AUSTRALIA
Patents Act 1990
REQUEST FOR A STANDARD PATENT
AND NOTICE OF ENTITLEMENT

The Applicant identified below requests the grant of a patent to the nominated person identified below for an invention described in the accompanying standard complete patent specification.

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[54]Invention Title:

INTERMEDIATES USEFUL IN THE PREPARATION OF HETEROARYLHYDRAZIDE DERIVATIVES OF MONOCYCLIC BETA-LACTAM ANTIBIOTICS

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[31,33,32]This application is to be made by virtue of Section 39; being a divisional of application no. 34847/89.

Applicant states the following:

The nominated person is the assignee of the actual inventor(s)

The nominated person is not an opponent or eligible person described in Section 33-36 of the Act.

11 October 1991

E.R. Squibb & Sons, Inc.
By PHILLIPS ORMONDE & FITZPATRICK
Patent Attorneys

By

Our Ref: 231391

6000q
1. A compound of the formula

![Chemical Structure](IV)

wherein $R_7$ is hydrogen, fluorine, chlorine, or bromine.
AUSTRALIA

Patents Act

COMPLETE SPECIFICATION
(ORIGINAL)

Application Number: 
Lodged:

Complete Specification Lodged: 
Accepted: 
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Related Art:

Name of Applicant: 
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Invention Title:
INTERMEDIATES USEFUL IN THE PREPARATION OF HETEROAROYLHYDRAZIDE DERIVATIVES OF MONOCYCLIC BETA-LACTAM ANTIBIOTICS

Our Ref : 231391
POF Code: 14C109/43804

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):
Intermediates useful in the Preparation of Heteroaryloxyhydrazide Derivatives of Monocyclic Beta-Lactam Antibiotics

The present application is a divisional application of Australian Patent Application 34847/89, the entire disclosure of which is incorporated herein by reference.

AU 34847/89 discloses compounds having the formula

\[ \text{H}_2\text{N} \]

and pharmaceutically acceptable salts thereof and possessing antibacterial activity. In formula I, and throughout the specification, the symbols are as defined below.

- \( R_1 \) and \( R_2 \) are the same or different and each is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, substituted phenyl or a 4, 5, 6 or 7-membered heterocycle (hereinafter referred to as \( R_a \)), or one of \( R_1 \) and \( R_2 \) is hydrogen and the other is azido, halomethyl, dihalomethyl, trihalomethyl, alkoxy carbonyl, 2-phenylethenyl, 2-phenylethynyl, carboxyl, \(-\text{CH}_2\text{X}_1\) [wherein \( \text{X}_1 \) is azido, amino \((-\text{NH}_2\)), hydroxy, carboxyl, alkoxy carbonyl, alkanoylamino, phenylcarbonylamino, (substituted phenyl) carbonylamino, alkylsulfonyloxy, phenyl sulfonyloxy, (substituted phenyl) sulfonyloxy,
phenyl, substituted phenyl, cyano, \(-A-C-NX_6^X_7\), \(-S-X_2\), or
\(-O-X_2\) (wherein \(A\), \(X_2\), \(X_6\) and \(X_7\) are as hereinafter
defined)], \(-S-X_2\) or \(-O-X_2\) [wherein \(X_2\) is alkyl,
substituted alkyl, phenyl, substituted phenyl, phenylalkyl,
(substituted phenyl)alkyl, alkanoyl, substituted alkanoyl,
phenylalkanoyl, (substituted phenyl)alkanoyl, phenylcarbonyl,
(substituted phenyl)carbonyl, or heteroarylcarbonyl], and in
the case of when \(X_1\) is \(-O-X_2\) then \(X_2\) can also be
alkylideneamino, alkanoylamino, carboxyalkylideneamino,
alkeysulphonylamino, alkoxy carbonylalkylsulphonylamino or
N,N-cyclodialkanoylamino,

\[
\begin{array}{c}
\begin{array}{c}
X_3 \\
O-C-X_4
\end{array}
\end{array}
\text{or}\ 
\begin{array}{c}
\begin{array}{c}
X_3 \\
S-C-X_4
\end{array}
\end{array}
\text{[wherein one of } X_3 \text{ and } X_4 \text{ is}
\begin{array}{c}
\begin{array}{c}
X_5 \\
O
\end{array}
\end{array}
\text{hydrogen and the other is hydrogen or alkyl, or } X_3 \text{ and } X_4
\text{ when taken together with the carbon atom to which they are}
\text{attached form a cycloalkyl group; and } X_5 \text{ is formyl,
akanoyl, phenyl carbonyl, (substituted phenyl) carbonyl,
phenyl alkyl carbonyl, (substituted phenyl) alkyl carbonyl,
}
\text{carboxyl, alkoxy carbonyl, aminocarbonyl (NH}_2-C-),
\text{(substituted amino) carbonyl, or cyano (-C=N)}], \text{ or}
\begin{array}{c}
\begin{array}{c}
X_6 \\
O
\end{array}
\end{array}
\text{A-C-NX}_6^X_7 \text{ [wherein } A \text{ is } -CH=CH-, -(CH}_2_\text{)}^m,-,
-(CH}_2_\text{)}^m-O-, -(CH}_2_\text{)}^m-NH-, \text{ or } -CH}_2_\text{)}^m-S-CH}_2_, \text{ } m \text{ is 0, 1
or 2, and } X_6 \text{ and } X_7 \text{ are the same or different and each is}
\text{hydrogen, alkyl, phenyl or substituted phenyl, or } X_6 \text{ is}
\text{hydrogen and } X_7 \text{ is amino, substituted amino, alkanoylamino
or alkoxy, or } X_6 \text{ and } X_7 \text{ when taken together with the}
\text{nitrogen atom to which they are attached form a 4, 5, 6 or 7-
membered heterocycle];}
\end{array}
\end{array}
\end{array}
\text{R}_3 \text{ and } R_4 \text{ are the same or different and each is}
\text{hydrogen or alkyl or } R_3 \text{ and } R_4 \text{ together with the carbon}
\text{atom to which they are attached are cycloalkyl;}
\text{R}_5 \text{ and } R_6 \text{ are the same or different and each is}
\text{hydrogen or alkyl or } R_5 \text{ and } R_6 \text{ taken together with the}
\text{nitrogen atoms to which they are attached form a}
1,2-diazacyclobutane, 1,2-diazacyclopentane, 1,2-diazacyclo-
hexane, or 1,2-diazacycloheptane ring.

R is hydrogen, fluorine, chlorine or bromine.

X is a nitrogen atom or CH;

Y is a nitrogen atom or CH;

provided that either X or Y is always a nitrogen atom;

Listed below are definitions of various terms used to describe the β-lactams of this invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or as part of a larger group.

The terms "alkyl" and "alkoxy" refer to both straight and branched chain groups. Those groups having 1 to 10 carbon atoms are preferred.

The term "cycloalkyl" refers to cycloalkyl groups having 3, 4, 5, 6 or 7 carbon atoms.

The terms "substituted alkyl" refers to alkyl groups substituted with one or more (preferably 1, 2 or 3) azido, amino (-NH₂), halogen, hydroxy, carboxy, cyano, alkoxycarbonyl, aminocarbonyl, alkanoyloxy, alkoxy, phenyloxy, (substituted phenyl)oxy, Rₐ-oxy, mercapto, alkylthio, phenylthio, (substituted phenyl)thio, alkylsulfinyl, or alkylsulfonyl groups.

The terms "alkanoyl", "alkenyl", and "alkynyl" refer to both straight and branched chain groups. Those groups having 2 to 10 carbon atoms are preferred.

The term "substituted alkanoyl" refers to alkyl groups substituted with one or more (preferably 1, 2 or 3) azido, amino (-NH₂), halogen, hydroxy, carboxy, cyano, alkoxycarbonyl, aminocarbonyl, alkanoyloxy, alkoxy, phenyloxy, (substituted phenyl)oxy, mercapto, alkylthio, phenylthio, (substituted phenyl)thio, alkylsulfinyl or alkylsulfonyl groups.

The term "substituted phenyl" refers to a phenyl group substituted with 1, 2 or 3 amino (-NH₂), halogen, hydroxyl, trifluoromethyl, alkyl (of 1 to 4 carbon atoms), alkoxy (of 1 to 4 carbon atoms), alkanoyloxy, aminocarbonyl, or carboxy groups.

The expression "a 4,5,6 or 7-membered heterocycle" (referred to as "Rₐ") refers to substituted and unsubstituted, aromatic and non-aromatic groups containing one
or more (preferably 1, 2 or 3) nitrogen, oxygen or sulfur atoms. Exemplary substituents are oxo (=O), halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, alkyl of 1 to 4 carbons, alkoxy of 1 to 4 carbons, alkylsulfonyl, phenyl, substituted phenyl, 2-furfurylideneamino (CH=N\(\text{-}\)), benzylideneamino and substituted alkyl groups (wherein the alkyl group has 1 to 4 carbons). One type of "4,5,6 or 7-membered heterocycle" is the "heteroaryl" group. The term "heteroaryl" refers to those 4,5,6 or 7-membered heterocycles which are aromatic. Exemplary heteroaryl groups are substituted and unsubstituted pyridinyl, furanyl, pyrrolyl, thiienyl, 1,2,3-triazolyl, 1,2,4-triazolyl, imidazolyl, thiazolyl, thiadiazolyl, pyrimidinyl, oxazolyl, triazinyl, and tetrazolyl. Exemplary nonaromatic heterocycles (i.e., fully or partially saturated heterocyclic groups) are substituted and unsubstituted azetidinyl, oxetanyl, thietanyl, piperidinyl, piperazinyl, imidazolidinyl, oxazolidinyl, pyrrolidinyl, tetrahydropyrimidinyl, dihyrothiazolyl and hexahydroazepinyl. Exemplary of the substituted 4,5,6 or 7-membered heterocycles are 1-alkyl-3-azetidinyl, 2-oxo-1-imidazolidinyl, 3-alkylsulfonyl-2-oxo-1-imidazolidinyl, 3-benzylideneamino-2-oxo-1-imidazolidinyl, 3-alkyl-2-oxo-1-imidazolidinyl, 3-phenyl (or substituted phenyl)-2-oxo-1-imidazolidinyl, 3-benzyl-2-oxo-1-imidazolidinyl, 3-(2-aminoethyl)-2-oxo-1-imidazolidinyl, 3-amino-2-oxo-1-imidazolidinyl, 3-[[(alkoxycarbonyl)amino]-2-oxo-1-imidazolidinyl, 3-[(alkoxycarbonyl)-amino]ethyl]-2-oxo-1-imidazolidinyl, 2-oxo-1-pyrrolidinyl, 2-oxo-3-oxazolidinyl, 4-hydroxy-6-methyl-2-pyrimidinyl, 2-oxo-1-hexahydroazepinyl, 2-oxo-3-pyrrolidinyl, 2-oxo-3-tetrahydrofurany1, 2,3-dioxo-1-piperazinyl, 2,5-dioxo-1-piperazinyl, 4-alkyl-2,3-dioxo-1-piperazinyl, and 4-phenyl-2,3-dioxo-1-piperazinyl.

The term "substituted amino" refers to a group having the formula -NX\(\text{X}_{8}\)X\(\text{X}_{9}\) wherein X\(\text{X}_{8}\) is hydrogen, alkyl, phenyl, substituted phenyl, phenylalkyl or (substituted phenyl)alkyl, and X\(\text{X}_{9}\) is alkyl, phenyl, substituted phenyl, phenylalkyl, (substituted phenyl)alkyl, hydroxy, cyano, alkoxy, phenylalkoxy, or amino (-NH\(_2\)).

The compounds of AU 34847/89 invention can be
prepared by coupling a compound having the formula

![Chemical Structure](image1.png)

II

with an anhydride of the formula

![Chemical Structure](image2.png)

III

in such solvents as dimethyl formamide or dichloromethane in the presence of a tertiary amine base such as triethylamine or tributylamine.

When X is not Y, two compounds of formula I can be obtained wherein X is nitrogen and Y is CH or X is CH and Y is nitrogen.

The compounds of the formula III wherein X and Y are nitrogen are prepared by reacting compounds of the formula

![Chemical Structure](image3.png)

XV
wherein X and Y are nitrogen with a dehydrating agent such as dicyclohexylcarbodiimide in a solvent such as dimethylformamide, or by heating with a dehydrating agent such as thionyl chloride or phosphorous oxychloride.

Compounds of the formula XV wherein X and Y are nitrogen are prepared by methods of deprotection well known in the art from compounds of the formula

![Diagram XVI](image)

wherein X and Y are nitrogen and R₉ is arylmethyl (such as benzyl or p-methoxybenzyl; deprotection can be achieved by heating with a strong acid such as hydrochloric acid, or by hydrogenolysis over a catalyst such as palladium or charcoal), acyl (such as acetyl or propanoyl; deprotection can be achieved by treating with a strong base such as sodium hydroxide in a solvent such as water or methanol), aroyl (such as benzoyl or p-nitrobenzoyl; deprotection can be achieved by treating with a strong base such as sodium hydroxide in a solvent such as water or methanol), or wherein R₉ taken together form a cyclic ketal (such as 2,2-propylidene or cyclohexylidene; deprotection can be achieved by heating with a strong acid such as hydrochloric acid).

Compounds of the formula XV wherein X and Y are nitrogen are novel and form this invention.

Therefore according to the present invention there is provided a compound of the formula

![Diagram IV](image)
wherein $R_7$ is hydrogen, fluorine, chlorine, or bromine.

Compounds of the formula XVI wherein $R_7$ is hydrogen and $R_9$ is methyl or $n$-butyl, and the ethyl and $n$-butyl esters of these compounds are reported in the literature (S. Oguchi, Nippon Kagaku Zasshi 86, 246 (1965); Chem. Abstracts 63:4295e).

Compounds of the formula XVI wherein $X$ and $Y$ are nitrogen and $R_7$ is hydrogen are prepared from compounds of the formula

![Formula XVII](image)

by heating with dihydroxytartaric acid in a solvent such as water, or in a mixture of water and an organic solvent such as ethanol or dioxane.

Compounds of the formula XVII are prepared from compounds of the formula

![Formula XVIII](image)

by methods of reduction well known in the art, such as hydrogenation in a solvent such as ethylacetate or ethanol over a catalyst such as platinum black or palladium on charcoal, or by treating with a reducing agent such as stannous chloride in a solvent such as ethyl acetate.

Compounds of the formula XVIII are either known or are prepared from known compounds of the formula

![Formula XIX](image)

by methods of nitration well known in the art (such as with fuming nitric acid in a solvent such as acetic acid).
The following examples are specific embodiments of this invention.

**Example 1**

**Preparation of 6,7-Dihydroxyquinoxaline-2,3-dicarboxylic acid**

2,2-Dimethyl-1,3-dioxolo[4,5g]-quinoxaline-6,7-dicarboxylic acid (the preparation of which is illustrated in AU 34847/89) (145 mg, 0.5 mmole) was slurried in 10 ml of concentrated HCl and heated at 75°C for 1 hour with stirring. On initial heating, the compound dissolved, then a precipitate eventually formed. The slurry was evaporated to dryness in vacuo. The residue was initially soluble in water but formed a yellow-brown precipitate within a few minutes. The water was evaporated again and the residue was dried in vacuo for 3 hours to give the title compound as a brown solid, 125 mg, m.p. > 300°C.

1H-NMR (DMSO): δ = 7.27 (s,2H).

**Example 2**

**Preparation of 5,8-Dichloro-6,7-dihydroxyquinoxaline-2,3-dicarboxylic acid**

4,9-Dichloro-1,3-dioxolo[4,5g]-quinoxaline-6,7-dicarboxylic acid (the preparation of which is illustrated in AU 34847-89) (359 mg, 1.0 mmole) was slurried in concentrated HCl and heated to 70°C for 11 hours. The volatile components of the resulting slurry were removed in vacuo, water was added and evaporated three times. The resulting solid was dissolved in DMF and evaporated, taken up in acetonitrile and evaporated twice and finally azotroped with benzene to give the title compound as an orange solid which contains some of the starting compound as judged by TLC and C-13 NMR.

13C-NMR (DMSO): δ = 112.9, 134.5, 142.3, 149.7, 166.2.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula

\[ \text{IV} \]

wherein \( R_7 \) is hydrogen, fluorine, chlorine, or bromine.

2. A compound according to claim 1, 6,7-dihydroxy-2,3-quinoxaline dicarboxylic acid.

3. A compound according to claim 1, 5,8-dichloro-6,7-dihydroxy-2,3-quinoxaline-dicarboxylic acid.

DATED: 11th October, 1991

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