulting oil from low-boiling petroleum ether gives benzyl - (RS) - 2 - isonicotinoyloxy - isocaproate of melting point 49°—50° C.

8.2 g of benzyl - (RS) - 2 - (isonicotinoyloxy) - isocaproate are hydrogenated in 50 ml of alcohol after the addition of 800 mg of palladium-on-charcoal (5%) until the theoretical amount of hydrogen has been taken up. The catalyst is then filtered off and the filtrate is evaporated under reduced pressure at 45° C. The oil is dissolved in excess sodium bicarbonate solution and extracted twice with 20 ml of ether each time and the bicarbonate solution is adjusted to pH 2.5 with 3-N hydrochloric acid. The acidic solution is extracted twice with 70 ml of ethyl acetate each time. After being washed twice with 20 ml of 5% sodium chloride solution each time, the ethyl acetate solution is dried with magnesium sulphate and evaporated under reduced pressure at 45° C. The resulting oil is crystallized from ether/petroleum ether to give (RS) - 2 - (isonicotinoyloxy) - isocaproic acid of melting point 98°—100° C.

Example 36.

In a manner analogous to that described in Example 2, with (RS)-2-(isonicotinoyloxy)-valeric acid there is obtained [(RS)-1-(isonicotinoyloxy) - butyl]penicillin sodium; $[\alpha]_D^{25} = +222^\circ$ (c=2 in water).

The (RS) - 2 - (isonicotinoyloxy) - valeric acid (melting point 152°-153° C.) which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 35.

Example 37.

In a manner analogous to that described in Example 1, with (R) - 2 - (nicotinoyloxy) - isocaproic acid there is obtained [(R)-1 - (nicotinoyloxy) - 3 - methylbutyl]penicillin potassium of melting point 195° C. (with

decomposition); $[\alpha]_D^{25} = +210.4^\circ$ (c=1 in water).

The (R) - 2 - (nicotinoyloxy) - isocaproic acid which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 22.

Example 38.

In a manner analogous to that described in Example 1, with (R) - 2 - (2 - thenoyloxy) - isocaproic acid there is obtained [(R) - 3 - methyl - 1 - (2 - thenoyloxy)butyl]penicillin sodium; $[\alpha]_D^{25} = +103^\circ$ (c=1 in water).

The (R) - 2 - (2 - thenoyloxy) - isocaproic acid $[\alpha]_D^{25} = +13.7^\circ$ (c=2 in ethanol) which was used as the starting material can be prepared via its tert-butyl ester in a manner analogous to that described for the preparation of the starting material in Example 16.

Example 39.

In a manner analogous to that described in Example 3, with 2 - (2 - pyrrolylcarbonyloxy) - isocaproic acid there is obtained [3 - methyl - 1 - [(pyrrol - 2 - ylcarbonyl)oxy]butyl]penicillin sodium as a diastereomeric mixture of melting point 208° C. (with decomposition); $[\alpha]_D^{25} = +187.5^\circ$ (c=1 in ethanol).

The 2 - (2 - pyrrolylcarbonyloxy) - isocaproic acid which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 35.

Example 40.

In a manner analogous to that described in Example 1, with (R) - 2 - (1 - oxido-isonicotinoyloxy) - isocaproic acid there is obtained [3 - methyl - 1 - [(1 - oxido-isonicotinoyl)oxy]butyl]penicillin sodium of melting point 195° C. (with decomposition); $[\alpha]_D^{25} = +187^\circ$ (c=2 in water).

The (R) - 2 - (1 - oxido - isonicotinoyloxy) - isocaproic acid [melting point 168°—169° C.; $[\alpha]_D^{25} = +4.2^\circ$ (c=2 in ethanol)] which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 22.

Example 41.

In a manner analogous to that described in Example 3, with (R) - 2 - (2,4 - dimethyl - 5 - pyrimidinylcarbonyloxy) - isocaproic acid there is obtained [(R) - 1 - [(2,4 - dimethyl - 5 - pyrimidinylcarbonyl)oxy] - 3 - methylbutyl]penicillin sodium of melting point 185° C. (with decomposition); $[\alpha]_D^{25} = +225^\circ$ (c=1 in water).

The (R) - 2 - (2,4 - dimethyl - 5 - pyrimidinylcarbonyloxy) - isocaproic acid, an

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oily substance, which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 42.

In a manner analogous to that described in Example 3, with (R) - 2 - (5 - pyrimidinylcarbonyloxy) - isocaproic acid there is obtained [(R) - 1 - [(5 - pyrimidinylcarbonyl)oxy] - 3 - methylbutyl]penicillin sodium of melting point 205° C. (with decomposition); $[\alpha]_D^{25} = +237^\circ$ (c=1 in ethanol).

The (R) - 2 - (5 - pyrimidinylcarbonyloxy) - isocaproic acid, an oily substance, which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 43.

In a manner analogous to that described in Example 3, with (R) - 2 - (2 - methoxycarbonyl - nicotinoyloxy) - isocaproic acid there is obtained [(R) - 1 - (2 - methoxycarbonyl - nicotinoyloxy) - 3 - methylbutyl]penicillin sodium which melts above 145° C. (with decomposition); $[\alpha]_D^{25} = +195^\circ$ (c=1 in water).

The (R) - 2 - (2 - methoxycarbonyl - nicotinoyloxy) - isocaproic acid [melting point 63°—65° C.; $[\alpha]_D^{25} = +27.1^\circ$ (c=1 in methanol)] which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 3.

Example 44.

In a manner analogous to that described in Example 1, with (R) - 2 - [(S) - 5 - oxotetrahydro - 2 - furoyloxy] - isocaproic acid there is obtained [(R) - 3 - methyl - 1 - [(S) - 5 - oxotetrahydro - 2 - furoyloxy] - butyl]penicillin sodium of melting point 216° C. (with decomposition); $[\alpha]_D^{25} = +235^\circ$ (c=1 in water).

The (R) - 2 - [(S) - 5 - oxotetrahydro - 2 - furoyloxy] - isocaproic acid [melting point 115°—116° C.; $[\alpha]_D^{25} = +23.4^\circ$ (c=0.5 in dioxan)] which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 22.

Example 45.

In a manner analogous to that described in Example 1, with (R) - 2 - [(R) - 5 - oxotetrahydro - 2 - furoyloxy] - isocaproic acid there is obtained [(R) - 3 - methyl - 1 - [(R) - 5 - oxotetrahydro - 2 - furoyloxy] - butyl]penicillin sodium of melting point 215°

C. (with decomposition); $[\alpha]_D^{25} = +196^\circ$ (c=1 in water).

The (R) - 2 - [(R) - 5 - oxotetrahydro - 2 - furoyloxy] - isocaproic acid, an oily substance, which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 22.

The following Examples illustrate pharmaceutical preparations containing a representative 6-aminopenicillanic acid derivative provided by the invention:

Example A.

Interlocking gelatine capsules containing the following ingredients are prepared in the usual manner:

	per capsule
[(R)-1-(2-furoyloxy)-3-methylbutyl]penicillin sodium	526 mg
Luviskol (Registered Trade Mark)	23 mg
mannitol	20 mg
talc	19 mg
magnesium stearate	2 mg

Example B.

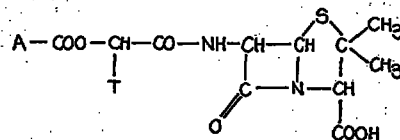
A lyophilisate containing the following ingredients per 2 ml of injectable solution is prepared in the usual manner:

[(R)-1-(2-furoyloxy)-3-methylbutyl]penicillin sodium	263 mg
methyl-p-hydroxybenzoate	1.1 mg
propyl-p-hydroxybenzoate	0.135 mg

This lyophilisate is filled into an ampoule; such an ampoule contains the lyophilised active ingredient for 2.2 ml of injectable solution. For the preparation of 2.2 ml of injectable solution, 2 ml of water are added to the lyophilisate.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



(I)

wherein A and T have the significance given group or the cyclopropylmethyl, cyclobutylmethyl or cyclopentyl group and A represents a furyl, tetrahydrofuryl, pyrrolyl, pyrrolidinyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-thiadiazolyl, pyridyl, imidazolyl, pyrazolyl, 1-oxidopyridyl, tetrahydropyranlyl, pyrimidinyl, pyrazinyl, benzofuranlyl, indolyl,

oily substance, which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 42.

In a manner analogous to that described in Example 3, with (R) - 2 - (5 - pyrimidinylcarbonyloxy) - isocaproic acid there is obtained [(R) - 1 - [(5 - pyrimidinylcarbonyloxy) - 3 - methylbutyl]penicillin sodium of melting point 205° C. (with decomposition); $[\alpha]_D^{25} = +237^\circ$ (c=1 in ethanol).

The (R) - 2 - (5 - pyrimidinylcarbonyloxy) - isocaproic acid, an oily substance, which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 1.

Example 43.

In a manner analogous to that described in Example 3, with (R) - 2 - (2 - methoxycarbonyl - nicotinoyloxy) - isocaproic acid there is obtained [(R) - 1 - (2 - methoxycarbonyl - nicotinoyloxy) - 3 - methylbutyl]penicillin sodium which melts above 145° C. (with decomposition); $[\alpha]_D^{25} = +195^\circ$ (c=1 in water).

The (R) - 2 - (2 - methoxycarbonyl - nicotinoyloxy) - isocaproic acid [melting point 63°—65° C.; $[\alpha]_D^{25} = +27.1^\circ$ (c=1 in methanol)] which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 3.

Example 44.

In a manner analogous to that described in Example 1, with (R) - 2 - [(S) - 5 - oxotetrahydro - 2 - furoyloxy] - isocaproic acid there is obtained [(R) - 3 - methyl - 1 - [(S) - 5 - oxotetrahydro - 2 - furoyloxy] - butyl]penicillin sodium of melting point 216° C. (with decomposition); $[\alpha]_D^{25} = +235^\circ$ (c=1 in water).

The (R) - 2 - [(S) - 5 - oxotetrahydro - 2 - furoyloxy] - isocaproic acid [melting point 115°—116° C.; $[\alpha]_D^{25} = +23.4^\circ$ (c=0.5 in dioxan)] which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 22.

Example 45.

In a manner analogous to that described in Example 1, with (R) - 2 - [(R) - 5 - oxotetrahydro - 2 - furoyloxy] - isocaproic acid there is obtained [(R) - 3 - methyl - 1 - [(R) - 5 - oxotetrahydro - 2 - furoyloxy] - butyl]penicillin sodium of melting point 215°

C. (with decomposition); $[\alpha]_D^{25} = +196^\circ$ (c=1 in water).

The (R) - 2 - [(R) - 5 - oxotetrahydro - 2 - furoyloxy] - isocaproic acid, an oily substance, which was used as the starting material can be prepared via its benzyl ester in a manner analogous to that described for the preparation of the starting material in Example 22.

The following Examples illustrate pharmaceutical preparations containing a representative 6-aminopenicillanic acid derivative provided by the invention:

Example A.

Interlocking gelatine capsules containing the following ingredients are prepared in the usual manner:

	per capsule
[(R)-1-(2-furoyloxy)-3-methylbutyl]penicillin sodium	526 mg
Luviskol (Registered Trade Mark)	23 mg
mannitol	20 mg
talc	19 mg
magnesium stearate	2 mg

Example B.

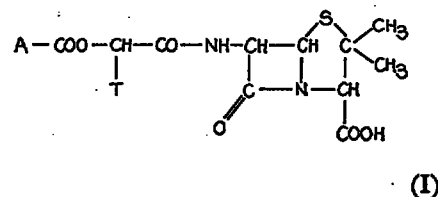
A lyophilisate containing the following ingredients per 2 ml of injectable solution is prepared in the usual manner:

[(R)-1-(2-furoyloxy)-3-methylbutyl]penicillin sodium	263 mg
methyl-p-hydroxybenzoate	1.1 mg
propyl-p-hydroxybenzoate	0.135 mg

This lyophilisate is filled into an ampoule; such an ampoule contains the lyophilised active ingredient for 2.2 ml of injectable solution. For the preparation of 2.2 ml of injectable solution, 2 ml of water are added to the lyophilisate.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



wherein A and T have the significance given group or the cyclopropylmethyl, cyclobutylmethyl or cyclopentyl group and A represents a furyl, tetrahydrofuryl, pyrrolyl, pyrrolidinyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-thiadiazolyl, pyridyl, imidazolyl, pyrazolyl, 1-oxidopyridyl, tetrahydropyranlyl, pyrimidinyl, pyrazinyl, benzofuranyl, indolyl,



quinolyl or isoquinolyl group and wherein the groups A can be substituted by halogen, oxo, hydroxy, amino, C₁₋₈ alkyl, C₁₋₈ alkoxy, C₁₋₈ alkoxy-carbonyl and/or C₁₋₈ alkanoyl-amino,

and pharmaceutically utilisable salts thereof and hydrates of said salts.

2. 6-Aminopenicillanic acid derivatives according to claim 1, wherein A represents a furyl, tetrahydrofuryl, pyrrolyl, pyrrolidinyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-thiadiazolyl, pyridyl, 1-oxidopyridyl, tetrahydropyranyl, primidinyl, pyrazinyl, benzofuranyl, indolyl, quinolyl or isoquinolyl group and wherein said groups can be substituted in the manner defined in claim 1.

3. 6-Aminopenicillanic acid derivatives according to claim 1 or claim 2, wherein A represents the 3-pyridyl, 2-methyl-4-pyridyl, 3-isoxazolyl, 4-oxazolyl, 2-oxo-2-pyrrolidinyl, pyrazinyl, tetrahydro-2-furyl, 2-acetamido-4-thiazolyl, 1,5-dimethyl-3-pyrazolyl, tetrahydro-4-pyranyl, 1,2,3-thiadiazol-4-yl, 2-furyl or 4-pyridyl group.

4. 6-Aminopenicillanic acid derivatives according to claim 1, claim 2 or claim 3, wherein T represents an alkyl or alkenyl group containing 4 or 5 C-atoms.

5. 6-Aminopenicillanic acid derivatives according to claim 4, wherein T represents the isobutyl group.

6. A 6-aminopenicillanic acid derivative according to claim 5, wherein A represents the 2-furyl group.

7. 6-Aminopenicillanic acid derivatives according to any one of claims 1 to 6 inclusive, wherein the acyl group has the R-configuration.

8. [(R)-1-(2-Furoyloxy)-3-methylbutyl]penicillin sodium.

9. A pharmaceutical preparation comprising a 6-aminopenicillanic acid derivative as set forth in any one of the preceding claims in association with a compatible pharmaceutical carrier.

10. A pharmaceutical preparation according to claim 9 wherein the 6-aminopenicillanic acid derivative is [(R)-1-(2-furoyloxy-3-methylbutyl)penicillin or a pharmaceutically utilisable salt thereof or hydrate of said salt.

11. A process for the manufacture of the 6-aminopenicillanic acid derivatives claimed in claim 1, which process comprises reacting 6-aminopenicillanic acid, the carboxyl group of which is present in protected form, with an acid of the general formula



(II)

wherein T represents a C₂₋₈ alkyl or alkenyl in claim 1,

or with an N-acylating functional derivative thereof, cleaving off the protecting group and if desired, converting the resulting product into a pharmaceutically utilisable salt.

12. A process according to claim 11, wherein in said acid of formula II or N-acylating functional derivative thereof A represents a furyl, tetrahydrofuryl, pyrrolyl, pyrrolidinyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-thiadiazolyl, pyridyl, 1-oxidopyridyl, tetrahydropyranyl, pyrimidinyl, pyrazinyl, benzofuranyl, indolyl, quinolyl or isoquinolyl group and wherein said groups can be substituted in the manner defined in claim 1.

13. A process according to claim 11 or claim 12, wherein in said acid of formula II or N-acylating functional derivative thereof A represents the 3-pyridyl, 2-methyl-4-pyridyl, 3-isoxazolyl, 4-oxazolyl, 2-oxo-2-pyrrolidinyl, pyrazinyl, tetrahydro-2-furyl, 2-acetamido-4-thiazolyl, 1,5-dimethyl-3-pyrazolyl, tetrahydro-4-pyranyl, 1,2,3-thiadiazol-4-yl, 2-furyl or 4-pyridyl.

14. A process according to claim 11, claim 12 or claim 13, wherein in said acid of formula II or N-acylating functional derivative thereof T represents an alkyl or alkenyl group containing 4 or 5 C-atoms.

15. A process according to claim 14, wherein T represents the isobutyl group.

16. A process according to claim 15, wherein A represents the 2-furyl group.

17. A process according to any one of claims 11 to 16 inclusive, wherein an acid of formula II, or an N-acylating functional derivative thereof, having the R-configuration is used.

18. A process according to claim 11 for the manufacture of the 6-aminopenicillanic acid derivatives claimed in claim 1, substantially as hereinbefore described with reference to Examples 1 to 46.

19. 6-Aminopenicillanic acid derivatives as set forth in claim 1, when manufactured by the process claimed in any one of claims 11 to 18 inclusive.

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