COMMONWEALTH of AUSTRALIA
PATENTS ACT 1952
APPLICATION FOR A STANDARD PATENT

XX
We, BEECHAM GROUP p.l.c. of Beecham House,
Great West Road, Brentford, Middlesex, England

hereby apply for the grant of a Standard Patent for an invention entitled:

PROCESS FOR THE PREPARATION OF PENAM DERIVATIVES

which is described in the accompanying provisional specification.

Details of basic application(s):

<table>
<thead>
<tr>
<th>Number</th>
<th>Convention Country</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td>8121303</td>
<td>UNITED KINGDOM</td>
<td>10 July 1981</td>
</tr>
</tbody>
</table>

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

(a member of the firm of DAVIES & COLLISON for and on behalf of the Applicant).

Davies & Collison, Melbourne and Canberra.
COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952

DECLARATION IN SUPPORT OF CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT

857 39/82

In support of the Application made for a patent for an invention entitled: Process for the preparation of penam derivatives

Ronald Smither
of Beecham House, Great West Road, Brentford, Middlesex, England

I do solemnly and sincerely declare as follows:

I am authorized by Beecham Group plc (formerly Beecham Group Limited)

the applicant for the patent to make this declaration on its behalf.

John Robert Mansfield Dales of 23 Farnet Way, Littlehampton,
West Sussex, England and Marguerita Anne Vallance of 14 Ontario
Close, Durrington, Worthing, West Sussex, England (formerly of
14 Jason Court, Heene Terrace, Worthing, West Sussex, England

are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follows:

by virtue of their employment by Beecham Group plc, whereby the applicant would, if a patent were granted upon an application made by the said actual inventors be entitled to have the patent assigned to it.

3. The basic application as defined by Section 141 of the Act was made in United Kingdom on the 10 July 1981

by Beecham Group plc

in

in

by

4. The basic application referred to in paragraph 3 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

Declared at Brentford this 15 day of June 1982

RONALD SMITHER, as Attorney for and on behalf of the said Beecham Group plc

Witness: S. HAW.

DAVIES & COLLISON, MELBOURNE and CANBERRA.
A process for the preparation of a penam derivative of formula (I):

\[
\begin{align*}
\text{R}^1\text{NH} & \quad \text{OCH}_3 \\
\text{S} & \quad \text{N} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CO}_2\text{R}^2
\end{align*}
\]

wherein \( \text{R}^1 \) is hydrogen or a group of formula (Ia):

\[
\begin{align*}
\text{R}^1\text{CH}_2\text{CO}- & \quad \text{X} \\
\text{X} & \quad -\text{CO}_2\text{R}^1, \text{SO}_2\text{R}^1
\end{align*}
\]

wherein \( \text{X} \) is \(-\text{CO}_2\text{R}^1, \text{SO}_2\text{R}^1\); \( \text{R}^1 \) is C\(_1\)-C\(_6\) alkyl, aryl, or heterocyclyl; \( \text{R}^1 \) is hydrogen, or a pharmaceutically acceptable salt-forming ion or ester-forming ion.
radical, and \( R^2 \) represents hydrogen or a pharmaceutically acceptable salt-forming ion or in vivo hydrolysable ester-forming radical; which process comprises reacting a compound of formula (II):

\[
\text{(II)}
\]

wherein \( R^B \) is hydrogen, a removable amino blocking group, or a group of formula (IIa):

\[
R^B \text{CHCO-} \quad \text{(IIa)}
\]

wherein \( Y \) is \(-\text{CO}_2R^X\) or \(-\text{SO}_3R^X\); \( R \) is as defined with respect to formula (I) above; \( R^X \) represents an ester-forming radical, \( R^Y \) represents hydrogen, a salt-forming radical or a carboxyl-blocking group, and \( R^3 \) represents an alkyl, benzyl, or aryl group; with methanol in the presence of copper ions; and thereafter if necessary carrying out one or more of the following steps:

1. removal of any blocking group;
2. converting the product to a pharmaceutically acceptable salt or ester thereof.
COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

(Original)

FOR OFFICE USE

Class Int. Class

Application Number: 85739-82

Lodged:

Complete Specification Lodged:

Accepted:

Published:

Priority:

Related Art:

Name of Applicant: BEECHAM GROUP p.l.c.

Address of Applicant: Beecham House
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       England

Actual Inventor(s):
       JOHN ROBERT MANSFIELD DALES
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Address for Service: DAVIES & COLLISON, Patent Attorneys,
       1 Little Collins Street, Melbourne, 3000.

Complete specification for the invention entitled:

PROCESS FOR THE PREPARATION OF PENAM DERIVATIVES

The following statement is a full description of this invention, including the best method of performing it known to us
This invention relates to a process for the preparation of antibacterially active penam derivatives having a 6a-methoxy substituent.

The present invention provides a process for the preparation of a penam derivative of formula (I):

\[
\text{R}^\text{A}.\text{NH} - \begin{array}{c}
\text{OCH}_3
\end{array} \begin{array}{c}
\text{S}
\end{array} \begin{array}{c}
\text{CH}_3
\end{array}
\]

wherein \( \text{R}^\text{A} \) is hydrogen or a group of formula (Ia):

\[
\text{R}.\text{CH}.\text{CO}-
\]

wherein \( \text{X} \) is \(-\text{CO}_2\text{R}^1\), or \( \text{SO}_2\text{R}^1 \); \( \text{R} \) is \( \text{C}_1-6 \) alkyl, aryl, or heterocyclyl; \( \text{R}^1 \) is hydrogen, or a pharmaceutically acceptable salt-forming ion or ester-forming radical,
and $R^2$ represents hydrogen or a pharmaceutically acceptable salt-forming ion or in vivo hydrolysable ester-forming radical; which process comprises reacting a compound of formula (II):

$$
\text{(II)}
$$

wherein $R^B$ is hydrogen, a removable amino blocking group, or a group of formula (IIa):

$$
R \text{CH.CO-} \begin{array}{c}
\text{Y}
\end{array}
$$

wherein $Y$ is $-\text{CO}_2R^X$ or $-\text{SO}_3R^X$; $R$ is as defined with respect to formula (I) above; $R^X$ represents an ester-forming radical, $R^Y$ represents hydrogen, a salt-forming radical or a carboxyl-blocking group, and $R^3$ represents an alkyl, benzyl, or aryl group; with methanol in the presence of copper ions; and thereafter if necessary carrying out one or more of the following steps:

(i) removal of any blocking group;

(ii) converting the product to a pharmaceutically acceptable salt or ester thereof.
Suitable examples of the group R include $C_1-6$ alkyl; an optionally substituted 5-membered heterocyclic ring containing one or two heteroatoms selected from oxygen, sulphur and nitrogen; phenyl; mono-substituted phenyl where the substituent is halogen, hydroxy, $C_1-6$ alkoxy, nitro, amino, $C_1-6$ alkyl, $C_1-6$ haloalkyl, $C_1-6$ alkylcarbonyloxy, or $C_1-6$ alkyl sulphonylamino (for example $-\text{NHSO}_2\text{CH}_3$); or di-substituted phenyl where the substituents are selected from hydroxy, halogen, methoxy, acetoxy and amino.

Suitably R is phenyl; mono-substituted phenyl where the substituent is fluorine, chlorine, hydroxy, methoxy, nitro, amino, acetoxy or trifluoromethyl; or di-substituted phenyl where the substituents are selected from acetoxy, hydroxy, and methoxy.

Suitable $C_1-6$ alkyl groups for the groups R and R¹ include methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl.

Suitable 5-membered heterocyclic rings for the group R include furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, iso-thiazolyl, imidazolyl; each such group may be substituted by various groups for example halogen, hydroxy, amino, or $C_1-6$ alkyl. Particular examples of such groups include 2- or 3- thienyl and 2-amino-thiazolyl.

Specific examples of the group R include phenyl, 2- or 3- thienyl, p-hydroxyphenyl, p-aminophenyl and p-acetoxyphenyl.
A preferred example of the group \( R^B \) is hydrogen.

Suitable pharmaceutically acceptable salt-forming ions for the groups \( R^1 \) and \( R^2 \) include metal salts, e.g. aluminium, alkali metal salts such as sodium or potassium, alkaline earth metal salts such as calcium or magnesium, and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy-lower alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylamine, \( N,N^-\text{dibenzylethylenediamine, }1^-\text{ephenamine, }N^-\text{ethylpiperidine, }N^-\text{benzyl-}\beta^-\text{phenethylamine, dehydroabietylamine, }N,N'^-\text{bisdehydroabietylethylenediamine, or bases of the pyridine type such as pyridine, collidine or quinoline, or other amines which have been used to form salts with known penicillins.}

The salt-forming ions included within the definition of the group \( R^Y \) include the above mentioned ions and also include other salt-forming ions which are not necessarily pharmaceutically acceptable.

When the group \( R^2 \) represents a pharmaceutically acceptable in vivo hydrolysable ester-forming radical, such esters are those which hydrolyse readily in the human body to produce the parent acid, and include, for example, acyloxyalkyl groups such as acetoxyethyl, pivaloxyloxyethyl, \( \alpha^-\text{acetoxyethyl, }\alpha^-\text{acetoxybenzyl and }\alpha^-\text{pivaloxyloxyethyl groups; alkoxy carbonyloxyalkyl groups, such as ethoxycarbonyloxymethyl and}
α-ethoxycarbonyloxyethyl; dialkylaminoalkyl groups such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl; and lactone groups such as phthalidyl or dimethoxyphthalidyl.

The group R₃ may be any of the ester-forming radicals as specified for the group R₂ and in addition R₃ may represent other pharmaceutically acceptable ester-forming groups such as alkyl, aryl or aralkyl groups any of which may be substituted. Examples of such groups include:

a) C₁₋₆ alkyl such as methyl, ethyl, n- and iso-propyl, n-, sec-, iso- and tert-butyl;

b) substituted C₁₋₆ alkyl wherein the substituent is at least one of: chloro, bromo, fluoro, nitro, C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl, cyano, C₁₋₆ alkylthio, C₁₋₆ alkylamino;

c) phenyl, benzyl or substituted phenyl or benzyl wherein the substituent is at least one of chloro, bromo, fluoro, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkoxy carbonyl, nitro or di-(C₁₋₆) alkylamino.

Preferred ester-forming radicals R₃ include C₁₋₆ alkyl, benzyl, phthalidyl, indanyl, phenyl and mono-, di-, and tri-(C₁₋₆)-alkyl substituted phenyl such as o-, m-, or p-methylphenyl, ethylphenyl, n- or iso-propylphenyl, or n-, sec-, iso- or t-butylphenyl.

Suitable carboxyl-blocking groups for the group R₄ are those which may be readily removed from the carboxylic acid under conventional conditions.
at a later stage of the reaction. Such groups include benzyl, p-methoxybenzyl, 2,4,6-trimethylbenzyl, 3,5-di-t-butyl-4-hydroxybenzyl, benzoylmethyl, p-nitrobenzyl, 4-pyridylmethyl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, t-butyl, t-amyl, diphenylmethyl, triphenylmethyl, adamantyl, 2-benzylxyphenyl, 4-methylthiophenyl, tetrahydrofur-2-yl, tetrahydro-pyran-2-yl, pentachlorophenyl, p-toluenesulphonyl-ethyl, methoxymethyl, a silyl, stannyl or phosphorus-containing group, an oxime radical of formula -N=CHR° where R° is aryl or heterocyclic, or an in vivo hydrolysable ester radical such as defined above.

The carboxyl group may be regenerated from any of the above esters by usual methods appropriate to the particular R° group, for example, acid- and base-catalysed hydrolysis, or by enzymically-catalysed hydrolysis, or by hydrogenation.

When it is desired to produce a compound of formula (I) wherein the group R¹ is hydrogen or a salt-forming ion, by the process of this invention, a compound of formula (II) is employed wherein R° is a blocking group. For the preparation of a compound of formula (I) wherein R¹ is a pharmaceutically acceptable ester-forming radical, a compound of formula (II) is employed wherein R° represents the desired R¹ group.

When the group R represents p-hydroxyphenyl, it may if desired be protected by means of a group which is readily removed chemically after the process of the invention. Such protecting groups include trialkylsilyl groups.
Suitable examples of the alkyl group R³ include C₁₋₆ alkyl groups such as methyl, ethyl, n- or iso-propyl, and n-, sec-, iso, or tert-butyl groups.

A preferred alkyl group for R³ is methyl.

Suitable examples of the aryl group R° include phenyl, optionally substituted with C₁₋₆ alkyl, C₁₋₆ alkoxy, halogen, or nitro. Preferred aryl groups for R° include phenyl, o-, m- or p-methylphenyl, o-, m- or p-nitrophenyl, in particular p-methylphenyl.

A suitable temperature range for the process of this invention is from 0°C to 40°C, conveniently 20°C to 30°C, preferably about 25°C. The time required for the reaction depends on the temperature and the reagents employed. Generally, the reaction is complete within one hour. The methanol used in the process is conveniently employed as a solvent for the reaction mixtures. Other compatible co-solvents may be additionally used if desired, for example, ethyl acetate, methyl isobutyl ketone and preferably isopropyl acetate. It will be appreciated that to give reasonable rate and extent of reaction that the reagents and starting materials should have at least partial solubility in the solvent system employed.

Suitable sources of copper ion include sources of cuprous or cupric ion. Suitable sources of copper ion include for example cuprous or cupric salts of carboxylic acid such as for example, cupric acetate, cuprous acetate, cupric formate, cupric propionate or cupric chloride, cupric sulphate or cupric nitrate.

When the group R° represents hydrogen, it is advantageous to carry out the reaction in the presence of organic base. Suitable organic bases include triethylamine, and preferably pyridine.
The starting material for the process of this invention, ie compound of formula (II) above, where \( R^B \) is not hydrogen, is disclosed, although not claimed, in US Patent No 3,965,093. It may be prepared by acylation, under conventional conditions of the compound (II) where \( R^B \) is hydrogen, ie a 6-amino compound of formula (III) or a salt or ester thereof:

![Formula III]

wherein \( R^3 \) is as defined with respect to formula (II) above. Compounds of formula (III) may be prepared from a Schiff's base derivative as described in US Patent No 3,965,093, or may be prepared by reacting a thiooxime compound of formula (IV):

![Formula IV]

(\( \text{where } R^3 \text{ is as defined with respect to formula (II) above} \)) with a tri(alkyl)phosphate or tri(aryl)phosphate,
followed by treatment with an acid catalyst such as silica gel. That process is described in US Patent No 4,119,778 and in J Amer Chem Soc, 1977, 99, 5504.

The compounds of formula (I) wherein R\textsuperscript{A} is not hydrogen, which are prepared by the process of this invention have good antibacterial activity, as disclosed in British Patents Nos 1,538,051 and 1,538,052. The compounds of formula (I) wherein R\textsuperscript{A} is hydrogen are useful as chemical intermediates.

The following Examples illustrate the process of this invention.
Example 1

Preparation of benzyl 6α-amino-6α-methoxypenicillanate from benzyl 6α-amino-6α-methylthiopenicillanate

Benzyl 6α-amino-6α-methylthiopenicillanate (17.6 g, 0.05 mole), methanol (140 ml) and pyridine (10 ml) were dissolved in isopropyl acetate (300 ml) and the solution warmed to 25°C. Cupric acetate monohydrate (11.03 g, 0.055 mole) was added and the solution stirred and maintained at 25°C for 40 minutes. The reaction mixture was cooled to 0°C, celite was added and the resulting slurry was filtered through a celite pad. The celite cake was washed with isopropyl acetate (2 x 50 ml) and the wash solution was combined with the filtrate. The bulked organic phases were washed with two water/saturated brine mixtures (300 ml/100 ml) and (100 ml/100 ml). The solution was then washed with a 1% solution of sodium sulphide (200 ml) and the black emulsion which formed was filtered through a celite pad. The celite cake was washed with an isopropyl acetate/water mixture (150 ml/150 ml) and the wash solution combined with the filtrate. Brine (300 ml) was added to the filtrate to improve separation and the organic layer was removed and washed with 0.1% sodium sulphide solution (2 x 100 ml), water (2 x 100 ml) and a brine/water mixture (50 ml/50 ml). The isopropyl acetate solution was dried over magnesium sulphate. The solution was filtered and the magnesium sulphate cake was washed with isopropyl acetate (2 x 50 ml). The wash solution was combined with the filtrate and the resulting solution evaporated to an orange oil (water bath temperature 35°C).

The weight yield was 20.1 g of 77.4% purity 6-methoxy-penicillin having an activity yield of 92.6%.
Example 2

**Preparation of benzyl 6β-amino-6α-methoxypenicillanate from benzyl 6β-amino-6α-methylthiopenicillanate toluene-4-sulphonic acid salt**

Benzyl 6β-amino-6α-methylthiopenicillanate toluene-4-sulphonic acid salt (26.25 g 0.05 mole) was stirred with isopropyl acetate (150 ml) and saturated sodium bicarbonate solution (100 ml) until all the solid had dissolved. The organic phase was separated and the aqueous phase extracted with isopropyl acetate (2 x 50 ml). The organic phases were combined and washed with water (50 ml) and brine (50 ml) and then dried over magnesium sulphate. The solution was filtered and the magnesium sulphate cake was washed with isopropyl acetate (50 ml).

The resulting isopropyl acetate solution containing the benzyl 6β-amino-6α-methylthiopenicillanate was reacted according to the conditions given in Example 1.

The weight yield was 21.7 g of 6.5% purity 6-methoxy-penicillin having an activity yield of 88.5%.
Example 3

Preparation of benzyl 6β-amino-6α-methoxypenicillanate from benzyl 6β-amino-6α-(4-methylphenylthio)penicillanate benzene sulphonic acid salt

Benzyl 6β-amino-6α-(4-methylphenylthio) penicillanate benzene sulphonic acid (29.3 g 0.05 mole) was subjected to the neutralisation and extraction procedure described in Example 2.

The resulting isopropyl acetate solution was reacted according to the conditions given in Example 1 except that the reaction time at 25°C was extended to 80 minutes.

The weight yield was 19.2 g of 70.8% purity 6-methoxy-penicillin having an activity yield of 80.9%.

Example 4

Preparation of benzyl 6β-amino-6α-methoxypenicillanate from benzyl 6β-amino-6α-methylthiopenicillanate and cupric acetate

The reaction was carried out as Example 1 except that ethyl acetate was used instead of isopropyl acetate as the reaction solvent.

The weight yield was 20.7 g of 73.9% purity 6-methoxy-penicillin having an activity yield of 91.0%.
Example 5

Preparation of benzyl 6β-amino-6α-methoxypenicillanate from benzyl 6β-amino-6α-methylthiopenicillanate and cupric acetate in methanol as the only reaction solvent

Benzyl 6β-amino-6α-methylthiopenicillanate (17.6g, 0.05 mole) was dissolved in a mixture of methanol (440 ml) and pyridine (10 ml). The solution was warmed and stirred at 25°C and treated with cupric acetate monohydrate (11.03g, 0.055 mole). The solution was stirred and maintained at 25°C for 5 minutes. The reaction mixture was evaporated to an oil (water bath temperature 35°C). The oil was slurried in isopropyl acetate (300 ml) for 10 minutes. The slurry was cooled to 0°C, celite was added and the resulting slurry was filtered through a celite pad. The celite cake was washed with isopropyl acetate (2 x 50 ml) and the washed solution was combined with the filtrate. The bulked organic phases were washed with two water/saturated brine mixtures (300 ml/100 ml) and (100 ml/100 ml), water (2 x 100 ml) and a brine/water mixture (50 ml/50 ml). The isopropyl acetate solution was dried over magnesium sulphate. The solution was filtered and the magnesium sulphate cake was washed with isopropyl acetate (2 x 50 ml). The washed solution was combined with the filtrate and the resulting solution evaporated to an orange oil. (Water bath temperature 35°C).

The weight yield was 21.6g of 60.9% purity 6-methoxypenicillin having an activity yield of 78.3%.
Example 6

Preparation of benzyl $\beta$-amino-$\alpha$-methoxypenicillanate from benzyl $\beta$-amino-$\alpha$-methylthiopenicillanate and cuprous acetate

The isopropyl acetate solution of benzyl $\beta$-amino-$\alpha$-methylthiopenicillanate was reacted according to the conditions in Example 1 except that cuprous acetate ($95\%, 7.1\text{ g}, 0.05$ mole) was used instead of cupric acetate monohydrate, and the reaction time at $25^\circ\text{C}$ was reduced to 15 minutes.

The weight yield was $20.9$ g of $71.1\%$ purity $\beta$-methoxypenicillin having an activity yield of $88.5\%$.

Example 7

Preparation of benzyl $\beta$-amino-$\alpha$-methoxypenicillanate from benzyl $\beta$-amino-$\alpha$-methylthiopenicillanate and cupric formate

The isopropyl acetate solution of benzyl $\beta$-amino-$\alpha$-methylthiopenicillanate was reacted according to the conditions in Example 1 except that cupric formate tetrahydrate ($12.4$ g, $0.055$ mole) was used instead of cupric acetate monohydrate and the reaction time at $25^\circ\text{C}$ was reduced to 30 minutes.

The weight yield was $19.8$ g of $74.2\%$ purity $\beta$-methoxypenicillin having an activity yield of $87.5\%$. 
Example 8

Preparation of benzyl 6α-amino-6α-methyloxypenicillanate from benzyl 6α-amino-6α-methylthiopenicillanate and cupric sulphate

The isopropyl acetate solution of benzyl 6α-amino-6α-methylthiopenicillanate was reacted according to the conditions in Example 1 except that cupric sulphate pentahydrate (13.73g, 0.055 mole) was used instead of cupric acetate monohydrate and the reaction time at 25°C was extended to 50 minutes. The product was isolated as a brown oil.

The weight yield was 16.9g of 14.6% purity 6-methoxypenicillin having an activity yield of 14.7%.

Example 9

Preparation of benzyl 6α-amino-6α-methyloxypenicillanate from benzyl 6α-amino-6α-methylthiopenicillanate and cupric nitrate

The isopropyl acetate solution of benzyl 6α-amino-6α-methylthiopenicillanate was reacted according to the conditions in Example 1 except that cupric nitrate trihydrate (13.29g, 0.055 mole) was used instead of cupric acetate monohydrate and the reaction time at 25°C was reduced to 5 minutes. The product was isolated as a brown oil.

The weight yield was 17.3 g of 20.9% purity 6-methoxypenicillin having an activity yield of 21.5%.
Example 10

Preparation of benzyl 68-amino-6a-methoxypenicillanate from benzyl 68-amino-6a-methylthiopenicillanate and cupric chloride

The isopropyl acetate solution of benzyl 68-amino-6a-methylthiopenicillanate was reacted according to the conditions in Example 1 except that cupric chloride (7.39 g, 0.055 mole) was used instead of cupric acetate monohydrate, and the reaction time at 25°C was extended to 4 hours. The product was isolated as a brownish sticky solid.

The weight yield was 16.8 g of 6.3% purity 6-methoxypenicillin having an activity yield of 6.3%.

Example 11

Preparation of benzyl 68-amino-6a-methoxypenicillanate from benzyl 68-amino-6a-methylthiopenicillanate and cupric propionate

The isopropyl acetate solution of benzyl 68-amino-6a-methylthiopenicillanate was reacted according to the conditions in Example 1, except that cupric propionate (11.5 g, 0.055 mole) was used instead of cupric acetate monohydrate and the reaction time at 25°C was reduced to 30 minutes.

The weight yield was 19.2 g of 65.0% purity 6-methoxy- penicillin having an activity yield of 74.5%.
Example 12
Preparation of benzyl 6β-amino-6α-methoxypenicillanate from benzyl 6β-amino-6α-methylthiopenicillanate and cupric acetate without pyridine present

The isopropyl acetate solution of benzyl 6β-amino-6α-methylthiopenicillanate was reacted according to the conditions in Example 1, except that pyridine was omitted from the reaction.

The weight yield was 20.8 g of 76.5% purity methoxy penicillin having an activity yield of 76.5%
CLAIMS
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A process for the preparation of a penam derivative of formula (I):

![Chemical Structure](image)

wherein R^A is hydrogen or a group of formula (Ia):

![Chemical Structure](image)

wherein X is -CO_2R^1, or SO_3R^1; R is C_1-6 alkyl, aryl, or heterocyclyl; R^1 is hydrogen, or a pharmaceutically acceptable salt-forming ion or ester-forming radical, and R^2 represents hydrogen or a pharmaceutically acceptable salt-forming ion or in vivo hydrolysable ester-forming radical; which process comprises reacting a compound of formula (II):

![Chemical Structure](image)
wherein \( R^B \) is hydrogen, a removable amino blocking group, or a group of formula (IIa):

\[
R.CH.CO- \quad (\text{IIa})
\]

wherein \( Y \) is \(-\text{CO}_2R^X\) or \(-\text{SO}_3R^X\); \( R \) is as defined with respect to formula (I) above; \( R^X \) represents an ester-forming radical, \( R^Y \) represents hydrogen, a salt-forming radical or a carboxyl-blocking group, and \( R^3 \) represents an alkyl, benzyl, or aryl group; with methanol in the presence of copper ions; and thereafter if necessary carrying out one or more of the following steps:

(i) removal of any blocking group;

(ii) converting the product to a pharmaceutically acceptable salt or ester thereof.

2. A process as claimed in claim 1 wherein \( R \) is \( \text{C}_{1-6}\text{-alkyl} \); an optionally substituted 5-membered heterocyclic ring containing one or two heteroatoms selected from oxygen, sulphur and nitrogen; phenyl; mono-substituted phenyl where the substituent is halogen, hydroxy, \( \text{C}_{1-6}\text{-alkoxy} \), nitro, amino, \( \text{C}_{1-6}\text{-alkyl} \), \( \text{C}_{1-6}\text{-haloalkyl} \), \( \text{C}_{1-6}\text{-alkylcarbonyloxy} \), or \( \text{C}_{1-6}\text{-alkylsulphonlamino} \); or di-substituted phenyl where the substituents are selected from hydroxy, halogen, methoxy, acetoxy and amino.
triethylamine, and preferably pyridine.

3. A process as claimed in claim 1 or claim 2 wherein R is phenyl; mono-substituted phenyl where the substituent is fluorine, chlorine, hydroxy, methoxy, nitro, amino, acetoxy or trifluoromethyl; or di-substituted phenyl where the substituents are selected from acetoxy, hydroxy, and methoxy.

4. A process as claimed in claim 1 wherein R is hydrogen.

5. A process as claimed in any one of claim 1 to 4 wherein R is C1-6 alkyl.

6. A process as claimed in any one of claim 1 to 5 wherein R is methyl.

7. A process as claimed in any one of claim 1 to 4 wherein R is phenyl, optionally substituted with C1-6 alkyl, C1-6 alkoxy, halogen or nitro.

8. A process as claimed in claim 7 wherein R is phenyl.

9. A process as claimed in any one of claim 1 to 8 wherein the source of copper ion is a cuprous or cupric salt of a carboxylic acid.

10. A process as claimed in any one of claim 1 to 9 wherein the source of copper ion is cuprous or cupric acetate.
11. A process for the preparation of a penam derivative, substantially as hereinbefore described with reference to the Examples.

12. Penam derivatives when prepared by the process claimed in any one of claims 1 to 11.

13. The steps or features disclosed herein or any combination thereof.

DATED this 8 day of July 1982.

DAVIES & COLLISON
Patent Attorneys for
BEECHAM GROUP p.l.c.
END