

PATENT SPECIFICATION

(11) 1 289 358

NO DRAWINGS

- (21) Application No. 46937/69 (22) Filed 24 Sept. 1969
 (31) Convention Application No. 70572 (32) Filed 28 Sept. 1968 in
 (33) Japan (JA)
 (45) Complete Specification published 20 Sept. 1972
 (51) International Classification C07D 99/16 // A61K 21/00
 (52) Index at acceptance
 C2A 1C1A 1C1E 1C2A 1C2B 1C2C 2C1



(54) SYNTHETIC PENICILLINS

(71) We, TAKEDA YAKUHI KOGYO KABUSHIKI KAISHA also known as TAKEDA CHEMICAL INDUSTRIES LTD. of 27, 2-Chome, Doshomachi, Higashi-ku, Osaka, Japan, a body corporate organised under the laws of Japan, 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 of value as antibacterial agents, as nutritional supplements in animal feeds, and as therapeutic agents for poultry and animals, in the treatment especially of infectious diseases caused by Gram-positive and Gram-negative bacteria. It relates more particularly to novel penicillins and to pharmaceutically acceptable salts thereof.

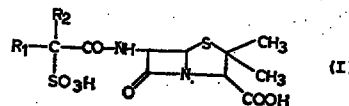
Many penicillins have proved effective in the therapy of infections caused by bacteria but these compounds suffer from at least one or more of drawbacks as follows:

- (1) being unstable in aqueous acid;
- (2) lacking in their ability to control *Pseudomonas* infections effectively;
- (3) being ineffective against so-called penicillin G-resistant strains of bacteria (e.g. many strains of *Staphylococcus aureus*); and
- (4) being unstable to penicillinase produced by various microorganisms.

Many of the compounds of the present invention, in addition to their strong activity against Gram-positive bacteria, exhibit a high resistance to decomposition by acid or by penicillinase, and have a particularly significant activity against Gram-negative microorganisms such as those of the genus *Pseudomonas*. Accordingly, the compounds of the present invention are believed to be unique in possessing a number of desirable activities.

There is provided, according to the present invention, a synthetic penicillin represented by

general formula (I) as well as its pharmaceutically acceptable salts:



wherein R_1 and R_2 are the same or different and each represents a hydrogen atom, an alkyl group having from 1 to 12 carbon atoms, an aralkyl group or a mono- or poly-substituted or unsubstituted phenyl, pyridyl, naphthyl or thienyl group the substituents being nitro, sulpho, carboxyl, halo, alkyl with from 1 to 6 carbon atoms or alkoxy with from 1 to 6 carbon atoms in the case of polysubstitution being the same or different; or alternatively, R_1 and R_2 , taken together, represent a polymethylene group having from 4 to 6 carbon atoms.

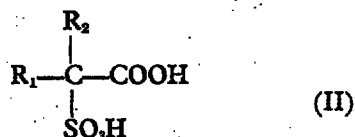
The alkyl group represented by R_1 and R_2 is preferably an aliphatic hydrocarbon group having from 2 to 12 carbon atoms, inclusive (e.g. ethyl, isopropyl, sec-butyl, tert-butyl, cyclohexyl or dodecyl). The aralkyl group is preferably an aralkyl group having from 7 to 10 carbon atoms, inclusive (e.g. benzyl or phenethyl).

The phenyl, naphthyl, pyridyl and thienyl groups include those substituted by one or more substituents such as nitro, carboxyl, sulpho, halo (e.g. F, Cl or Br), alkoxy having from 1 to 6 carbon atoms (e.g. methoxy, ethoxy, or *n*-propoxy) and alkyl having from 1 to 6 carbon atoms (e.g. methyl, ethyl, *n*-propyl, iso-propyl, *n*-pentyl or cyclohexyl). The pharmaceutically acceptable salts include salts with non-toxic metals (e.g. sodium, potassium, calcium, aluminium or magnesium), and salts with amines (e.g. ammonia, triethylamine, procaine, dibenzylamine, and other amines which have been used for various known penicillins).

For the production of the synthetic penicillins of this invention, any of the *per se*

[Price 25p]

known means for synthesising penicillins from 6-aminopenicillanic acid can generally be applied. More specifically, they may be prepared conveniently by reacting 6-aminopenicillanic acid in free or in salt form or a silyl derivative thereof with an acylating agent derived from an α -sulphocarboxylic acid of the general formula (II):



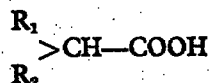
wherein R_1 and R_2 have the same meaning as defined above.

The acylating agents include acid halides (e.g. chloride or bromide) corresponding to the carboxylic acid of the general formula (II), corresponding carboxylic acid anhydrides, particularly mixed anhydrides prepared from the carboxylic acid of the general formula (II) and a stronger acid such as a C_1 to C_6 alkyl or an aralkyl monoester of carbonic acid (e.g. benzyloxycarbonic acid or ethoxycarbonic acid), an acetic acid substituted by an electron withdrawing group or groups (e.g. dichloroacetic acid or trichloroacetic acid or an alkyl- or aryl-sulfonic acid (e.g. toluenesulfonic acid or methanesulfonic acid). In addition, the acylating agent also includes the corresponding acid azide or the corresponding active ester or thioester, i.e., an ester prepared from the carboxylic acid with a phenol or a thiophenol (e.g. *p*-nitrophenol, 2,4-dinitrophenol, pentachlorophenol or thiophenol). Furthermore, the acylating agent should include the carboxylic acid coupled with an N,N -carbonylditriazole, a carbodiimido reagent (e.g. N,N' -dicyclohexylcarbodiimide, N,N' -diisopropylcarbodiimide, or N -cyclohexyl- N' -(2-morpholinoethyl)carbodiimide), a ketenimine reagent or an isoxazolium salt reagent. Another acylating agent derived from the carboxylic acid of the general formula (II) is the corresponding azolide, i.e., the corresponding acid amide whose amide nitrogen is a member of an aromatic five-membered ring-containing at least two nitrogen atoms (e.g. imidazole, pyrazole or benzimidazole).

Among these acylating agents acid halides are preferred, particularly acid chloride, in view of convenience and low production costs.

For example, α -sulphobenzyl penicillin may be prepared by the method according to the invention using an acylating agent derived from α -sulphophenylacetic acid.

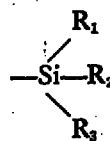
The acylating agent is produced by a *per se* known method. For example, the corresponding acid halide is easily produced by first reacting the carboxylic acid of the general formula:



(wherein R_1 and R_2 have the same meaning as defined above) with sulphur trioxide or its dioxane complex in dichloroethane at $10^\circ C$ to $60^\circ C$ and then treating the thus produced carboxylic acid (II) with a halogenating agent (e.g. thionyl chloride, phosphorus oxychloride or phosphorus oxybromide) at $0^\circ C$ to $100^\circ C$, preferably at $10^\circ C$ to $40^\circ C$ in the presence of a catalyst (e.g. dimethylformamide).

It should be noted that 6-aminopenicillanic acid may be provided either as 6-aminopenicillanic acid itself or as a salt thereof. In general, it is preferable to employ it in the form of a salt (e.g. sodium salt, potassium salt or triethylamine salt).

As is well known, the silyl derivatives of 6-aminopenicillanic acid include mono-silyl derivatives and di-silyl derivatives, and both can be employed in the method of the present invention, although the latter generally give preferable results. Preferred examples of the silyl group in the silyl derivatives are of the formula:



in which R_1 , R_2 and R_3 may be the same or different and are each an alkyl group with from 1 to 5 carbon atoms, benzyl, phenethyl, cyclohexyl, phenyl or tolyl.

The acylation of the present invention is preferably performed by reacting 6-aminopenicillanic acid with an acylating agent in a solvent in the presence of a base.

The acylation may be conducted at room temperature, below room temperature, or even above room temperature; however, since 6-aminopenicillanic acid and its acylation products are liable to be decomposed at an elevated temperature, the reaction is desirably carried out at a temperature below $50^\circ C$, and preferably from $-20^\circ C$ to $40^\circ C$ provided the reaction mixture retains its liquid form.

Suitable bases are organic bases (e.g. triethylamine, tributylamine, pyridine, piperidine or morpholine) and inorganic bases (e.g. sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate). The amount of the base is generally 1 to 3 mols per mol of the acylating agent. Any solvent which does not disturb the reaction may be employed for the acylation reaction, and such solvent is exemplified by water, dioxane, acetone, dimethylformamide, tetrahydrofuran, chloroform, ethylene dichloride, toluene, benzene, or a mixture thereof. However, in cases where the silyl derivatives are employed, it is recommended to use an inert solvent, e.g.,

ether, dioxane, benzene, tetrahydrofuran or chloroform.

It should be noted that hydrolysis or alcoholysis of an acylation product produced by the reaction of an acylating agent and a silyl derivative of 6-aminopenicillanic acid may be performed by merely treating the acylation product with water or an aliphatic alcohol having from 1 to 3 carbon atoms (e.g. methanol or ethanol), so as to obtain the compound of the general formula (I).

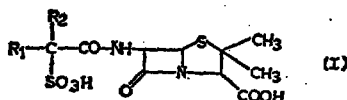
After the reaction, the derived compound of the present invention is recovered from the reaction mixture by a *per se* known process. If desired, these products may be purified by way of *per se* conventional means, e.g. recrystallization or chromatography.

Accordingly, the desired compound of the present invention is normally recovered from the reaction mixture in which it exists either as the free acid or the salt thereof. If desired, the salts may be converted to other salts by conventional double decomposition reactions.

It should be noted that the penicillins of the general formula (I) are characterised by at least two acidic functional groups; the carboxyl and sulpho moieties. Because of the difference in the relative degree of acidity of these acid groups, it is possible to prepare either an acid salt or a normal salt.

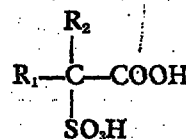
Among the penicillins (I) of the present invention, when R_1 represents a different group from R_2 , the α -carbon atom of the acyl group constitutes an asymmetric carbon atom, and in those cases there exist two optical isomers, and it is to be understood that all such individual isomeric forms as well as their mixture are included in the scope of the present invention.

Accordingly, it is possible to prepare particular optical isomers of the penicillins (I) in which R_1 and R_2 represent different groups. For example, the optically active D-form of a synthetic penicillin of the general formula I:



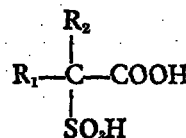
wherein R_1 and R_2 are different and each represents a hydrogen atom, an alkyl group having from 2 to 12 carbon atoms, an aralkyl group or a mono- or poly-substituted phenyl, pyridyl, naphthyl or thienyl group, the substituents being nitro, sulpho, carboxyl, halo, alkyl with from 1 to 6 carbon atoms or alkoxy with from 1 to 6 carbon atoms, in the case of polysubstitution being the same or different, or a pharmaceutically acceptable salt or acid salt thereof, may be prepared. This may be achieved by reacting 6-aminopenicillanic acid in free or salt form or a silyl derivative thereof with an acylating agent derived from the optically active D-isomer of

an α -sulphocarboxylic acid having the general formula:



wherein R_1 and R_2 are different and have the same meanings as above, and optionally treating the penicillin formed with a base.

Alternatively, the optically active D-isomers may be prepared by reacting 6-aminopenicillanic acid in free or salt form or a silyl derivative thereof with an acylating agent derived from a racemic α -sulphocarboxylic acid having the general formula:



wherein R_1 and R_2 are different and have the meanings as above, to form a racemic penicillin; and recovering therefrom the optically active D-isomer of the penicillin or a salt or acid salt thereof by means of chromatography or recrystallisation and optionally treatment with a base.

The optically active D-isomer of α -sulphobenzyl penicillin, salts and acid salts thereof, for example, may be prepared by either of these methods.

Known methods of chromatography or recrystallisation may be used to resolve optically a mixture of isomers obtained as acylation products if such resolution is required.

When it is desired to use a resolved carboxylic acid of the general formula (II), optical resolution of the carboxylic acid may be carried out by submitting it to a *per se* known means of resolution, e.g. recrystallisation of an optically active base (e.g. brucine or quinine) salt of the carboxylic acid.

As stated hereinabove, the novel penicillins of the present invention exhibit strong anti-bacterial activities against Gram-negative bacteria or penicillin G-resistant strains as well as against common Gram-positive bacteria. The following test is an example demonstrating the peculiar anti-bacterial activities of typical compounds of the present invention, i.e.:

(A) D- and DL - α - sulphobenzylpenicillin (disodium salts) in terms of minimum inhibitory concentration (MIC; microgram/milliliter) against a variety of bacteria in comparison with commercially available synthetic penicillins:

- (B) Ampicillin sodium salt;
 (C) Hexacillin;
 (D) Nafcillin sodium salt;
 (E) Dicloxacillin sodium salt.

The test also shows that different optical isomers of the synthetic penicillins according to the invention may show quite different levels of activity.

Tested Penicillins	(A)		(B)	(C)	(D)	(E)
	D	DL	D(—)			
<i>Pseudomonas aeruginosa</i>	10	20	>100	>100	>100	>100
<i>Escherichia coli</i>	20	20	20—50	100	>100	>100
<i>Proteus vulgaris</i>	1	2	5	20	>100	>100
<i>Proteus morgani</i>	2	5	100	50	>100	>100
<i>Proteus mirabilis</i>	0.5	2	5	20	>100	>100
<i>Staphylococcus aureus</i>	0.5	2	<0.2	<0.2	<0.2	0.1
<i>Bacillus subtilis</i>	0.1	<0.2	<0.2	0.2	0.5	0.1
<i>Staphylococcus aureus</i> (penicillin G-resistant strain)	10	20	>100	100	<1	<1
resistance (%) [*] against <i>Bacillus cereus</i> penicillinase	66	57	0	0	76	90

^{*}Remaining potency in percentage after a mixture of 0.5 milliliter of an aqueous penicillinase solution (0.1 milligram/milliliter) and 0.5 milliliter of an aqueous solution of the penicillin 2 milligram/milliliter) was kept at 34°C. for 30 minutes.

- 10 The penicillins of the present invention are of very low toxicity towards mammalian species and are well-tolerated, even in a large dosage. They can be administered orally in capsules or tablets as well as parenterally in solutions or suspensions. For example, in the treatment of *Pseudomonas* infections in mammals such as mice, man or the like, the penicillins are administered with conventional procedures in an amount of from 5 to 50 mg./Kg./day, but usually 10 to 30 mg./Kg./day, in divided dosages, e.g. two to four times a day.

- 25 The following examples will serve to illustrate the present invention without limiting it thereto. In these examples, the parts by weight bear the same relationship to parts by volume as do grams to milliliters. The infrared absorption spectrum (IR) is expressed in terms of $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹, and the nuclear magnetic resonance spectrum (NMR) is expressed in terms of δ (in D₂O, 60MHz). The abbreviations s., d., t., q. and m. mean that the

signal is an apparent singlet, doublet, triplet, quartet and multiplet.

Example 1

To a suspension of 1.08 parts by weight of 6-amino-penicillanic acid in 8 parts by volume of water are added 1.8 parts by weight of sodium bicarbonate. After the mixture is dissolved, a solution of 1.18 parts by weight of α -sulphonphenylacetyl chloride in 10 parts by volume of diethylether is gradually added thereto. The mixture is stirred at a temperature in the neighbourhood of 0° C for 1 hour. The aqueous layer is washed twice with 10 parts by volume of portions of ether and adjusted to pH 1.2 with a cationexchange resin of polystyrene sulphonic acid type under constant cooling. Then the solution is washed twice with 15 parts by volume of portions of ethyl acetate, followed by extraction twice with 15 parts by volume of portions of *n*-butanol. The extracts are combined and washed twice with 15 parts by volume portions of water and then extracted with an aqueous

solution of sodium bicarbonate. The extract is adjusted to pH 6.5, washed with ether and lyophilised to give the sodium salt of α -sulpho-

benzylpenicillin. The yield is 1.2 parts by weight. Upon recrystallisation with water-acetone, the compound shows:—

Elementary analysis as $C_{16}H_{16}N_2O_5S_2Na_2 \cdot 3H_2O$

Calculated C, 37.50; H, 4.29; N, 5.48; S, 12.50 %
Found C, 37.49; H, 4.15; N, 5.58; S, 12.25 %

10 IR: 3000 (phenyl CH str.), 1770 (lactam C=O), 1675 (—CONH—), 1615 (—COO—), 1530, 1405, 1325, 1210, 1050 (—SO₃), 700

NMR: 1.60 (6H, t.), 4.32 (1H, d.), 5.16 (1H, S.), 5.64 (2H, d.), 7.56 (5H, diffused s.).

15 6 parts by weight of optically resolved D - α sulphophenylacetic acid ([α] D = - 23.9° (C = 2.0, H₂O)) are halogenated to give the corresponding D - α sulphonphenylacetyl chloride and this is treated by the same procedure as above, and 6.2 parts by weight of D - α - sulphobenzylpenicillin are obtained. [α] D = + 146.0° (C = 1.0, H₂O).

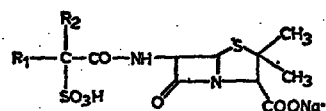
Example 2

25 To a suspension of 3.01 parts by weight of 6-aminopenicillanic acid in 25 parts by volume of dry chloroform are added 2.24 parts by weight of hexamethyl disilazane. After reflux for 1.5 hours on a water bath of 78° C, the solvent is distilled off from the clear reaction mixture under reduced pressure at 40° C to leave trimethylsilyl N-trimethylsilyl-6-aminopenicillanate.

30 The residue is dissolved in 50 parts by weight of chloroform which had been purified by distillation in the presence of phosphorus pentoxide, and 1.2 parts by weight of triethylamine are added thereto at - 3° C. To the solution are added dropwise 2.6 parts by weight of α -sulphophenylacetyl chloride under stirring at - 3° C, over 20 minutes. The stirring is continued for an additional 30 minutes at 0° C. The reaction mixture is washed with cold water, and the organic layer is extracted with an aqueous sodium bicarbonate solution (pH 6.5). The extract is washed with ether, and is lyophilised to give the sodium salt of α -sulfo-benzylpenicillin, which is identified as the product of Example 1.

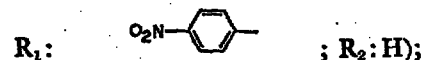
Examples 3 to 18

50 The following penicillins of the general formula:



are prepared from 6-aminopenicillanic acid by way of the corresponding acid halide in accordance with the procedures of Example 1 (referred to as Procedure A) and/or as in Example 2 (referred to as Procedure B):

3) α - Sulfo - *p* - nitrobenzylpenicillin

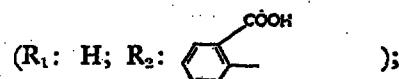


Procedure: A

IR: 3000 (phenyl, —CH—, st.), 1770 (C=O), 1675 (—CO—NH—), 1530, 1350 (—NO₂), 1050 (—SO₃—)

NMR: 1.60 (6H, t.), 4.25 (1H, broad S.), 5.12 (1H, S.), 5.65 (2H, d.), 7.84 (2H, d.), 8.27 (2H, q.)

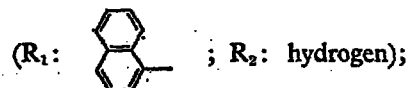
4) α - Sulpho - *o* - carboxybenzylpenicillin



Procedure: A

IR: 3450 (—OH), 2990 (—CH—, st.), 1770 (C=O), 1675 (—CO—NH—), 1610 (—COO—), 1530, 1350 (—NO₂), 1050 (—SO₃—)

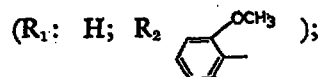
5) α - Sulfo - naphthylmethylpenicillin



Procedure: A, B

IR: 3350 (—OH), 3070, 3000 (—CH—), 1770 (C=O), 1670 (—CO—NH—), 1615 (—COO—), 1515, 1400, 1325, 1210, 1125, 1045 (—SO₃—), 830, 790, 770, 700

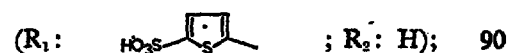
6) α - Sulfo - *o* - methoxybenzylpenicillin



Procedure: A, B

IR: 3335 (—OH), 3000 (—CH—), 1780 (C=O), 1610 (COO—), 1500, 1402, 1042 (—SO₃—)

7) α - Sulfo - 5 - sulfo - 2 - thienylmethylpenicillin



Procedure: A

IR: 3450 (OH), 2950 ($-\text{CH}=\text{}$), 1760 ($\text{C}=\text{O}$), 1690 ($-\text{CONH}-$), 1605 ($-\text{COO}-$), 1235, 1043 ($-\text{SO}_3-$)

- 5 8) α - Sulfo - ethylpenicillin (R_1 : H; R_2 : CH_3-);

Procedure: A, B

IR: 3450 (broad, $-\text{OH}$), 2980 ($-\text{CH}-$), 1770 ($\text{C}=\text{O}$), 1670 ($-\text{CONH}-$), 1615 ($-\text{COO}-$), 1460, 1400, 1200 (broad), 1049 ($-\text{SO}_3-$)

- 10 9) α - Sulfo - *n* - pentylpenicillin (R_1 : $\text{CH}_3(\text{CH}_2)_4-$; R_2 : H);

Procedure: A, B

IR: 3420 ($-\text{OH}$), 2980, 2850 ($-\text{CH}-$), 1770 ($\text{C}=\text{O}$), 1670 ($-\text{CONH}-$), 1615 ($-\text{COO}-$), 1470, 1410, 1220 (broad), 1052 ($-\text{SO}_3-$)

- 15 NMR: 0.98 (3H, t.), 1.2—1.35 (6H, m.), 1.60 (3H, s.), 1.71 (3H, s.), 3.68, 3.90 (1H, t.), 4.26, 4.35 (1H), 5.50—5.72 (2H, m.)

- 20 10) α - Sulfo - *n* - undecylpenicillin (R_1 : $\text{CH}_3(\text{CH}_2)_{10}-$; R_2 : H);

Procedure: A, B

IR: 3370 ($-\text{OHO}$), 2920, 2840 ($-\text{CH}-$), 1765 ($\text{C}=\text{O}$), 1665 ($-\text{CONH}-$), 1612 ($-\text{COO}-$), 1050 ($-\text{SO}_3-$)

- 25 NMR: 0.92 (3H), 1.33 (16H, broad s.), 1.59 (3H, s.), 1.68 (3H, s.), 3.65, 3.87 (1H, t.), 4.23, 4.30 (1H), 5.59 (2H, m.)

- 30 11) α - Sulfo - *p* - chlorobenzylpenicillin

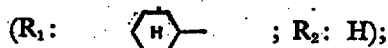


Procedure: A, B

IR: 3360 (broad, $-\text{OH}$), 2950 ($-\text{CH}-$), 1760 ($\text{C}=\text{O}$), 1670 ($-\text{CO}-\text{NH}-$), 1610 ($-\text{COO}-$), 1490, 1408, 1320, 1240, 1210, 1091, 1047 ($-\text{SO}_3-$), 1015

- 35 NMR: 1.49, 1.55, 1.63 (6H, t.), 4.25, 4.28, (1H, d.), 5.11 (1H, s.), 5.55, 5.61 (2H, d.), 7.50, 7.52 (4H, d.)

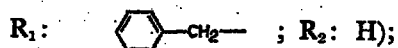
- 40 12) α - Sulfo - cyclohexylmethylpenicillin



Procedure: A, B

IR: 3420 ($-\text{OH}$), 2980 ($-\text{CH}-$), 1770 ($\text{C}=\text{O}$), 1680 (Shoulder), 1612 ($-\text{COO}-$), 1410, 1210—1250 (broad), 1051 ($-\text{SO}_3-$)

- 45 13) α - Sulfo - phenethylpenicillin

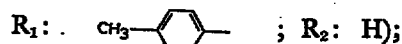


Procedure: A, B

IR: 3390 ($-\text{OH}$), 1765 ($\text{C}=\text{O}$), 1670 ($-\text{CO}-\text{NH}-$), 1610 ($-\text{COO}-$), 1250—1210, 1043 ($-\text{SO}_3-$)

NMR: 1.53, 1.58 (3H, d.), 1.62, 1.68 (3H, d.), 3.42 (2H, m.), 4.22 (1H, s.), 4.20 (1H, s.), 5.42, 5.55 (2H, q.), 7.39 (5H, s.)

- 55 14) α - Sulfo - *p* - methylbenzylpenicillin



Procedure: A, B

IR: 3400 ($-\text{OH}$), 2980, 2940 ($-\text{CH}-$), 1765 ($\text{C}=\text{O}$), 1672 ($-\text{CONH}-$), 1612 ($-\text{COO}-$), 1250—1215, 1050 ($-\text{SO}_3-$)

NMR: 1.51, 1.55, 1.63 (6H, t.), 2.35 (3H, s.), 4.26, 4.30 (1H, d.), 5.06 (1H, s.), 5.56, 5.60 (2H, d.), 7.28, 7.48 (4H, q.)

- 60 15) α - Sulfo - cyclohexylpenicillin (R_1 and R_2 , taken together, $-(\text{CH}_2)_6-$);

Procedure: A, B

IR: 3420 ($-\text{OH}$), 2950 ($-\text{CH}-$), 1770 ($\text{C}=\text{O}$), 1664 ($-\text{CONH}-$), 1610 ($-\text{COO}-$), 1045 (SO_3-)

NMR: 0.7—1.54 (10H, m.), 1.68, 1.70 (3H, d.), 1.61, 1.65 (3H, d.), 4.33 (1H, s.), 5.63 (2H, d.)

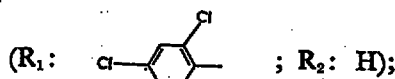
- 65 16) α - Sulfo - *p* - cyclohexylbenzylpenicillin



Procedure: A, B

IR: 3420 ($-\text{OH}$), 1770 ($\text{C}=\text{O}$), 1660 ($-\text{CO}-\text{NH}-$), 1615 ($-\text{COO}-$), 1410 ($-\text{CH}-$), 1250—1215, 1046 ($-\text{SO}_3-$)

- 70 17) α - Sulfo - 2,4 - dichlorobenzylpenicillin

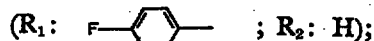


Procedure: A, B

IR: 3410 ($-\text{OH}$), 2980, 2920 ($-\text{CH}-$), 1768 ($\text{C}=\text{O}$), 1675, 1618 ($-\text{COO}-$), 1515, 1475, 1407, 1325, 1220—45 (broad), 1045 ($-\text{SO}_3-$)

NMR: 1.49 (3H, s.), 1.58 (3H, s.), 4.26 (1H, s.), 5.54 (1H, s.), 5.60, 5.70 (2H, d.), 7.3—8.02 (3H, m.)

- 80 18) α - Sulfo - *p* - fluorobenzylpenicillin



Procedure: A

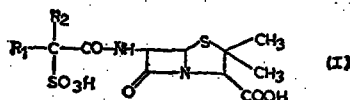
IR: 3400 (OH), 2960 ($-\text{CH}-$), 1765 (β -lactum), 1670 ($-\text{CONH}-$), 1609 ($-\text{COO}-$), 1225 ($-\text{SO}_2-$), 1045 ($-\text{SO}_3-$)

NMR: 1.53, 1.57, 1.65 (6H, t.), 4.28, 4.31 (1H, d.), 5.16 (1H, s.), 5.57, 5.62 (2H, d.), 6.95—7.85 (4H, m.)

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WHAT WE CLAIM IS:—

1. A synthetic penicillin of the general formula (I):



wherein R_1 and R_2 are the same or different and each represents a hydrogen atom, an alkyl group having from 2 to 12 carbon atoms, an aralkyl group or a mono- or poly-substituted or unsubstituted phenyl, pyridyl, naphthyl or thienyl group, the substituents being nitro, sulpho, carboxyl, halo, alkyl with from 1 to 6 carbon atoms or alkoxy with from 1 to 6 carbon atoms, in the case of polysubstitution being the same or different; or, alternatively, R_1 and R_2 , taken together, represent a polymethylene group having from 4 to 6 carbon atoms;

and a pharmaceutically acceptable salt or acid salt thereof.

2. A penicillin as claimed in claim 1, wherein the pharmaceutically acceptable salt is the sodium, potassium, magnesium, calcium, aluminium, ammonia, triethylamine, procaine or dibenzylamine salt.

3. A compound as claimed in claim 1 or 2, wherein R_1 is phenyl and R_2 is hydrogen.

4. A compound as claimed in claim 1 or 2, wherein R_1 is *p*-nitrophenyl and R_2 is hydrogen.

5. A compound as claimed in claim 1 or 2, wherein R_1 is hydrogen and R_2 is *o*-carboxyphenyl.

6. A compound as claimed in claim 1 or 2, wherein R_1 is naphthyl and R_2 is hydrogen.

7. A compound as claimed in claim 1 or 2, wherein R_1 is hydrogen and R_2 is *o*-methoxyphenyl.

8. A compound as claimed in claim 1 or 2, wherein R_1 is 5-sulpho-2-thienyl and R_2 is hydrogen.

9. A compound as claimed in claim 1 or 2, wherein R_1 is hydrogen and R_2 is methyl.

10. A compound as claimed in claim 1 or 2, wherein R_1 is *n*-butyl and R_2 is hydrogen.

11. A compound as claimed in claim 1 or 2, wherein R_1 is decyl and R_2 is hydrogen.

12. A compound as claimed in claim 1 or 2, wherein R_1 is cyclohexyl and R_2 is hydrogen.

13. A compound as claimed in claim 1 or 2, wherein R_1 is *p*-chlorophenyl and R_2 is hydrogen.

14. A compound as claimed in claim 1 or 2, wherein R_1 is benzyl and R_2 is hydrogen.

15. A compound as claimed in claim 1 or 2, wherein R_1 is *p*-tolyl and R_2 is hydrogen.

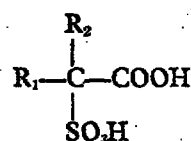
16. A compound as claimed in claim 1 or 2, wherein R_1 is *p*-cyclohexylphenyl and R_2 is hydrogen.

17. A compound as claimed in claim 1 or 2, wherein R_1 and R_2 taken together, represent pentamethylene.

18. A compound as claimed in claim 1 or 2, wherein R_1 is 2,4-dichlorophenyl and R_2 is hydrogen.

19. A compound as claimed in claim 1 or 2, wherein R_1 is *p*-fluorophenyl and R_2 is hydrogen.

20. A method of producing a penicillin of the general formula (I) as defined in claim 1, in which 6-aminopenicillanic acid in free or salt form or a silyl derivative thereof is reacted with an acylating agent derived from an α -sulphocarboxylic acid having the general formula:—



wherein R_1 and R_2 have the same meaning as defined above and if desired the penicillin compound thus produced is treated with a base to form a pharmaceutically acceptable salt or acid salt thereof.

21. A method as claimed in Claim 20, wherein the acylating agent is an α -sulphocarboxylic acid halide.

22. A method as claimed in Claim 21, wherein the acid halide is a chloride.

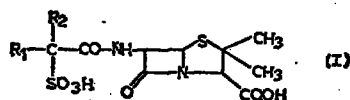
23. A method as claimed in Claim 20 to 21, wherein the 6-aminopenicillanic acid is in the form of a salt.

24. Synthetic penicillins and salts thereof as claimed in Claim 1 substantially as herein described with reference to any of the specific Examples.

25. A method according to claim 20 substantially as herein described with reference to any of the specific Examples.

26. Synthetic penicillins and salts thereof as defined in claim 1 when made by a method as claimed in any of claims 20 to 23 and 25.

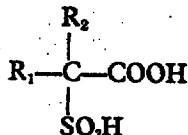
27. The optically active D isomer of a synthetic penicillin of the general formula (I)



wherein R_1 and R_2 are different and each represents a hydrogen atom, an alkyl group having from 1 to 12 carbon atoms, an aralkyl group or a mono- or poly-substituted phenyl, pyridyl, naphthyl or thienyl group, the substituents being nitro, sulpho, carboxyl, halo, alkyl with from 1 to 6 carbon atoms, or alkoxy with from 1 to 6 carbon atoms, in the case of polysubstitution being the same or different, or a pharmaceutically acceptable salt or acid salt thereof.



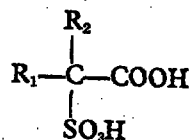
28. A method for producing the optically active D-isomer of a penicillin of the general formula (I), as defined in claim 27, or a pharmaceutically acceptable salt or acid salt thereof, which process comprises reacting 6-aminopenicillanic acid in free or salt form or a silyl derivative thereof with an acylating agent derived from the optically active D-isomer of an α -sulphocarboxylic acid having the general formula:



wherein R_1 and R_2 have the same meanings as in claim 27, and optionally treating the penicillin formed with a base.

29. A method for producing the optically active D-isomer of a penicillin of the general formula (I), as defined in claim 27, or a

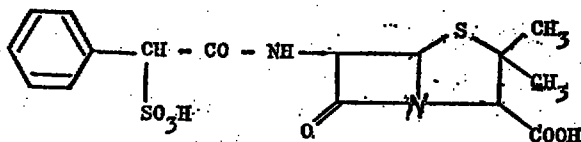
pharmaceutically acceptable salt or acid salt thereof, which process comprises reacting 6-aminopenicillanic acid in free or salt form or a silyl derivative thereof with an acylating agent derived from a racemic α -sulphocarboxylic acid having the general formula:



wherein R_1 and R_2 have the same meanings as in claim 27,

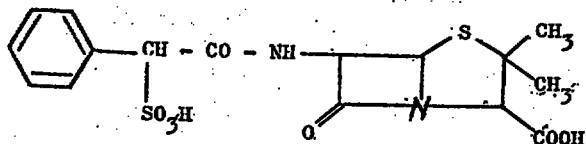
to form a racemic penicillin; and recovering therefrom the optically active D-isomer of the penicillin or a salt or acid salt hereof by means of chromatography or recrystallisation and optionally treatment with a base.

30. The DL isomer mixture of α -sulphobenzyl penicillin of the formula:



- or pharmaceutically acceptable salts or acid salts thereof.

31. The optically active D-form of α -sulphobenzyl penicillin of the formula:



32. A pharmaceutically acceptable salt or acid salt of the compound claimed in claim 31.

33. A method as claimed in claim 28 for producing a compound as claimed in claim 31 or 32 in which the acylating agent is derived from the optically active D-isomer of α -sulphophenylacetic acid.

34. A method as claimed in claim 29 for producing a compound as claimed in claim 31 or 32 in which the acylating agent is derived from racemic α -sulphoacetic acid.

35. A method as claimed in claim 28 or 29, substantially as herein described with reference to any of the specific Examples.

36. The optically active D-isomer of a synthetic penicillin as claimed in claim 27 when prepared by a process as claimed in any of claims 28 to 35.

37. A method as claimed in claim 20, in which α -sulphobenzyl penicillin or a salt or acid salt thereof is prepared from an acylating agent derived from α -sulphophenylacetic acid.

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