APPLICATION FOR A (c) STANDARD/PATENT

L/Wc (e) BRISTOL-MYERS COMPANY

of (a) 345 Park Avenue, New York 10154, United States of America

hereby apply for the grant of a (c) Standard/Patent for an invention entitled

"CARBAPENEM ANTIBIOTICS"

which is described in the accompanying (g) complete specification.

(Note: The following applies only to Convention applications)

Details of basic application(s)

<table>
<thead>
<tr>
<th>Application No.</th>
<th>Country</th>
<th>Filing Date</th>
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</thead>
<tbody>
<tr>
<td>656,838</td>
<td>United States of America</td>
<td>2 October, 1984</td>
</tr>
</tbody>
</table>

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Dated 10 September, 1985

By its Patent Attorneys:

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AS:DN

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DECLARATION FOR A PATENT APPLICATION

__INSTRUCTIONS__

(1) Insert "Convention" if applicable.
(2) Insert FULL name(s) of applicant(s).
(3) Insert "of addition" if applicable.
(4) Insert TITLE of invention.
(5) Insert FULL name(s) AND address(es) of actual inventor(s).
(6) Insert country, filing date, and basic applicant(s) as follows:

BRISTOL-MERYS COMPANY

Filing Date 2 October, 1984.

I, Isaac Jarkovsky, Assistant General Counsel - Patents
of the Applicant Company, of 345 Park Avenue, New
York, New York 10014, United States of America
do solemnly and sincerely declare as follows:

1. I am/We are the applicant(s).
   (Or, in the case of an application by a body corporate)

2. I am/We are the actual inventor(s) of the invention.
   (Or, where the applicant(s) is/are not the actual inventor(s))

3. The basic application(s) for patent or similar protection on which the application is based
   is/are identified by country, filing date, and basic applicant(s) as follows:
   United States October 2, 1984 Choung Un Kim of America.

4. The basic application(s) referred to in paragraph 3 hereof were/ were the first application(s)
   made in a Convention country in respect of the invention the subject of the application.

Declared at New York, N.Y., U.S.A.
Dated September 27, 1985

To: The Commissioner of Patents

Isaac Jarkovsky
Assistant General Counsel - Patents

P10781

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trade Mark Attorneys
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Melbourne, Australia
DOCUMENTS LODGED WITH THIS APPLICATION ARE UNSUITABLE FOR REPRODUCTION AND MAY BE INSPECTED AT THE PATENT OFFICE A.C.T.
1. A compound of the formula

wherein R^8 is hydrogen and R^1 is selected from the group consisting of hydrogen; substituted and unsubstituted: alkyl, alkenyl and alkynyl, having from 1-10 carbon atoms; cycloalkyl and cycloalkylalkyl, having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moieties; phenyl; aralkyl, aralkenyl and aralkynyl wherein the aryl moiety is phenyl and the aliphatic portion has 1-6 carbon atoms; heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl wherein the hetero atom or atoms
in the above-named heterocyclic moieties are selected from the group consisting of 1-4 oxygen, nitrogen or sulfur atoms and the alkyl moieties associated with said heterocyclic moieties have 1-6 carbon atoms; wherein the substituent or substituents relative to the above-named radicals are independently selected from the group consisting of

\[ \text{C}_{1-6} \text{ alkyl optionally substituted by amino, halo, hydroxy or carboxyl halo} \]

-OR³
-OCNR³R⁴
-CNR³R⁴
-NR³R⁴

NR³

NR³R⁴
wherein, relative to the above-named substituents, the groups $R^3$ and $R^4$ are independently selected from hydrogen; alkyl, alkenyl and alkynyl; having from 1-10 carbon atoms; cycloalkyl, cycloalkylalkyl and alkylcycloalkyl, having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl noieties; phenyl; aralkyl, aralkenyl and aralkynyl wherein the aryl moiety is phenyl and the aliphatic portion has 1-6 carbon atoms; and
heteroaryl, heteroaralkyl, heterocycl and heterocyclalkyl wherein the hetero atom or atoms in the above-named heterocyclic moieties are selected from the group consisting of 1-4 oxygen, nitrogen or sulfur atoms and the alkyl moieties associated with said heterocyclic moieties have 1-6 carbon atoms, or R³ and R⁴ taken together with the nitrogen to which at least one is attached may form a 5-or 6-membered nitrogen-containing heterocyclic ring; R⁹ is as defined for R³ except that it may not be hydrogen; or wherein R¹ and R⁸ taken together represent C₂-C₁₀ alkylidene or C₂-C₁₀ alkylidene substituted by hydroxy; A is C₂-C₆ straight or branched chain alkylene; R² is hydrogen, an anionic charge or a conventional readily removable carboxyl protecting group, providing that when R² is hydrogen or a protecting group, there is also present a counter anion.

R¹⁵ is selected from the group consisting of substituted and unsubstituted: alkyl, alkenyl and alkynyl, having from 1-10 carbon atoms; cycloalkyl, cycloalkylalkyl and alkycycloalkyl, having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moieties; spirocycloalkyl having 3-6 carbon atoms; phenyl; aralkyl, aralkenyl and aralkynyl wherein the aryl moiety is phenyl and the aliphatic portion has 1-6 carbon atoms; heteroaryl, heteroaralkyl, heterocycl and heterocyclalkyl wherein the hetero atom or atoms in the above-named heterocyclic moieties are selected from the group consisting of 1-4 oxygen, nitrogen and sulfur atoms and the alkyl moieties associated with said heterocyclic moieties have 1-6 carbon atoms; wherein the substituent or substituents relative to the above-named radicals are selected from the group consisting of: amino, mono-, di- and trialkylamino, hydroxyl, alkoxyl, mercapto, alkylthio, phenylthio, sulfamoyl, amidino, guanidino, nitro, chloro, bromo, fluoro, cyano and carboxyl; and wherein the alkyl moieties of the above-recited substituents have 1-6 carbon atoms; and R¹⁰ and R¹¹ each independently represents
(a) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cyclo-alkyl or cycloalkylalkyl having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moiety, said alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkyl-alkyl group being optionally substituted by 1-3 substituents independently selected from hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkanoyloxy, carboxy, C_1-C_6 alkoxycarbonyl, amino, C_1-C_6 alkylamino, di(C_1-C_6) alkylamino, C_1-C_6 alkanoylamino, phenyl, phenyl substituted by 1-3 halo, C_1-C_6 alkoxy, C_1-C_6 alkyl, carboxy, carboxy(C_1-C_6) alkyl, amino, C_1-C_6 alkylamino, di(C_1-C_6) alkylamino or di-(C_1-C_6) alkylamino(C_1-C_6) alkyl, halo or oxo;
(b) phenyl optionally substituted by 1-3 halo, C_1-C_6 alkoxy, C_1-C_6 alkyl, carboxy, amino, C_1-C_6 alkylamino or di(C_1-C_6) alkylamino groups;
(c) heterocyclyl or heterocyclylalkyl wherein the hetero-cyclic moiety is a 4-6 membered ring having 1-3 hetero atoms selected from O, N and S and the alkyl moiety has 1-6 carbon atoms, said heterocyclyl or heterocyclylalkyl ring being optionally substituted by 1-3 C_1-C_6 alkyl or C_1-C_6 alkoxy groups; or
(d) heteroaryl or heteroaralkyl wherein the heterocyclic moiety is a 5-6 membered aromatic ring having 1-3 hetero atoms selected from O, N and S and the alkyl moiety has 1-6 carbon atoms, said heteroaryl or heteroaralkyl ring being optionally substituted by 1-3 C_1-C_6 alkyl, C_1-C_6 alkoxy, carboxy, carboxy(C_1-C_6) alkyl, amino, C_1-C_6 alkylamino, di(C_1-C_6) alkylamino, amino(C_1-C_6) alkyl or di-(C_1-C_6) alkylamino(C_1-C_6) alkyl groups; or wherein R^{10} and R^{11} taken together with the
to which they are attached represent a 4-6 member sulfur-containing heterocyclic ring containing 0-2 double bonds and 0-2 additional heteroatoms selected from O, N and S, said ring being attached to A through a sulfur atom, thereby forming a sulfonium group, said heterocyclic ring being optionally substituted by 1-3 substituents independently selected from:

C₁-C₆ alkyl optionally substituted by 1-3 hydroxy, C₁-C₆ alkoxy, carboxy, halo, amino, C₁-C₆ alkylamino or di(C₁-C₆) alkylamino groups, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkanoyloxy, amino, C₁-C₆ alkylamino, di(C₁-C₆)- alkylamino, C₁-C₆ alkanoylamino, carboxy, C₁-C₆ alkoxy-carbonyl, halo, oxo or phenyl; or wherein said heterocyclic ring

\[
\begin{array}{c}
\text{R}^{10} \\
\text{S} \\
\text{R}^{11}
\end{array}
\]

is fused to a C₅-C₆ carbocyclic ring, a phenyl ring, a 3-6 member heterocyclic ring or a 5-6 member heteroaryl ring, all of which rings may be optionally substituted by 1-3 of the substituents referred to above for the

\[
\begin{array}{c}
\text{R}^{10} \\
\text{S} \\
\text{R}^{11}
\end{array}
\]

ring; or a pharmaceutically acceptable salt thereof.
AUSTRALIA

Patents Act

COMPLETE SPECIFICATION
(ORIGINAL)

Application Number: 48102/85
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority

Related Art:

APPLICANT'S REF.: SY-1708A

Name(s) of Applicant(s): BRISTOL-MYERS COMPANY

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Complete Specification for the invention entitled:

"CARBAPENEM ANTIBIOTICS"

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):
BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is directed to new carbapenem antibiotics in which the 2-substituent has the formula

\[ \text{R}^1 \text{R}^2 \text{A} \text{S} \text{R}^3 \text{S} \text{R}^4 \text{R}^5 \text{S} \text{R}^6 \text{R}^7 \text{S} \text{R}^8 \text{R}^9 \text{S} \text{R}^{10} \text{S} \text{R}^{11} \]

wherein A is \( \text{C}_2 \text{C}_6 \) straight or branched chain alkylene and \( \text{R}^1 \) and \( \text{R}^2 \) each independently represent optionally substituted aliphatic, cycloaliphatic, cycloaliphatic-aliphatic, aryl, heterocyclyl, heterocyclyl-aliphatic, heteroaryl or heterocyclyl-aliphatic radicals, or \( \text{R}^1 \) and \( \text{R}^2 \) when taken together with the sulfur to which they are attached represent an optionally substituted sulfur-containing heterocyclic ring.

2. Description of the Prior Art

A number of \( \delta \)-lactam derivatives containing the carbapenem nucleus

\[ \text{N} \]

have been disclosed in the literature. These carbapenem derivatives have been reported to possess utility as antibacterial agents and/or \( \delta \)-lactamase inhibitors.

The initial carbapenem compounds were natural products such as thienamycin of the formula
obtained by fermentation of *Streptomyces cattleya* (U.S. Patent 3,950,357). Thienamycin is an exceptionally potent broad-spectrum antibiotic which possesses notable activity against various *Pseudomonas* species, organisms which have been notoriously resistant to β-lactam antibiotics.

Carbapenems of the general formula

wherein $R^1$ is H or acyl and $R^8$ is H or substituted or unsubstituted: alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, alkylcycloalkyl, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heterocyclyl or heterocyclylalkyl, are disclosed in U.S. Patent 4,218,463. There is no disclosure of any $R^8$ substituents of the type

\[ \text{---A---S} \]

in which A is alkylene.
Compounds of the formula

wherein $R^5$, $R^6$ and $R^7$ are independently selected from $H$ and substituted or unsubstituted: alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl are disclosed in U.S. Patent 4,235,920.

Among the compounds disclosed in U.S. Patent 4,235,920 is

wherein $A$ is a pharmaceutical acceptable anion. The above-mentioned quaternary amine derivative is also described in Recent Advances in Chemistry of $\beta$-Lactam Antibiotics, Royal Society of Chemistry, London, 1981, pg 240-254, where its antibacterial activity on average is reported as approximately $1/2$ to $2/3$ that of thienamycin.
Compounds of the formula

\[
\begin{align*}
\text{attached to the amino nitrogen group of thienamycin represents a mono- or polycyclic N-containing heterocyclic group and } R \text{ is H, substituted or unsubstituted: alkyl, aryl, alkenyl, heterocyclyalkenyl, aralkenyl, heterocyclyalkyl, aralkyl, } & -\text{NR}_2, \text{ COOR, CONR}_2, -\text{OR}, \text{ or CN, are disclosed in European Patent Application } \text{21082.}
\end{align*}
\]

European Patent Application 40,408 discloses compounds of the formula
wherein $R^1$ is $H$, methyl or hydroxyl and $R_{51}$ is a monovalent organic group including inter alia heterocyclicalkyl.

European Patent Application 38,869 discloses compounds of the formula

![Chemical Structure Diagram]

wherein $R^6$, $R^7$, and $R^8$ are independently selected from the group consisting of hydrogen, substituted and unsubstituted: alkyl, alkenyl, and alkynyl, having from 1-10 carbon atoms; cycloalkyl, cycloalkylalkyl, and alkylcycloalkyl, having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moieties; aryl, such as phenyl; aralkyl, aralkenyl, and aralkynyl wherein the aryl moiety is phenyl and the aliphatic portion has 1-6 carbon atoms; heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl; wherein the substituent or substituents relative to the above-named radicals are selected from the group consisting of:

- $X^*$ halo (chloro, bromo, fluoro)
- $OH$ hydroxy
- $OR^1$ alkoxyl, aryloxyl
- $OCNR^1R^2$ carbamoyloxy
- $CNR^1R^2$ carbamoyl
- $NR^1R^2$ amino
- $NR^1$ amidino

in represents a group and $R$ is $H$, $CH_3$, $CH_2CH_3$, hetero-$R$, $-NR_2$, COOR,
from the group: alkyl, cycloalkyl, and heterocyclic groups relative to the above listed substituents on R1, R2, and R3, the groups R1 and R2 are independently selected from: hydrogen, alkyl, alkenyl, and alkynyl, having from 1-10 carbon atoms; cycloalkyl, cycloalkylalkyl, and alkylcycloalkyl, having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the
alkyl moieties; aryl, such as phenyl; aralkyl, aralkenyl, and aralkynyl wherein the aryl moiety is phenyl and the aliphatic portion has 1-6 carbon atoms; heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl and wherein the hetero atom or atoms in the above-named heterocyclic moieties are selected from the group consisting of 1-4 oxygen, nitrogen or sulphur atoms and wherein the alkyl moieties associated with said heterocyclic moieties have 1-6 carbon atoms. (See also European Patent Applications 1627, 1628, 10317, 17992, 37080, 37081 and 37082).

European Patent Application 24832 discloses compounds of the formula

![Chemical structure](attachment:structure.png)

wherein R' is H or a group selected from OR, OSO₂H or a salt or C₁-₄ alkyl ester thereof, OR', SR', OCOR', OCO₂R' or OCONH₂, where R² is a C₁-₆ alkyl group or an optionally substituted benzyl group and R₃ is a C₁-₆ alkyl group or an optionally substituted benzyl or phenyl group and R¹₂ is C₁-₆ alkyl, C₂-₆ alkenyl, C₃-₆ alkynyl wherein the triple bond is not present on the carbon adjacent to the sulfur atom, aralkyl, C₁-₆ alkanoyl, aralkanoyl, aryloxyalkanoyl or arylcarbonyl, any of such R¹₂ groups being optionally substituted, as antibacterial agents.

European Patent Application 38,869 mentioned above discloses synthesis of the carbapenem derivatives via intermediates of the general formula
wherein \( R^6 \) and \( R^7 \) are as defined above and \( R^{2'} \) is a readily removable carboxyl protecting group. Also disclosed as intermediates are the compounds of the formula

\[
\begin{align*}
\text{R}^6 & \quad \text{R}^7 \\
\text{N} & \quad \text{CO}_2 \text{R}^{2'}
\end{align*}
\]

wherein \( X \) is described as a leaving group.

European Patent Application 7973 discloses the intermediates of the formula

\[
\begin{align*}
\text{OH} & \quad \text{NH} \\
\text{CO}_2 \text{R} & \quad \text{N}_2
\end{align*}
\]

and

\[
\begin{align*}
\text{OH} & \quad \text{N} \\
\text{COOR} &
\end{align*}
\]
where R is hydrogen or an ester group. The diazo intermediate is also disclosed in U.S. Patent 4,378,315 while the keto intermediate is disclosed in U.S. Patent 4,318,912.

At the Gordon Research Conference on Medicinal Chemistry held at New London, New Hampshire on August 2-6, 1982, a handout was distributed in which a variety of carbapenem antibiotics were disclosed. Among the compounds disclosed on page 9 of the handout is the carbapenem of the formula

![Chemical Structure](image)

The above-mentioned carbapenem derivative is also disclosed on page 145 of European Patent Application 38869 and on page 252 of European Patent Application 17992.

U.S. 4,309,346 discloses carbapenem derivatives having 2-substituents of the formula

\[-SR^8\]

where R^8 may be inter alia heterocar^9 l in which the hetero atom or atoms in heteroaralkyl may be selected from the group consisting of 1-4 oxygen, nitrogen or sulfur atoms. No disclosure is made of any sulfonium groups such as are present in the compounds of the present invention.
European Patent Application 74,599 discloses 5,6-cis-carbapenem derivatives of the formula

wherein \( R^1 \) is optionally substituted alkyl, cycloalkyl, cycloalkenyl, alkynyl, aryl, aralkyl or a 5 to 8 membered heterocyclic group containing 1 to 4 hetero atoms, and \( R^2 \) is hydrogen or a hydroxy-protecting group. There is no disclosure, however, of compounds where \( R^1 \) is

\[
+ \quad -A-S- 
\]

in which \( A \) is alkylene.

European Patent Application 90,366 discloses carbapenem antibiotics of the formula

wherein \( R^1 \) is hydroxy, protected hydroxy or (lower)alkoxy, \( R^2 \) is carboxy or protected carboxy and \( R^3 \) is substituted aryl,
optionally substituted pyridyl or an optionally substituted heterocyclic group containing 3-5 hetero atoms.

With respect to the 1-substituted carbapenems of the present invention, there is extensive literature disclosing carbapenems having a non-hydrogen 1-substituent and a 2-substituent similar to those disclosed in the above-mentioned references. Again, however, no art has been found teaching a 2-substituent of the type

\[ \text{-----S--A--S-----} \]

Examples of 1-substituted carbapenem references are indicated below.

European Patent Application 54,917 (equivalent to U.S. 4,350,631) discloses intermediates of the formula

\[ \text{-----S--A--S-----} \]

where \( R^1, R^2, R^3 \) and \( R^4 \) are independently selected from the group consisting of hydrogen (\( R^1 \) and \( R^2 \) are not both hydrogen), substituted and unsubstituted: alkyl, alkenyl, and alkynyl, having from 1-10 carbon atoms; cycloalkyl, cycloalkylalkyl, and alkyl-cycloalkyl, having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms; phenyl; aralkyl, aralkenyl, and aralkynyl wherein the aryl moiety is phenyl and the alkyl chain has 1-6
carbon atomns; heteroaryl, heteroaralkyl, heterocyclal and heterocyclalkyl wherein the substituent or substituents relative to the above-named radicals are selected from the group consisting of: amino, mono-, di- and trialkylamino, hydroxyl, alkoxyl, mercapto, alkylthio, phenylthio, sulfamoyl, amidino, guanidino, nitro, chloro, bromo, fluoro, iodo, cyano and carboxy; and wherein the hetero atom or atoms in the above-named heterocyclic moeties are selected from the group consisting of 1-4 oxygen, nitrogen or sulfur atoms; and wherein the alkyl moeties of the above-recited substituents have 1-6 carbon atoms; R^5 is hydrogen, salt cation, a pharmaceutically acceptable ester moiety or a removable blocking group. Also disclosed are intermediates of the formula

![Chemical Structure](image)

where R^7 is a carboxyl protecting group and R^1, R^2, R^3 and R^4 are as defined above.

European Patent Application 10,317 (see also U.S. Patent 4,232,036) discloses carbapenem compounds of the general formula

![Chemical Structure](image)
where $R^0$ is $H$ or $-SR^8$; $R^1$, $R^6$, $R^7$ and $R^8$ are independently selected from the group consisting of hydrogen ($R^1$ is not $H$), substituted and unsubstituted: alkyl, alkenyl and alkynyl, having from 1-10 carbon atoms; cycloalkyl, cycloalkylalkyl and alkyl-cycloalkyl, having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moieties; phenyl; aralkyl, aralkenyl, and aralkynyl wherein the aryl moiety is phenyl and the alkyl chain has 1-6 carbon atoms; heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl wherein the substituent or substituents relative to the above-named radicals are selected from the group consisting of: amino, mono-, di-, and trialkylamino, hydroxyl, alkoxyl, mercapto, alkylthio, phenylthio, sulfamoyl, amidino, guanidino, nitro, chloro, bromo, fluoro, cyano and carboxy; and wherein the hetero atom or atoms in the above-named heterocyclic moieties are selected from the group consisting of 1-4 oxygen, nitrogen or sulfur atoms; and wherein the alkyl moieties of the above-recited substituents have 1-6 carbon atoms.

Despite a vast number of literature references teaching preparation of carbapenem derivatives, including derivatives having 2-substituents of the type

$$-S-A-Het$$

applicant believes he is the first to prepare carbapenem derivatives having a 2-substituent wherein the alkylene group $A$ is attached directly to a sulfonium group, i.e. a group of the type

$$-S-A-S$$
Although there are a vast number of carbapenem derivatives disclosed in the literature, there is still a need for new carbapenems since known derivatives may be improved upon in terms of spectrum of activity, potency, stability and/or toxic side effects.
SUMMARY OF THE INVENTION

The present invention provides a novel series of carbapenem derivatives characterized by a 2-substituent of the formula

![Chemical structure]

wherein A is C_2-C_6 straight or branched chain alkyne and R^{10} and R^{11} each independently represent optionally substituted aliphatic, cycloaliphatic, cycloaliphatic-aliphatic, aryl, heterocyclic, heterocyclic-aliphatic, heteroaryl or heteroaraliphatic radicals, or R^{10} and R^{11} when taken together with the sulfur-containing heterocyclic ring containing 0-2 double bonds and 0-2 additional heteroatoms selected from O, N and S, said ring being attached to A through a sulfur atom, thereby forming a sulfonium group. More specifically, the present invention provides carbapenem derivatives of the formula

![Chemical structure]

wherein R^{8} is hydrogen and R^{1} is selected from the group consisting of hydrogen; substituted and unsubstituted alkyl, alkenyl and alkynyl, having from 1-10 carbon atoms;
cycloalkyl and cycloalkylalkyl, having 3-6 carbon atoms in
the cycloalkyl ring and 1-6 carbon atoms in the alkyl moieties;
phenyl; aralkyl, aralkenyl and aralkynyl wherein the aryl
moiety is phenyl and the aliphatic portion has 1-6 carbon
atoms; heteroaryl, heteroaralkyl, heterocyclyl and hetero-
cyclylalkyl wherein the hetero atom or atoms in the above-
named heterocyclic moieties are selected from the group con-
sisting of 1-4 oxygen, nitrogen or sulfur atoms and the alkyl
moieties associated with said heterocyclic moieties have 1-6
carbon atoms; wherein the substituent or substituents relative
to the above-named radicals are independently selected from
the group consisting of

\[
\begin{align*}
&\text{C}_1-\text{C}_6 \text{ alkyl optionally substituted by} \\
&\text{amino, halo, hydroxy or carboxyl} \\
&\text{halo} \\
&\text{OR}^3 \\
&\text{OCNR}^3 \text{R}^4 \\
&\text{CNR}^3 \text{R}^4 \\
&\text{NR}^3 \text{R}^4 \\
&\text{SO}_2\text{NR}^3 \text{R}^4 \\
&\text{NHCNR}^3 \text{R}^4 \\
&\text{RCN} \\text{R}^3 \text{CNR}^4 \\
&\text{CO}_2\text{R}^3 \\
&\text{=O}
\end{align*}
\]
wherein, relative to the above-named substituents, the groups
R³ and R⁴ are independently selected from hydrogen; alkyl,
alkenyl and alkynyl, having from 1-10 carbon atoms; cycloalkyl,
cycloalkylalkyl and alkylcycloalkyl, having 3-6 carbon atoms
in the cycloalkyl ring and 1-6 carbon atoms in the alkyl
moieties; phenyl; aralkyl, aralkenyl and aralkynyl wherein
the aryl moiety is phenyl and the aliphatic portion has 1-6
carbon atoms; and heteroaryl, heteroaralkyl, heterocyclyl
and heterocyclylalkyl wherein the hetero atom or atoms in the
above-named heterocyclic moieties are selected from the group
consisting of 1-4 oxygen, nitrogen or sulfur atoms and the
alkyl moieties associated with said heterocyclic moieties have
1-6 carbon atoms, or R³ and R⁴ taken together with the nitrogen
to which at least one is attached may form a 5- or 6-membered
nitrogen-containing heterocyclic ring; R⁹ is as defined for R³.
except that it may not be hydrogen; or wherein R\(^1\) and R\(^8\) taken together represent C\(_2\)-C\(_{10}\) alkylidene or C\(_2\)-C\(_{10}\) alkylidene substituted by hydroxy; \(\Lambda\) is C\(_2\)-C\(_6\) straight or branched chain alkylene; R\(^2\) is hydrogen, an anionic charge or a conventional readily removable carboxyl protecting group, providing that when R\(^2\) is hydrogen or a protecting group, there is also present a counter anion; R\(^{10}\) and R\(^{11}\) each independently represents

(a) C\(_1\)-C\(_6\) alkyl, C\(_2\)-C\(_6\) alkenyl, C\(_2\)-C\(_6\) alkynyl, C\(_3\)-C\(_6\) cycloalkyl or cycloalkylalkyl having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moiety, said alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkylalkyl group being optionally substituted by 1-3 substituents independently selected from hydroxy, C\(_1\)-C\(_6\) alkoxy, C\(_1\)-C\(_6\) alkanoyloxy, carboxy, C\(_1\)-C\(_6\) alkoxyacarbonyl, amino, C\(_1\)-C\(_6\) alkylamino, di(C\(_1\)-C\(_6\))alkylamino, C\(_1\)-C\(_6\) alkynlamino, phenyl, phenyl substituted by 1-3 halo, C\(_1\)-C\(_6\) alkoxy, C\(_1\)-C\(_6\) alkyl, carboxy, carboxy(C\(_1\)-C\(_6\))alkyl, amino, C\(_1\)-C\(_6\) alkylamino, di(C\(_1\)-C\(_6\))alkylamino or di-(C\(_1\)-C\(_6\))alkylamino(C\(_1\)-C\(_6\))alkyl, halo or oxo;

(b) phenyl optionally substituted by 1-3 halo, C\(_1\)-C\(_6\) alkoxy, C\(_1\)-C\(_6\) alkyl, carboxy, amino, C\(_1\)-C\(_6\) alkylamino or di(C\(_1\)-C\(_6\))alkylamino groups;

(c) heterocyclyl or heterocyclylalkyl wherein the heterocyclic moiety is a 4-6 membered ring having 1-3 heteroatoms selected from O, N and S and the alkyl moiety has 1-6 carbon atoms, said heterocyclyl or heterocyclylalkyl ring being optionally substituted by 1-3 C\(_1\)-C\(_6\) alkyl or C\(_1\)-C\(_6\) alkoxy groups; or

(d) heteroaryl or heteroaralkyl wherein the heterocyclic moiety is a 5-6 membered aromatic ring having 1-3 heteroatoms selected from O, N and S and the alkyl moiety has 1-6 carbon atoms, said heteroaryl or heteroaralkyl ring being optionally substituted by 1-3 C\(_1\)-C\(_6\) alkyl, C\(_1\)-C\(_6\) alkoxy, carboxy, carboxy(C\(_1\)-C\(_6\))alkyl, amino, C\(_1\)-C\(_6\) alkyl-
amino, di(C₁⁻C₆) alkylamino, amino(C₁⁻C₆) alkyl or di(C₁⁻C₆) alkylamino(C₁⁻C₆) alkyl groups; or wherein R¹₀ and R¹¹ are taken together with the

to which they are attached represent a 4-6 member sulfur-containing heterocyclic ring containing 0-2 double bonds and 0-2 additional heteroatoms selected from O, N and S, said ring being attached to A through a sulfur atom, thereby forming a sulfonium group, said heterocyclic ring being optionally substituted by 1-3 substituents independently selected from:

C₁⁻C₆ alkyl optionally substituted by 1-3 hydroxy, C₁⁻C₆ alkoxy, carboxy, halo, amino, C₁⁻C₆ alkylamino or di(C₁⁻C₆)alkylamino groups, hydroxy, C₁⁻C₆ alkoxy, C₁⁻C₆ alkanoyloxy, amino, C₁⁻C₆ alkylamino, di(C₁⁻C₆) alkylamino, C₁⁻C₆ alkanoylamino, carboxy, C₁⁻C₆ alkoxy-carbonyl, halo, oxo or phenyl; or wherein said heterocyclic ring

is fused to a C₅-C₆ carbocyclic ring, a phenyl ring, a 5-6 member heterocyclic ring or a 5-6 member heteroaryl ring, any of which rings may be optionally substituted by 1-3 of the substituents referred to above for the

wherein the aryl moiety is phenyl and the aliphatic portion has
a 4-6 member sulfur-containing 0-2 double bonds
from O, N and S,

a sulfur atom,

id heterocyclic ring
substituents

1-3 hydroxy,

\( \text{C}_6 \text{H}_5 \)

alkylamino

\( \text{C}_2 \text{H}_4 \text{O} \)

alkoxy,

amino, di(\( \text{C}_1 \text{C}_6 \))

alkoxy, \( \text{C}_1 \text{C}_6 \) alkoxy

rein said hetero-

-phenyl ring,

6 member hetero-

portionally sub-

ferred to above

ng of

1 and alkynyl,

cloalkylalkyl and
the cycloalkyl ring
pyrroloalkyl

lkenyl and aralkynyl

hatic portion has

1-6 carbon atoms; heteroaryl, heteroarylalkyl, heterocyclyl and
heterocyclylalkyl wherein the hetero atom or atoms in the
above-named heterocyclic moieties are selected from the group
consisting of 1-4 oxygen, nitrogen and sulfur atoms and the
alkyl moieties associated with said heterocyclic moieties have
1-6 carbon atoms; wherein the substituent or substituents relative
to the above-named radicals are selected from the group consisting
of: amino, mono-, di- and trialkylamino, hydroxyl, alkoxyl,
mercapto, alkylthio, phenylthio, sulfamoyl, amidino, guanidino,
nitro, chloro, bromo, fluoro, cyano and carboxy; and wherein
the alkyl moieties of the above-recited substituents have 1-6
carbon atoms; and pharmaceutically acceptable salts thereof. The
compounds of formula I are potent antibacterial agents or
intermediates useful in the preparation of such agents.

Also included in the invention are processes for preparing
the novel carbapenam derivatives described above and pharmaceutical
compositions containing the biologically active carbapenam
derivatives in combination with pharmaceutically acceptable
carriers or diluents.
DETAILED DESCRIPTION

The novel compounds of general formula I above contain the carbapenem nucleus

![Chemical Structure](image)

and may thus be named as 1-carba-7-penam-3-carboxylic acid derivatives. Alternatively, the compounds may be considered to have the basic structure

![Chemical Structure](image)

and named as 7-oxo-1-azabicyclo(3.2.0)hept-2-ene-2-carboxylic acid derivatives. While the present invention includes compounds wherein the relative stereochemistry of the 5,6-protons is cis as well as trans, the preferred compounds have the 5R,6S (trans) stereochemistry as in the case of thienamycin.

The compounds of formula I may be unsubstituted in the 6-position or substituted by substituent groups previously disclosed for other carbapenem derivatives. More specifically, R⁸ may be hydrogen and R¹ may be hydrogen or a non-hydrogen substituent disclosed, for example, in European Patent Application 38,869 (see definition of R⁶). Alternatively, R⁸ and R¹ taken together may be C₂-C₁₀ alkylidene or C₂-C₁₀ alkylidene substituted, for example, by hydroxy.
The compounds of formula I are substituted at the 1-position (R^1\text{5}) by substituent groups previously disclosed for other carbapenem derivatives. More specifically, R^1\text{5} is any of the non-hydrogen 1-substituents disclosed for example, in European Patent Application 54,917 (see definition of R^1 or R^2 therein) or in U.S. Patent 4,350,631. Preferred non-hydrogen R^1\text{5} substituents include C_1-C_6 alkyl, most preferably methyl; phenyl; and phenyl (C_1-C_6) alkyl. The non-hydrogen R^1\text{5} substituent may be in either the alpha- or alpha- configuration, and it is intended that the present invention include the individual alpha- and alpha- isomers, as well as mixtures thereof. The most preferred 1-substituted compounds are those having the alpha- configuration, especially those having the alpha-methyl substituent.

To elaborate on the definitions for R^1, R^6, and R^1\text{5}: (a) The aliphatic "alkyl," "alkenyl" and "alkynyl" groups may be straight or branched chain having 1-10 carbon atoms; preferred are 1-6, most preferably 1-4, carbon atoms; when part of another substituent, e.g. as in cycloalkylalkyl, or heteroaralkyl or azalkenyl, the alkyl, alkenyl and alkynyl group preferably contains 1-6, most preferably 1-4, carbon atoms.

(b) "heteroaryl" includes mono-, bi- and polycyclic aromatic heterocyclic groups containing 1-4 O, N or S atoms; preferred are 5- or 6-membered heterocyclic rings such as thiienyl, furyl, thiazolyl, oxadiazolyl, triazolyl, isothiazolyl, thiazolyl, imidazolyl, isoaxazolyl, tetrazolyl, oxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, pyrazolyl, etc.

(c) "heterocyclyl" includes mono-, bi- and polycyclic saturated or unsaturated non-aromatic heterocyclic groups containing 1-4 O, N or S atoms; preferred are 5- or 6-membered heterocyclic rings such as morpholiny, piperazinyl, piperidyl, pyrazoliny, pyrazolidinyl, imidazoliny, imidazolidinyl, pyrroliny, pyrrolidinyl, etc.
(d) "halo" (used also to define \( R^{10} \) and \( R^{11} \)) includes chloro, bromo, fluoro and iodo and is preferably chloro or bromo.

The term "conventional readily removable carboxyl protecting group" refers to a known ester group which has been employed to block a carboxyl group during the chemical reaction steps described below and which can be removed, if desired, by methods which do not result in any appreciable destruction of the remaining portion of the molecule, e.g. by chemical or enzymatic hydrolysis, treatment with chemical reducing agents under mild conditions, irradiation with ultraviolet light or catalytic hydrogenation. Examples of such ester protecting groups include benzhydryl, allyl, p-nitrobenzyl, 2-naphthylmethyl, benzyl, trichloroethyl, silyl such as tri-methylsilyl, phenoxy-, p-methoxybenzyl, acetyl, o-nitrobenzyl, 4-pyridylmethyl and \( C_{1-6} \) alkyl such as methyl, ethyl or t-butyl. Included within such protecting groups are those which are hydrolyzed under physiological conditions such as pivaloyloxymethyl, acetoxyethyl, phthalidyl, indanyl and methoxymethyl. A particularly advantageous carboxyl protecting group is p-nitrobenzyl which may be readily removed by catalytic hydrogenolysis.

The pharmaceutically acceptable salts referred to above include the nontoxic acid addition salts, e.g. salts with mineral acids such as hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, etc. and salts with organic acids such as maleic, acetic, citric, succinic, benzoic, tartaric, fumaric, mandelic, ascorbic,
lactic, gluconic and malic. Compounds of formula I in the form of acid additions salts may be written as

\[
\text{R}^8 \text{H} \text{R}^{15} \text{S-A-S} \text{R}^{10} \text{R}^{11} \text{COOR}^2 \text{X}^\ominus
\]

where \( \text{X}^\ominus \) represents the acid anion. The counter anion \( \text{X}^\ominus \) may be selected so as to provide pharmaceutically acceptable salts for therapeutic administration but, in the case of intermediate compounds of formula I, \( \text{X}^\ominus \) may also be a toxic anion. In such a case the ion can be subsequently removed or substituted by a pharmaceutically acceptable anion to form an active end product for therapeutic use. When acidic or basic groups are present in the \( \text{R}^1 \) group or on the \( \text{R}^{10}, \text{R}^{15} \) or \( \text{R}^{11} \) substituents, the present invention may also include suitable base or acid salts of these functional groups, e.g. acid addition salts in the case of a basic group and metal salts (e.g. sodium, potassium, calcium and aluminum), the ammonium salt and salts with nontoxic amines (e.g. trialkylamines, procaine, dibenzylamine, l-ephenamine, N-benzyl-8-phenethylamine, N,N'-dibenzylethlenediamine, etc.) in the case of an acidic group.

Compounds of formula I wherein \( \text{R}^2 \) is hydrogen, an anionic charge or a physiologically hydrolyzable ester group together with pharmaceutically acceptable salts thereof are useful as antibacterial agents. The remaining compounds of formula I are valuable intermediates which can be converted into the above-mentioned biologically active compounds.
A preferred embodiment of the present invention comprises compounds of formula I wherein \( R^8 \) is hydrogen and \( R^1 \) is hydrogen, \( \text{CH}_3\text{CH}_2^- \).

\[
\begin{align*}
\text{CH}_3 & \quad \text{OH} & \quad \text{CH}_3\text{CH}_2^- \\
\text{OH} & & \quad \text{CH}_3\text{CH}_2^- \\
\text{CH}_3 & & \quad \text{OH}
\end{align*}
\]

Among this subclass, the preferred compounds are those in which \( R^1 \) is \( \text{CH}_3\text{CH}_2^- \), most preferably compounds having the absolute configuration 5R, 6S, 8R.

Another preferred embodiment comprises compounds of formula I in which \( R^1 \) and \( R^8 \) taken together form an alkylidene radical of the formula

\[
\text{HOCE}_2^2 \quad \text{C} = \quad \text{CH}_3
\]

The alkylene (i.e. substituent "A") radical in the compounds of formula I may be straight or branched chain and may contain from 2 to 6 carbon atoms. A preferred embodiment comprises those compounds in which \( A \) is \(-(\text{CH}_2)_n-\) in which \( n \) is 2, 3 or 4 and a particularly preferred embodiment comprises those compounds where \( A \) is \( -\text{CH}_2\text{CH}_2^- \).
The 2-substituent of the present compounds is characterized by the presence of a sulfonium group attached to the alkylene radical A. As indicated above, \( R^{10} \) and \( R^{11} \) may each independently be selected from optionally substituted aliphatic, cycloaliphatic, cycloaliphatic-aliphatic, aryl, heterocyclic, heterocyclic-aliphatic, heteroaryl or heterocaraliphatic. Alternatively, the \( R^{10} \) and \( R^{11} \) substituents when taken together with the sulfonium group may form a 4-6 membered, optionally substituted, sulfur-containing heterocyclic ring containing 0-2 double bonds and 0-2 additional heteroatoms selected from O, N and S, said ring being attached to A through a sulfur atom, thereby forming a sulfonium group. In the latter case where
\[ R^{10} + S + R^{11} \]
represents a heterocyclic ring, the ring may also be fused to a \( C_5-C_6 \) carbocyclic ring, a phenyl ring or a 5-6 membered heteroaryl ring (containing 1-4 O, N or S) and any of such fused rings may also be optionally substituted.

The aliphatic \( R^{10} \) and/or \( R^{11} \) substituents are preferably \( C_1-C_6 \) alkyl, \( C_2-C_6 \) alkenyl or \( C_2-C_6 \) alkynyl. Cycloaliphatic substituents are preferably \( C_3-C_6 \) cycloalkyl while cycloaliphatic-aliphatic refers especially to \( C_3-C_6 \) cycloalkyl-\( C_1-C_6 \) alkyl. Such aliphatic, cycloaliphatic and cycloaliphatic-aliphatic substituents may be unsubstituted or substituted (preferably by 1-3 substituents) by the following: hydroxy, \( C_1-C_6 \) alkoxy, \( C_1-C_6 \) alkanoyloxy, carboxy, \( C_1-C_6 \) alkoxy carbonyl (e.g. \(-\text{OC}_2\text{H}_5\) or \(-\text{OC}_3\text{H}_7\)), amino, \( C_1-C_6 \) alylamino, \( \text{di}(C_1-C_6)-\text{alkylamino}, \( C_1-C_6 \) alkanoylamino, phenyl, phenyl substituted by, preferably 1-3 and most preferably 1-2, halo, \( C_1-C_6 \) alkoxy,
C$_1$-$C_6$ alkyl, carboxy, carboxy-$C_1$-$C_6$ alkyl, amino, $C_1$-$C_6$ alkylamino, di($C_1$-$C_6$)alkylamino or di($C_1$-$C_6$)alkylamino-$C_1$-$C_6$)alkyl, halo or oxo.

The $R^{10}$ and/or $R^{11}$ substituents may also be aryl ($C_6$-$C_{10}$ aromatic hydrocarbon) which is most especially phenyl. The aryl group or groups may be unsubstituted or substituted by 1-3, preferably 1-2, substituents selected from halo, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkyl, carboxy, amino, $C_1$-$C_6$ alkylamino and di($C_1$-$C_6$)alkylamino.

When $R^{10}$ and/or $R^{11}$ represent heterocyclyl or heterocyclyl-aliphatic, the heterocyclyl moiety is a 4-6 membered non-aromatic ring containing 1-3 hetero atoms selected from O, N and S. The aliphatic moiety associated with heterocyclyl-aliphatic is preferably $C_1$-$C_6$ alkyl. The heterocyclic ring of such groups may be unsubstituted or substituted by 1-3, preferably 1-2, $C_1$-$C_6$ alkyl or $C_1$-$C_6$ alkoxy substituents.

When $R^{10}$ and/or $R^{11}$ represents heteroaryl or heteroaryl-aliphatic, the heterocyclic moiety is a 5-6 membered aromatic ring containing 1-3 hetero atoms selected from O, N and S and the aliphatic (preferably alkyl) moiety has 1-6 carbon atoms. The heteroaryl ring of such substituents may be unsubstituted or substituted by 1-3, preferably 1-2, substituents selected from $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, carboxy, carboxy($C_1$-$C_6$)alkyl, amino, ($C_1$-$C_6$)alkylamino, di($C_1$-$C_6$)alkylamino, amino($C_1$-$C_6$)alkyl and di($C_1$-$C_6$)alkylamino($C_1$-$C_6$)alkyl.

The $R^{10}$ and $R^{11}$ substituents taken together with the S + to which they are attached may also represent a 4-6 member sulfur-containing heterocyclic ring containing 0-2 (preferably 0) double bonds and 0-2 additional heteroatoms selected from O, N, and S, said ring being attached to the alkylene (A) group through a sulfur atom, thereby forming a sulphonium group. The heterocyclic ring formed by

$$R^{10} + S + R^{11}$$

-28-
may be unsubstituted or substituted by 1-3, preferably 1-2, substituents selected from:

C₈₋C₆ alkyl optionally substituted by 1-3 hydroxy,
C₈₋C₆ alkoxy, carboxy, halo, amino, C₈₋C₆ alkyamino or di(C₈₋C₆) alkyamino groups;
hydroxy;
C₈₋C₆ alkoxy;
C₈₋C₆ alkanoyloxy;
amino;
C₈₋C₆ alkyamino;
di(C₈₋C₆) alkyamino;
C₈₋C₆ alkanoylamino;
carboxy;
C₈₋C₆ alkoxy carbonyl;
halo;
oxo; and
phenyl.

The heterocyclic ring may also be fused to a C₅₋C₆ carbocyclic ring, a phenyl ring, a 5-6 member heterocyclic (containing 1-4 hetero atoms selected from O, N and S) ring or a 5-6 member heteroaryl (containing 1-4 hetero atoms selected from O, N and S) ring, all of which fused rings may be optionally substituted by 1-3, preferably 1-2, of the substituents described above in connection with the sulfur-containing heterocyclic ring.
A preferred embodiment of the present invention comprises compounds of the formula

wherein A is C<sub>2</sub>-C<sub>6</sub> straight or branched chain alkylene; R<sup>2</sup> is hydrogen, an anionic charge or a conventional readily removable carboxyl protecting group; R<sup>15</sup> is a 9-methyl substituent and R<sup>10</sup> and R<sup>11</sup> each independently represents

(a) C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl or cycloalkylalkyl having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moiety, said alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkyl-alkyl group being optionally substituted by 1-3 substituents independently selected from hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkanoyloxy, carboxy, C<sub>1</sub>-C<sub>6</sub> alkoxycarbonyl, amino, C<sub>1</sub>-C<sub>6</sub> alkylamino, di(C<sub>1</sub>-C<sub>6</sub>) alkylamino, C<sub>1</sub>-C<sub>6</sub> alkanoylamino, phenyl, phenyl substituted by 1-3 halo, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alky, carboxy, carboxy(C<sub>1</sub>-C<sub>6</sub>) alkyl, amino, C<sub>1</sub>-C<sub>6</sub> alkylamino, di(C<sub>1</sub>-C<sub>6</sub>) alkylamino, or di-(C<sub>1</sub>-C<sub>6</sub>) alkylamino, (C<sub>1</sub>-C<sub>6</sub>)alkyl, halo or oxo;

(b) phenyl optionally substituted by 1-3 halo, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, carboxy, amino, C<sub>1</sub>-C<sub>6</sub> alkylamino or di(C<sub>1</sub>-C<sub>6</sub>) alkylamino groups;

(c) heterocyclyl or heterocyclylalkyl wherein the heterocyclic moiety is a 4-6 membered ring having 1-3 hetero atoms selected from O, N and S and the alkyl moiety has 1-6 carbon atoms, said heterocyclyl or heterocyclylalkyl ring being optionally substituted by 1-3 C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>1</sub>-C<sub>6</sub> alkoxy groups; or
(d) heteroaryl or heteroaralkyl wherein the heterocyclic moiety is a 5-6 membered aromatic ring having 1-3 heteroatoms selected from O, N and S and the alkyl moiety has 1-6 carbon atoms, said heteroaryl or heteroaralkyl ring being optionally substituted by 1-3 C1-C6 alkyl, C1-C6 alkoxy, carboxy, carboxy(C1-C6)alkyl, amino, C1-C6 alkylamino, di(C1-C6)alkylamino, amino(C1-C6)alkyl or di(C1-C6)-alkylamino(C1-C6)alkyl groups; or wherein R10 and R11 taken together with the  

S  

to which they are attached represent a 4-6 member sulfur-containing heterocyclic ring containing 0-2 double bonds and 0-2 additional heteroatoms selected from O, N and S, said ring being attached to A through a sulfur atom, thereby forming a sulfonium group, said heterocyclic ring being optionally substituted by 1-3 substituents independently selected from:  

C1-C6 alkyl optionally substituted by 1-3 hydroxy,  
C1-C6 alkoxy, carboxy, halo, amino, C1-C6 alkylamino or di(C1-C6)alkylamino groups, hydroxy, C1-C6 alkoxy, C1-C6 alkanoyloxy, amino, C1-C6 alkylamino, di(C1-C6)-alkylamino, C1-C6 alkanoylamino, carboxy, C1-C6 alkoy-carbonyl, halo, oxo or phenyl; or wherein said heterocyclic ring is connected to a C5-C6 carbocyclic ring, a phenyl ring, a 5-6 member heterocyclic ring or a 5-6 member heteroaryl ring, all of which rings may be optionally substituted by 1-3 of the substituents referred to above for  

R10—S—R11  

ring; and pharmaceutically acceptable salts thereof.
Within the above group of compounds, a preferred subclass comprises those compounds wherein \( A \) is \(-\text{CH}_2\text{CH}_2-\).

Another preferred embodiment of the present invention comprises compounds of the formula

\[
\text{[Chemical Structure Image]}
\]

wherein \( R^2 \) is hydrogen, an anionic charge or a conventional readily removable carboxyl protecting group, \( R^{15} \) is \( \text{C}_3\text{H}_7\) and \( \text{R}^{10} \) represents:

1. \(+\text{-CH}_2\text{C}_6\text{H}_5\)
2. \(+\text{-C}_2\text{H}_5\)
3. \(+\text{-CH}_3\)
4. \(+\text{-S-(CH}_2)_2\text{CH}=\text{CH}_2\)
5. \(+\text{-S-CH}_2\text{CH}_2\text{C}_6\text{H}_5\)
6. \(+\text{-S-CH}_2\text{CH}_2\text{C}_6\text{H}_5\)
7. \(+\text{-S-CH}_2\text{CH}_2\text{OCH}_3\)
A particularly preferred embodiment of the present invention comprises compounds of formula I wherein either (a) R\textsuperscript{10} and R\textsuperscript{11} each independently represents C\textsubscript{1}-C\textsubscript{6} alkyl or (b) R\textsuperscript{10} and R\textsuperscript{11} taken together with the S to which they are attached represent

and pharmaceutically acceptable salts thereof.
pharmaceutically acceptable salts thereof.

Examples of preferred 2-substituents wherein R\textsuperscript{10} and R\textsuperscript{11} are alkyl include

\begin{align*}
-S-\text{CH}_2\text{CH}_2-\text{S} & \text{CH}_3 \\
-S-\text{CH}_2\text{CH}_2\text{CH}_2-\text{S} & \text{CH}_3 \\
-S-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{S} & \text{C}_2\text{H}_5 \\
-S-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{S} & \text{i-propyl} \\
-S-\text{CH}_2\text{CH}_2-\text{S} & \text{C}_5\text{H}_{11} \\
-S-\text{CH}_2\text{CH}_2-\text{S} & \text{C}_5\text{H}_{11} \\
-S-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{S} & \text{CH}_3 \\
-S-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{S} & \text{C}_2\text{H}_5 \\
\end{align*}

Within this subclass, the preferred compounds are those wherein A is \(-\text{CH}_2\text{CH}_2\) - in which n is 2, 3 or 4, most preferably those in which A is \(-\text{CH}_2\text{CH}_2\) - and wherein either (a) R\textsuperscript{1} and R\textsuperscript{8} taken together represent

\begin{align*}
\text{HOCH}_2 & \text{C=} \\
\text{CH}_3 & \\
\end{align*}

or (b) R\textsuperscript{8} is hydrogen and R\textsuperscript{1} represents hydrogen, \text{CH}_3-\text{CH}_2-,
Particularly preferred are the compounds wherein R₈ is hydrogen and R¹ is preferably compounds having the absolute configuration 5R, 6S, 8R.

A most preferred embodiment of the present invention comprises compounds of formula I wherein

\[
R^{10} \rightarrow S \rightarrow R^{11}
\]

represents

and pharmaceutically acceptable salts thereof. Within this subclass, the preferred compounds are those wherein \( \Lambda = (\text{CH}_2)_n \) in which \( n \) is 2, 3 or 4, most preferably those in which \( \Lambda = \text{CH}_2\text{CH}_2^- \) and wherein either (a) \( R^1 \) and \( R^8 \) taken together represent

\[
\text{HOCH}_2 \rightarrow C= \quad \text{CH}_3.
\]

(b) \( R^8 \) is hydrogen and \( R^1 \) represents hydrogen, \( \text{CH}_3\text{CH}_2^- \),

\[
\text{CH}_3 \rightarrow C \rightarrow \text{OH} \quad \text{or \ \text{CH}_3\text{CH}_2^-}.
\]

Particularly preferred are the compounds wherein \( R^8 \) is hydrogen and \( R^1 \) is

\[
\text{CH}_3\text{CH}^- \text{, preferably compounds having the absolute configuration 5R, 6S, 8R.}
\]

Preparation of p-nitrobenzyl-3-((2-methanesulfonyloxyethylthio)-6a-[1-(R)hydroxyethyl]-4R-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate
It will be appreciated that when $R^{10}$ and $R^{11}$ in formula I are different, there may be forms of both the R and S optical isomers of such compounds as well as epimeric mixtures thereof. It is intended that the present invention include within its scope all such optical isomers and epimeric mixtures. Similarly, the 6-substituent may in certain cases, e.g. as in hydroxyethyl, be in either the R or S configuration and the resulting isomers as well as epimeric mixtures thereof are encompassed by the present invention.

The carbapenem derivatives of general formula I are prepared from starting materials of the formula

![Formula III](image)

wherein $R^1$, $R^8$, and $R^{15}$ are defined above and wherein $R^{2'}$ represents
a conventional readily removable carboxyl protecting groups. Compounds of formula III have been disclosed, for example, in European Patent Applications 38,869 (compound 7), and 54,917 and may be prepared by the general methods described therein.

The process for preparing compounds I from starting materials III may be summarized by the following reaction scheme:

\[
\begin{align*}
\text{III} & \quad \text{COOR}' \\
\text{IV} & \quad \text{COOR}' \\
\text{V} & \quad \text{COOR}'
\end{align*}
\]
To elaborate on the above process, starting material III is reacted in the inert organic solvent such as methylene chloride, acetonitrile or dimethylformamide with about an equimolar amount of diphenyl chlorophosphate in the presence of a base such as diisopropylethylamine, triethylamine, 4-dimethylaminopyridine or the like to give intermediate IV. The acylation to establish the diphenylphosphoryloxy leaving group at the

Preparation of 3-[2-((1-tetrahydrothiophenium)ethylthio]-6a-[1-(R)-hydroxyethyl]-4R-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate
2-position of intermediate III is advantageously carried out at a temperature of from about -20° to +40° C, most preferably at about 0°C. Intermediate IV may be isolated if desired, but is conveniently used for the next step without isolation or purification.

Intermediate IV is next converted to intermediate V by a conventional displacement reaction. Thus, intermediate IV may be reacted with approximately an equimolar amount of a mercaptan reagent of the formula

$$\text{HS-A-OH}$$

wherein A represents C$_2$-$C_6$ straight or branched chain alkyene in an inert organic solvent such as dioxane, dimethylformamide, dimethylsulfoxide or acetonitrile and in the presence of a base such as diisopropylethylamine, triethylamine, sodium hydrogen carbonate, potassium carbonate or 4-dimethylamino-pyridine. The temperature for the displacement is not critical, but an advantageous temperature range is from about -40°C to 25°C. Most conveniently, the reaction is carried out with cooling, e.g. at about 0°C.

Intermediate V is then acylated with methanesulfonyl chloride or a functional acylating equivalent thereof such as methanesulfonic acid anhydride in an inert organic solvent and in the presence of base to provide the methanesulfonyloxy leaving group of intermediate VI. The acylation is carried out in an inert organic solvent such as tetrahydrofuran, methylene chloride, acetonitrile or dimethylformamide and in the presence of a suitable base such as diisopropylethylamine, triethylamine, 4-dimethylaminopyridine, and the like. The reaction may be carried out over a wide temperature range, e.g. -40°C to +40°C, but is most advantageously conducted with cooling, e.g. at about -30°C to -40°C.

Intermediate VI is next subjected to a displacement reaction so as to provide in intermediate II the iodo leaving group. This particular group has been found to greatly facilitate preparation of the carbapenem end-products of formula...
I. The intermediates of general formula II, therefore, comprise a preferred embodiment of the present invention.

The displacement of the methanesulfonyloxy leaving group is carried out by reacting intermediate VI with a source of iodide ions in an inert organic solvent such as acetone, dimethylformamide or dimethylsulfoxide. Any compound which ionizes in the solvent employed to provide iodide ions may be used, e.g. an alkali metal iodide such as NaI or KI. The temperature for the displacement is not critical, but temperatures of room temperature or above are most advantageous for achieving completion of the reaction in a reasonable time period. The source of iodide ions is employed in an amount so as to provide approximately an equivalent or excess of iodide ion relative to intermediate VI.

Preparation of the desired carbapenem derivatives of formula I is carried out by a nucleophilic displacement of the iodo leaving group of intermediate II by the desired sulfide of the general formula

\[
\begin{align*}
S & \quad \text{(general formula II)} \\
& \quad \text{Intermediate II is reacted with at least an equivalent, preferably an excess, of the desired sulfide in an inert organic solvent and in the presence of silver ion. Suitable inert organic solvents include, for example, tetrahydrofururan, dioxane, methylene chloride, diglyme, dimethoxyethane, and the like. Any silver compound which substantially ionizes in the solvent and to give silver ions and an inert anion may be used as the source of silver ion, e.g. AgClO}_4. \text{ Generally, we prefer to use approximately an equivalent amount (relative to intermediate II) of silver ion to facilitate the displacement. The reaction may be carried out over a wide temperature range, e.g. from about -25°C to about +25°C, but is preferably conducted at around 0°C.}
\end{align*}
\]
Intermediate \( I' \) will have a counter anion (derived from the silver salt used) associated with it which may at this stage be substituted by a different counter anion, e.g. one which is pharmaceutically acceptable, by conventional procedures. Alternatively, the counter ion may be subsequently removed during the de-blocking step.

The de-blocking step to remove the carboxyl protecting group \( R^- \) of intermediate \( I' \) is accomplished by conventional procedures such as solvolysis, chemical reduction or hydrogenation. Where a protecting group such as p-nitrobenzyl, benzyl, benzhydryl or 2-naphthylmethyl is used which can be removed by catalytic hydrogenation, intermediate \( I' \) in a suitable solvent such as dioxane-water-ethanol, tetrahydrofuran-aqueous dipotassium hydrogen phosphate-isopropanol or the like may be treated under a hydrogen pressure of from 1 to 4 atmospheres in the presence of a hydrogenation catalyst such as palladium-on charcoal, palladium hydroxide, platinum oxide or the like at a temperature of from 0 to 50°C for from about 0.24 to 4 hours. When \( R^2' \) is a group such as o-nitrobenzyl, photolysis may also be used for de-blocking. Protecting groups such as 2,2,2-trichloroethyl may be removed by mild zinc reduction. Similarly, other conventional carboxyl protecting groups may be removed by methods known to those skilled in the art. Finally, as mentioned above, compounds of formula \( I' \) where \( R^2' \) is a physiologically hydrolyzable ester such as acetoxyethyl, phthalidyl, indanyl, pivaloyloxymethyl, methoxymethyl, etc. may be administered directly to the host without de-blocking since such esters are hydrolyzed in vivo under physiological conditions.

It will be understood that where the \( R^1, R^3, R^5 \), and/or \( R^8 \) substituent or the sulfide nucleophile attached to substituent \( A \) contain a functional group which might interfere with the intended course of reaction, such group may be protected by a conventional blocking group and then subsequently de-blocked to regenerate the desired functional group. Suitable blocking
groups and procedures for introducing and removing such groups are well known to those skilled in the art.

As in the case of other β-lactam antibiotics, compounds of general formula I may be converted by known procedures to pharmaceutically acceptable salts which, for purposes of the present invention, are substantially equivalent to the non-salted compounds. Thus, for example, one may dissolve a compound of formula I wherein $R^2$ is an anionic charge in a suitable inert solvent and then add an equivalent of a pharmaceutically acceptable acid. The desired acid addition salt may be recovered by conventional procedures, e.g. solvent precipitation, lyophilization, etc.

Where other basic or acidic functional groups are present in the compound of formula I, pharmaceutically acceptable base addition salts and acid addition salts may be similarly prepared by known methods.

A compound of formula I where $R^2$ is hydrogen or an anionic charge, or a pharmaceutically acceptable salt thereof may also be converted by conventional procedures to a corresponding compound where $R^2$ is a physiologically hydrolyzable ester group, or a compound of formula I wherein $R^2$ is a conventional carboxyl protecting group may be converted to the corresponding compound where $R^2$ is hydrogen, an anionic charge or a physiologically hydrolyzable ester group, or a pharmaceutically acceptable salt thereof.

The novel carbapenem derivatives of general formula I wherein $R^2$ is hydrogen, an anionic charge or a physiologically hydrolyzable carboxyl protecting group, or the pharmaceutically acceptable salts thereof, are potent antibiotics active against various gram-positive and gram-negative bacteria and they may be used, for example, as animal feed additives for promotion of growth, as preservatives in food, as bactericides in industrial applications, for example in waterbased paint and in the white water of paper mills to inhibit the growth of harmful bacteria and as disinfectants for destroying or
inhibiting the growth of harmful bacteria on medical and
dental equipment. They are especially useful, however,
in the treatment of infectious disease in humans and other
animals caused by gram-positive or gram-negative bacteria.

The pharmaceutically active compounds of this
invention may be used alone or formulated as pharmaceutical
compositions comprising, in addition to the active carba-
penem ingredient, a pharmaceutically acceptable carrier or
diluent. The compounds may be administered by a variety of
means; those of principal interest include: orally, topically
or parenterally (intravenous or intramuscular injection).
The pharmaceutical compositions may be in solid form such as
capsules, tablets, powders, etc. or in liquid form such as
solutions, suspensions or emulsions. Compositions for injection,
the preferred route of delivery, may be prepared in unit dose
form in ampules or in multidose containers and may contain
formulatory agents such as suspending, stabilizing and dis-
persing agents. The compositions may be in ready to use form
or in powder form for reconstitution at the time of delivery
with a suitable vehicle such as sterile water.

The dosage to be administered depends to a large extent
on the particular compound being used, the particular composition
formulated, the route of administration, the nature and condition
of the host and the particular situs and organism being treated.
Selection of the particular preferred dosage and route of
application, then, is left to the discretion of the therapist.
In general, however, the compounds may be administered paren-
terally or orally to mammalian hosts in an amount of from about
5 to 200 mg/kg/day. Administration is generally carried out in
divided doses, e.g. three to four times a day.

To illustrate the potent broad-spectrum antibacterial
activity of the carbapenems of the present invention, both in
vitro and in vivo, and the low toxicity of the compounds,
biological data is provided below relating to the preferred
carbapenem compound of the present invention, i.e. 3- [2-(1-
tetrahydrothiophenium)ethylthio]-6-alpha-[1-(R)-hydroxyethyl]-4-R-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate prepared in Example 1.

In Vitro Activity

A sample of the above-identified carbapenem compound after solution in water and dilution with Nutrient Broth was found to exhibit the following Minimum Inhibitory Concentrations (M.I.C.) in mcg/ml versus the indicated microorganisms as determined by overnight incubation at 37°C by tube dilution. Imipenem was included as a comparison compound.

<table>
<thead>
<tr>
<th>Organism</th>
<th>New Compound</th>
<th>Imipenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td>A 9585</td>
<td>0.004</td>
</tr>
<tr>
<td>S. pyogenes</td>
<td>A 9604</td>
<td>0.004</td>
</tr>
<tr>
<td>S. faecalis</td>
<td>A20688</td>
<td>1</td>
</tr>
<tr>
<td>S. aureus</td>
<td>A 9537</td>
<td>0.008</td>
</tr>
<tr>
<td>S. aureus (+50% serum)</td>
<td>A 9537</td>
<td>0.06</td>
</tr>
<tr>
<td>S. aureus (Pen. Res.)</td>
<td>A 9606</td>
<td>0.008</td>
</tr>
<tr>
<td>S. aureus (Meth. Res.)</td>
<td>A20699</td>
<td>63</td>
</tr>
<tr>
<td>E. coli</td>
<td>A15119</td>
<td>0.016</td>
</tr>
<tr>
<td>E. coli</td>
<td>A20341-1</td>
<td>0.03</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>A 9664</td>
<td>0.03</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>A20468</td>
<td>0.25</td>
</tr>
<tr>
<td>E. cloacae</td>
<td>A 9659</td>
<td>0.13</td>
</tr>
<tr>
<td>E. cloacae</td>
<td>A 9656</td>
<td>0.06</td>
</tr>
<tr>
<td>P. mirabilis</td>
<td>A 9900</td>
<td>0.06</td>
</tr>
<tr>
<td>P. vulgaris</td>
<td>A21359</td>
<td>0.06</td>
</tr>
<tr>
<td>M. morganii</td>
<td>A15153</td>
<td>0.13</td>
</tr>
<tr>
<td>P. rettgeri</td>
<td>A22424</td>
<td>0.25</td>
</tr>
<tr>
<td>S. marcescens</td>
<td>A20019</td>
<td>0.13</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>A 9843a</td>
<td>0.25</td>
</tr>
<tr>
<td>P. aeruginosa (Carb. Res.)</td>
<td>A21628</td>
<td>-</td>
</tr>
</tbody>
</table>
**In Vivo Activity**

The *in vivo* therapeutic efficacy of the compound of Example 1 and Imipenem after intramuscular administration to mice experimentally infected with various organisms is shown in the following Table. The PD$_{50}$ (dose in mg/kg required to give protection to 50% of the infected mice) is indicated.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Compound of Example 1</th>
<th>Imipenem</th>
<th>MIC (ug/ml)</th>
<th>Compound of Example 1</th>
<th>Imipenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. a.</td>
<td>0.39</td>
<td></td>
<td></td>
<td>0.25</td>
<td>0.06</td>
</tr>
<tr>
<td>P. m.</td>
<td>1.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P. a.</td>
<td>0.39</td>
<td>3.1**</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. c.</td>
<td>2</td>
<td></td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P. m.</td>
<td>4.7</td>
<td></td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. a.</td>
<td>0.29</td>
<td></td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


** P. aeruginosa A20599.

** Treatment schedule: Mice were infected i.p. with 2x10$^4$ organisms A9843a, 3x10$^5$ of A20599, 2x10$^9$ of A9606, 9x10$^5$ of A99000, or 5x10$^5$ of Al5119. Drugs were given i.m. 0 and 2 post infection (1 and 3.5 h for Al5119).
Blood Levels in Mice
After Intramuscular Administration

Blood levels and the half-life of the compound of Example 1 after intramuscular administration of 20 mg/kg in mice are shown in the Table below.

**Mouse Blood Levels of Antibiotics**

<table>
<thead>
<tr>
<th>Compounds*</th>
<th>Dose (mg/kg)</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>90</th>
<th>Half-Life (T 1/2)</th>
<th>BCH-1*</th>
<th>AUC 100(-/+ Sol</th>
<th>Sol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 1</td>
<td>20</td>
<td>32.7</td>
<td>25.8</td>
<td>17.9</td>
<td>9.0</td>
<td>4.7</td>
<td>&gt;2.5</td>
<td>15 (-)</td>
<td>-</td>
<td>16.3 (0.018)</td>
<td>96 Sol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(±1.3)</td>
<td>(±1.2)</td>
<td>(±3.5)</td>
<td>(±2.3)</td>
<td>(±1.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Example 1</td>
<td>20</td>
<td>33.2</td>
<td>27.6</td>
<td>18.4</td>
<td>9.4</td>
<td>4.7</td>
<td>&gt;2.5</td>
<td>15 (+)</td>
<td>+</td>
<td>16.9 (0.0186)</td>
<td>7.0 Sol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(±6.4)</td>
<td>(±4.3)</td>
<td>(±3.6)</td>
<td>(±1.9)</td>
<td>(±1.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* BCH-1 given 5-10 minute prior to dosing

* Each group consisted of animals, blood samples were taken from each mouse each time period.

Compounds prepared in 0.1M Phosphate Buffer pH 7.0, and dosed IM.

Values in parentheses are Standard Deviation.

Assay Organism: *B. subtilis* ATCC 6633

(pH 7.0, 0.1% inoculum), (Base/Base layers)

BCH-1 is a renal dihydropeptidase inhibitor

AUC refers to the area under the curve
Urinary Recovery

The urinary recovery of the compound of Example 1 after intramuscular administration (20 mg/kg) to mice is shown in the following Table.

### Mouse Urinary Recovery of Antibiotics

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mice</th>
<th>Dose (mg/kg)</th>
<th>Dosing Route</th>
<th>% Recovered</th>
<th>Sol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 1</td>
<td>3</td>
<td>20 mg/kg</td>
<td>IM</td>
<td>61.7</td>
<td>64.5±14.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>2.8</td>
<td>7.0</td>
</tr>
</tbody>
</table>

Compounds prepared in 0.1 M phosphate buffer and dosed IM
Assay Organism: *B subtilis* ATCC 6633 pH 7 1ml/l (B/B)
BCH-1 is a renal dihydropeptidase inhibitor

The following examples illustrate but do not limit the scope of the present invention.
Example 1

Preparation of 3-[2-(1-Tetrahydrothiophenium)ethythio]-6-alpha-[1-(R)-hydroxyethyl]-4-R-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

Preparation of p-nitrobenzyl-3-(2-methanesulfonyloxyethythio)-6-alpha-(1-(R)hydroxyethyl)-4R-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate
Preparation of p-nitrobenzyl-3-(2-methanesulfonyloxyethylthio)-6α-[1-(R)hydroxyethyl]-4R-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

To a cooled (-15°C) solution of (5R,6S)p-nitrobenzyl 6-(1'R-hydroxyethyl-4-methyl-3,7-dioxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (3.78 g, 10.44 mmol) in dry acetonitrile (40 mL) over nitrogen atmosphere was added diphenyl chlorophosphate (2.38 mL, 11.5 mmol) dropwise followed by diisopropylethylamine (1.97 mL, 11.5 mmol). After 1.5 h at -15°C, trimethylsilyl chloride (1.48 mL, 11.5 mmol) was added followed by diisopropylethylamine (1.97 mL, 11.5 mmol). After stirring for 30 minutes at -15°C, mercaptoethanol (0.95 mL, 13.56 mmol) and diisopropylethylamine (2.38 mL, 13.65 mmol) was added. After stirring for 30 minutes at 5°C, a second equivalent of mercaptoethanol and diisopropylethylamine was added. The solution stirred at 5°C for 1.5 hours longer and then was cooled to -15°C. Methanesulfonyl chloride (0.89 mL, 11.5 mmol) followed by diisopropylethylamine (1.97 mL, 11.5 mmol) was added and continued stirring at -15°C for 45 minutes. A second equivalent of methanesulfonyl chloride and base was added followed by a third equivalent 30 minutes later. The reaction mixture was then stirred at -20°C for 20 h (overnight). The mixture was diluted with ethyl acetate (400 mL) and washed successively in the cold with water (2x200 mL), 0.5N HCl (200 mL), water (200 mL), 0.5 M sodium bicarbonate (200 mL), water (200 mL) and brine (200 mL). After drying over anhydrous magnesium sulfate, the solvent was removed in vacuo and purified.
by flash chromatography on silica gel (mesh 200-400) eluting with a cold (-78°C) dichloromethane-acetonitrile mixture (% acetonitrile, amount: 0% (400 mL), 2% (1000 mL), 5% (1000 mL), 10% (2000 mL), 20% (1000 mL)) to give 2.54 g (42.5%) of the title compound: \( \text{ir (CH}_2\text{Cl}_2) \nu_{\text{max}}: 1775 \text{ cm}^{-1} (\text{C=O of } \beta\text{-lactam}) \) 1520 cm\(^{-1}\) (CO \( \text{ester} \)); \( \text{Hmr (CDCl}_3 \) \( \delta: 1.26 (d, J=7.6 \text{ Hz}, 3H, \text{CH}_2-4), 1.36 \) (d, J=6.6 Hz, 3H, CH\(_3\)-4), 1.69 (bs, 1H, OH), 3.02 (s, 3H, CH\(_3\)SO\(_2\), 3.05-3.57 (M, 4H, H-4, H-6 and \( \text{SCH}_2 \) overlapping), 4.19-4.43 (M, 4H, CH\(_2\)-O, H-1' and H-5 overlapping), 5.36 (AB', J=13.8 Hz, 2H, CH\(_2\)-PNB), 7.63 (d, J=8.6 Hz, 2H, ArH), 8.22 ppm (d, J=8.6 Hz, 2H ArH).
Preparation of p-nitrobenzyl 3-(2-iodoethylthio)-6α-[1-(R)-hydroxyethyl]-4R-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

A solution of p-nitrobenzyl 3-(2-methanesulfonyloxyethylthio)-6α-[1-(R)hydroxyethyl]-4R-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (2.54 g, 5.08 mmol), sodium iodide (5.6 g, 37.6 mmol) in acetone (150 mL) was heated under reflux for 2.5 h. The solvent was removed in vacuo and the residue was triturated with cold water (100 mL) and extracted with cold dichloromethane (5x100 mL). The combined extracts were washed with cold water (2x100 mL), dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. The product was purified by flash chromatography on silica gel (80 g, mesh 200-400) eluting with a cold (−78°C) mixture of acetonitrile-dichloromethane (% acetonitrile, quantity mL; 0% (500 mL), 5% (1 L), 10% (1.5 L) to give 2.36 g (87%) of the title compound after removal of the solvent: ir (CH2Cl2) v max: 1775 (CO of β-lactam); 1520 cm−1 (CO ester); 1Hmr (CDCl3) δ: 1.28 (d, J=7.4 Hz, 3H, CH3-4) 1.36 (d, J=6.5 Hz, 3H, CH3CHOH), 1.69 (d, J=2.5 Hz, 1H, OH), 3.13-3.47 (m, 6H, SCH2, CH2I, H-6 and H-4), 4.16-4.33 (M, 2H, H-5 and H-1 overlapping), 5.36 (ABq, J=13.7 Hz, 2H, CH2PNB), 7.64 (d, J=8.8 Hz, 2H, ArH), 8.22 ppm (d, J=8.8 Hz, 2H, ArH).
Preparation of 3-[2-(1-tetrahydrothiophenium)ethylthio]-6α-[1-(R)-hydroxyethyl]-4R-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

To a cooled (5°C) solution of p-nitrobenzyl 3-(2-idoethyl-thio)-6α-[1-(R)-hydroxyethyl]-4R-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.100 g, 0.188 mmol) in tetrahydrofuran (4 mL) was added tetrahydrothiophene (0.084 mL, 0.94 mmol) dropwise followed by a solution of silver perchlorate (0.0586 g, 0.28 mmol) in tetrahydrofuran (1 mL). After 45 minutes of stirring at room temperature, the reaction mixture was cooled to 5°C and diluted with cold 0.05 M pH 7.0 phosphate buffer (9.0 mL, 0.45 mmol) and washed with ether (2x10 mL). Then, 10% Pd/C (100 mg), ether (16 mL) and tetrahydrofuran (16 mL) was added to the aqueous phase. The mixture was hydrogenated at 15°C at 40-45 psi for 1 hour and then additional 10% Pd/C (50 mg) was added. Hydrogenolysis continued for 1 hour longer at room temperature and at 45 psi. The reaction mixture was filtered through glass fiber and the catalyst was washed with water (5 mL) to give a 2 phase filtrate. The aqueous phase was washed with ether (2x10 mL) and then purged under vacuum. The product was purified by reversed phase chromatography on µBondapak C\textsubscript{18} silica gel (25 g) eluting in the cold with water (200 mL), 2% acetonitrile-water (200 mL) and 5% acetonitrile-water (200 mL) to give 0.024 g (36%) of the title compound as a white solid: purity >99% by hplc having 3.47 minute retention time (C\textsubscript{18} µBondapak, uv detector 298 nm, 13% CH\textsubscript{3}CN-H\textsubscript{2}O, flow rate 1 mL/min); uv (H\textsubscript{2}O, pH 7.4) λ\textsubscript{max}': 298 nm (8538); ir (Nujol) ν\textsubscript{max}': 1750 (CO of β-lactam), 1595 cm\textsuperscript{-1} (CO carboxylate); \textsuperscript{1}Hmr (D\textsubscript{2}O)
6:1.21 (d, J=7.23 Hz, 3H, CH$_3$-4), 1.29 (d, J=6.35 Hz, 3H, CH$_3$CHO
2.23-2.80 (M, 4H, SCH$_2$CH$_2$CH$_2$), 3.04-3.19 (M, 1H, H-4), 3.35-3.70
(M, 9H, SCH$_2$CH$_2$SCH$_2$, H-6), 4.19-4.31 ppm (M, 2H, H-1' and H-5'
overlapping); the half-life was evaluated to be 27.4 h at 37°C in pH 7.4 phosphate buffer.
Example 2

Preparation of 3-[2-(1-Tetrahydrothiophenium)ethyldiene]-6a-[1-(R-hydroxyethyl)-48-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

A. p-Nitrobenzyl 3-(2-Hydroxyethylthio)-6a-[1-(R)-hydroxyethyl]-48-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate
A solution of 1.75 g (4.85 mmole) of p-nitrobenzyl 6α-[1-(R)-hydroxyethyl]-3,7-dioxo-4α-methyl-1-azabicyclo-(3.2.0)hept-2-ene-2-carboxylate (24) in 20 mL of acetonitrile is cooled to 0°C under a nitrogen atmosphere. A solution of 726 mg (7.18 mmole) of diisopropylethylamine is 2 mL of acetonitrile is added followed by a dropwise addition of 1.51 g (5.60 mmole) of diphenyl chlorophosphate in 12 mL of acetonitrile over a period of 3 minutes. The resulting solution is stirred at 0°C for 20 minutes to provide p-nitrobenzyl 3-(diphenylphosphoryloxy)-6α-[1-(R)-hydroxyethyl]-4α-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate. To this solution is added a solution of 726 mg (7.18 mmole) of diisopropylethylamine in 2 mL of acetonitrile followed by a solution of 439 mg (5.63 mmole) of 2-mercaptoethanol in 2 mL of acetonitrile. The reaction solution is stirred at 0°C for 3 hours and then diluted with 200 mL of ethyl acetate and washed with 200 mL of water, 100 mL of 20% aqueous H₃PO₄, and brine. Evaporation of the dried (MgSO₄) solution gives the title compound 25.
B. \( p \)-Nitrobenzyl 3-(2-Methanesulfonyloxyethylthio)-6α-[1-(R)-hydroxyethyl]-4β-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

To a solution of 4.5 g (10.3 mmole) of 25 in 200 mL of tetrahydrofuran is added to -40°C, 1.3 g (11.3 mmole) of methanesulfonyl chloride followed by a dropwise addition of 1.26 g (12.4 mmole) of triethylamine in 5 mL of tetrahydrofuran. The reaction mixture is stirred for 5 hours at -40°C, and then 2 hours at -30°C under a nitrogen atmosphere. It is then poured into a mixture of ethyl acetate (700 mL) and 5% aqueous phosphoric acid (1000 mL). The organic layer is washed with brine, dried over \( \text{MgSO}_4 \), filtered and condensed to a syrup. This material was purified by silica gel column chromatography (elution with methylene chloride-ethyl acetate (3:1 v/v)) to give the title compound 26.
carbapenem compound of the present invention, i.e. 3-[(2-(1-

C. \( \text{p-Nitrobenzyl3-}(2\text{-Iodoethylthio})\text{-6a-}[1-(R)\text{-hydroxyethyl}]\text{-48-}
\text{methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate} \)

A solution of 367 mg (0.72 mmmole) of intermediate 26 and 216 mg (1.4 mmmole) of sodium iodide in 20 mL of acetone is heated at reflux for 4 hours. Evaporation of the acetone leaves a white amorphous solid which is suspended in ether (10 mL), water (10 mL). Filtration of the white solid and vacuum drying gives the title compound 27.
D. 3-[2-(1-Tetrahydrothiophenium)ethylthio]-8a-[1-(R)-hydroxyethyl]-4β-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

Tetrahydrothiophene (0.03 mL; 0.35 mmole) is added to a solution of p-nitrobenzyl 3-(2-iodoethylthio)-6a-[1-(R)-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (104 mg; 0.2 mmole) in tetrahydrofuran (5 mL) followed by a solution of silver perchlorate (60 mg; 0.3 mmole) in tetrahydrofuran (0.5 mL). After stirring at room temperature for 1 h, the solvent is
removed to leave crude 28. This is taken directly and hydrogenated in the following manner. The compound in a mixture of ether (20 mL), tetrahydrofuran (20 mL), water (20 mL) containing potassium bicarbonate (40 mg; 0.4 mmole) and dibasic potassium phosphate (35 mg; 0.2 mmole), and 10% palladium on charcoal (120 mg) is hydrogenated at 40 psi on a Parr shaker for 60 minutes. The mixture is then filtered and the catalyst washed with water (2 x 5 mL). The filtrate is combined with the water washings and this is extracted with ether (2 x 50 mL). The aqueous phase is taken and lyophilized. The residual material is purified on a C₁₈ BONDAPAK reversed phase column (7 g, Waters Associates), eluting with water under a pressure of 8 psi. Combining those fractions which absorb at 290 nm followed by lyophilization gives the title compound.
Example 3

Preparation of 3-[2-[4-(1,4-Oxathianium)]ethylthio]-6α-[1-(R)-hydroxyethyl]-48-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate
1,4-Oxathiane (0.033 mL; 0.35 mmole) is added to a solution of p-nitrobenzyl 3-(2-iodoethylthio)-6α-[1-(R)-hydroxyethyl]-4β-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (104 mg; 0.2 mmole) in tetrahydrofuran (5 mL) followed by a solution of silver perchlorate (60 mg; 0.3 mmole) in tetrahydrofuran (0.5 mL). After stirring at room temperature for 1 h, the solvent is removed to leave crude 29. This is taken directly and hydrogenated in the following manner. The compound in a mixture of ether (20 mL), tetrahydrofuran (20 mL), water (20 mL) containing potassium bicarbonate (40 mg; 0.4 mmole) and dibasic potassium phosphate (35 mg; 0.2 mmole), and 10% palladium on charcoal (120 mg) is hydrogenated at 40 psi on a Parr shaker for 60 minutes. The mixture is then filtered and the catalyst washed with water (2 x 5 mL). The filtrate is combined with the water washings and this is extracted with ether (2 x 50 mL). The aqueous phase is taken and lyophilized. The residual material is purified on a C18 BONDAPAK reversed phase column (7 g, Waters Associates), eluting with water under a pressure of 8 psi. Combining those fractions which absorb at 290 nm followed by lyophilization gives the title compound.
Example 4

Preparation of 3-[(2-(p-Chlorophenyl)methylene)sulfonyl]ethylthio]-6α-[1-(R)-hydroxymethyl]-4β-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate
CONT'D
p-Chlorothioanisole (56 mg; 0.35 mmole) is added to a solution of p-nitrobenzyl 3-(2-idoethyliothio)-6α-[1-(R)-hydroxyethyl]-4β-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (104 mg; 0.2 mmole) in tetrahydrofuran (5 mL) followed by a solution of silver perchlorate (60 mg; 0.3 mmole) in tetrahydrofuran (0.5 mL). After stirring at room temperature for 2 h, the solvent is removed to leave crude 30. This is taken directly and hydrogenated in the following manner. The compound in a mixture of ether (20 mL), tetrahydrofuran (20 mL), water (20 mL) containing potassium bicarbonate (40 mg; 0.4 mmole) and dibasic potassium phosphate (35 mg; 0.2 mmole), and 10% palladium on charcoal (120 mg) is hydrogenated at 40 psi on a Parr shaker for 60 minutes. The mixture is then filtered and the catalyst washed with water (2 x 5 mL). The filtrate is combined with the water washings and this is extracted with ether (2 x 50 mL). The aqueous phase is taken and lyophilized. The residual material is purified on a C18 BONDApak reversed phase column (7 g, Waters Associates), eluting with water under a pressure of 8 psi. Combining those fractions which absorb at 290 nm followed by lyophilization gives the title compound.
-hydroxy-carboxylate. by a relative for water Palladium at al with the and the amer. M, Kat-er.Sad by re2.ative ~rc~ -N 3 3 -050-R Jk
The claims defining the invention are as follows:

1. A compound of the formula

   \[
   \text{Structure image}
   \]

   wherein \( R^3 \) is hydrogen and \( R^1 \) is selected from the group consisting of hydrogen; substituted and unsubstituted: alkyl, alkenyl and alkynyl, having from 1-10 carbon atoms; cycloalkyl and cycloalkylalkyl, having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moieties; phenyl; aralkyl, aralkenyl and aralkynyl wherein the aryl moiety is phenyl and the aliphatic portion has 1-6 carbon atoms; heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl wherein the hetero atom or atoms in the above-named heterocyclic moieties are selected from the group consisting of 1-4 oxygen, nitrogen or sulfur atoms and the alkyl moieties associated with said heterocyclic moieties have 1-6 carbon atoms; wherein the substituent or substituents relative to the above-named radicals are independently selected from the group consisting of
C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted by amino, halo, hydroxy or carboxyl

\[-\text{halo}\]
\[-\text{OR}\]
\[-\text{ONR}_{\text{3-R}}\]
\[-\text{CN}_{\text{3-R}}\]
\[-\text{NR}_{\text{3-R}}\]
\[-\text{NR}_{\text{3-R}}\]
\[-\text{SO}_{\text{2-NA}_{\text{3-R}}\text{4}}\]
\[-\text{NH}_{\text{3-R}}_{\text{4}}\]
\[-\text{R-CNR}_{\text{4}}\]
\[-\text{CO}_{\text{2-R}}\]
\[-\text{O}_{\text{R}}\]
\[-\text{Si}_{\text{2-R}}\]
\[-\text{Cl}\]
R\textsuperscript{15} is selected from the group consisting of substituted and unsubstituted: alkyl, alkenyl and alkynyl, having from 1-10 carbon atoms; cycloalkyl, cycloalkylalkyl and alkylcycloalkyl, having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moieties; spirocycloalkyl having 3-6 carbon atoms; phenyl; aralkyl, aralkenyl and aralkynyl wherein the aryl moiety is phenyl and the aliphatic portion has 1-6 carbon atoms; heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl wherein the hetero atom or atoms in the above-named heterocyclic moieties are selected from the group consisting of 1-4 oxygen; nitrogen and sulfur atoms and the alkyl moieties associated with said heterocyclic moieties have 1-6 carbon atoms; wherein the substituent or substituents relative to the above-named radicals are selected from the group consisting of: amino, mono-, di- and trialkylamino, hydroxyl, alkoxy, mercapto, alkylthio, phenylthio, sulfanoyl, amidino, guanidino, nitro, chloro, bromo, fluoro, cyano and carboxy; and wherein the alkyl moieties of the above-recited substituents have 1-6 carbon atoms; and R\textsuperscript{10} and R\textsuperscript{11} each independently represents

(a) C\textsubscript{1-6} alkyl, C\textsubscript{2-5} alkenyl, C\textsubscript{2-6} alkynyl; C\textsubscript{3-6} cycloalkyl or cycloalkylalkyl having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moiety, said alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkyl-alkyl group being optionally substituted by 1-3 substituents
C₁⁻C₆ alkyl optionally substituted by 1-3 hydroxy, C₁⁻C₆ alkoxy, carboxy, halo, amino, C₁⁻C₆ alkylamino or di(C₁⁻C₆)alkylamino groups, hydroxy, C₁⁻C₆ alkoxy, C₁⁻C₆ alkanoyloxy, amino, C₁⁻C₆ alkylamino, di(C₁⁻C₆)alkylamino, C₁⁻C₆ alkanoylamino, carboxy, C₁⁻C₆ alkoxy-carboxyl, halo, oxo or phenyl; or wherein said heterocyclic ring

\[ \text{R}^{10} - \text{R}^{11} \]

is fused to a C₅-C₆ carbocyclic ring, a phenyl ring, a 5-6 member heterocyclic ring or a 5-6 member heteroaryl ring, all of which rings may be optionally substituted by 1-3 of the substituents referred to above for the

\[ \text{R}^{10} - \text{R}^{11} \]

ring; or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1, wherein \( R^1 \) is hydrogen,

\[ \text{CH}_3 \]

3. A compound according to Claim 1, wherein \( R^1 \) and \( R^8 \) taken together represent

\[ \text{BOCH}_2 \]

4. A compound according to Claim 1, wherein \( R^4 \) is

\[ \text{OH} \]

\[ \text{CH}_3 \text{C}^- \]
5. A compound according to Claim 1, wherein \( R^1 \) is

\[
\text{CH}_3\text{-CH-}
\]

and the absolute configuration is 5R, 6S, 6R.

6. A compound according to Claim 1, 2, 3, 4, or 5 wherein

\( A \) is \(-\text{CH}_2\text{CH}_2-\).

7. A compound according to Claim 1, 2, 3, 4, or 5 wherein

\( A \) is \(-\text{CH}_2\text{CH}_2-\) and \( R^{15} \) is \( C_1-C_6 \) alkyl, phenyl or phenyl\( (C_1-C_6) \)alkyl.

8. A compound of the formula

\[
\begin{align*}
\text{(R)} & \quad \text{OH} \\
\text{S} & \quad \text{A} \quad \text{S} \\
\text{COOH}^2 & \quad \text{R}^{10} \quad \text{R}^{11}
\end{align*}
\]

wherein \( A \) is \( C_2-C_6 \) straight or branched chain alkylene; \( R^2 \) is hydrogen, an anionic charge or a conventional readily removable carboxyl protecting group; and \( R^{10} \) and \( R^{11} \) each independently represents

(a) \( C_1-C_6 \) alkyl, \( C_2-C_6 \) alkenyl, \( C_2-C_6 \) alkynyl, \( C_3-C_6 \) cycloalkyl or cycloalkylalkyl having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moiety, said alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkylalkyl group being optionally substituted by 1-3 substituents.
independently selected from hydroxy, \( C_1-C_6 \) alkoxy, \( C_1-C_6 \) alkanoyloxy, carboxy, \( C_1-C_6 \) alkoxy-carbonyl, amino, \( C_1-C_6 \) alkylamino, di-(\( C_1-C_6 \) alkylamino, \( C_1-C_6 \) alkanoylamino, phenyl, phenyl substituted by 1-3 halo, \( C_1-C_6 \) alkoxy, \( C_1-C_6 \) alkyl, carboxy, carboxy(\( C_1-C_6 \) alkyl, amino, \( C_1-C_6 \) alkylamino, di-(\( C_1-C_6 \) alkylamino or di-(\( C_1-C_6 \) alkylamino(\( C_1-C_6 \) alkyl, halo or oxo;

(b) phenyl optionally substituted by 1-3 halo, \( C_1-C_6 \) alkoxy, \( C_1-C_6 \) alkyl, carboxy, amino, \( C_1-C_6 \) alkylamino or di-(\( C_1-C_6 \) alkylamino groups;

(c) heterocyclyl or heterocyclylalkyl wherein the heterocyclic moiety is a 4-6 membered ring having 1-3 heteroatoms selected from O, N and S and the alkyl moiety has 1-6 carbon atoms, said heterocyclyl or heterocyclylalkyl ring being optionally substituted by 1-3 \( C_1-C_6 \) alkyl or \( C_1-C_6 \) alkoxy groups; or

(d) heteroaryl or heteroaralkyl wherein the heterocyclic moiety is a 5-6 membered aromatic ring having 1-3 heteroatoms selected from O, N and S and the alkyl moiety has 1-6 carbon atoms, said heteroaryl or heteroaralkyl ring being optionally substituted by 1-3 \( C_1-C_6 \) alkyl, \( C_1-C_6 \) alkoxy, carboxy, carboxy(\( C_1-C_6 \) alkyl, amino, \( C_1-C_6 \) alkylamino, di-(\( C_1-C_6 \) alkylamino, amino(\( C_1-C_6 \) alkyl or di-(\( C_1-C_6 \) alkylamino(\( C_1-C_6 \) alkyl groups; or wherein \( R^{10} \) and \( R^{11} \) taken together with the

\[ + \]

S
to which they are attached represent a 4-6 member sulfur-containing heterocyclic ring containing 0-2 double bonds and 0-2 additional heteroatoms selected from O, N and S, said ring being attached to A through a sulfur atom, thereby forming a sulfonium group, said heterocyclic ring being optionally substituted by 1-3 substituents independently selected from:
C₆₋₆ alkyl optionally substituted by 1-3 hydroxy, 
C₆₋₆ alkox, carboxy, halo, amino, C₆₋₆ alkylamino 
or di(C₁₋₆)alkylamino group, hydroxy, C₆₋₆ alkox, 
C₆₋₆ alkanoyloxy, amino, C₆₋₆ alkyamino, di(C₁₋₆)- 
alkylamino, C₆₋₆ alkanoylamino, carboxy, C₆₋₆ alkoxy- 
carbonyl, halo, o xo or phenyl; or wherein said hetero- 
cyclic ring

\[ \bigoplus \]

is fused to a C₅₋₆ carbocyclic ring, a phenyl ring, 
a 5-6 member heterocyclic ring or a 5-6 member hetero-
carbonyl ring, all of which rings may be optionally sub-
stituted by 1-3 of the substituents referred to above 
for the

\[ \bigoplus \]

ring; or a pharmaceutically acceptable salt thereof.

9. A compound according to Claim 8, wherein \( A \) is \(-CH₂CH₂-\).

10. A compound of the formula

\[ \text{OH} \]
\[ \text{(R)} \]
\[ - \]
\[ \text{N} \]
\[ \text{SC₂H₅-S} \]
\[ \text{COOR} \]

wherein \( R \) is hydrogen, an anionic charge or a conventional 
readily removable carboxyl protecting group; and

\[ \bigoplus \]

represents

\[ \bigoplus \]

wherein \( R₁, A², \) and \( A²₅ \) are as defined above and \( R² \) is a con-
or a pharmaceutically acceptable salt thereof.

11. A compound of the formula

wherein $R^2$ is hydrogen, an anionic charge or a conventional readily removable carboxyl protecting group, providing that when $R^2$ is hydrogen or a protecting group, there is also present a counter anion, or a pharmaceutically acceptable salt thereof.
12. The compound according to Claim 11, wherein $R^2$ is p-nitrobenzyl or allyl.

13. The compound according to Claim 11; wherein $R^2$ is an anionic charge.

14. A process for the preparation of a compound of the formula

$$\text{I}$$

wherein $R^8$ is hydrogen and $R^1$ is selected from the group consisting of hydrogen, substituted and unsubstituted alkyl, alkenyl and alkynyl, having from 1-16 carbon atoms; cycloalkyl and cycloalkylalkyl, having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moieties; phenyl, aralkyl, aralkenyl and aralkynyl wherein the aryl moiety is phenyl and the aliphatic portion has 1-6 carbon atoms; heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl wherein the hetero atom or atoms in the above-named heterocyclic moieties are selected from the group consisting of 1-4 oxygen, nitrogen or sulfur atoms and the alkyl moieties associated with said heterocyclic moieties have 1-6
carbon atoms; wherein the substituent or substituents relative to the above-named radicals are independently selected from the group consisting of

\[ \text{C}_1-\text{C}_6 \text{ alkyl optionally substituted by } \]

- amin, halo, hydroxy or carboxyl

- halo

- \(-\text{OR}^3\)

- \(-\text{OCNR}_3^3\)

- \(-\text{CNR}_3^3\)

- \(-\text{NR}_3^3\)

- \(-\text{SO}_2\text{NR}_3^3\)

- \(-\text{N}_3\text{CNR}_3^3\)

- \(-\text{CO}_2\text{R}_3^3\)

- \(-\text{NR}_3^3\)

- \(-\text{CR}_3^3\)

- \(-\text{SNR}_3^3\)

- \(-\text{NR}_3^3\)

- \(-\text{CR}_3^3\)

- \(-\text{ONR}_3^3\)

- \(-\text{CR}_3^3\)

- \(-\text{ONR}_3^3\)

- \(-\text{CR}_3^3\)

- \(-\text{CN}^3\)
wherein, relative to the above-named substituents, the groups $R_3$ and $R_4$ are independently selected from hydrogen; alkyl, alkenyl and alkynyl; having from 1-10 carbon atoms; cycloalkyl, cycloalkylalkyl and alkycycloalkyl, having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moieties; phenyl; aralkyl, aralkenyl and aralkynyl wherein the aryl moiety is phenyl and the aliphatic portion has 1-6 carbon atoms; and heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl wherein the hetero atom or atoms in the above-named heterocyclic moieties are selected from the group consisting of 1-4 oxygen, nitrogen or sulfur atoms and the alkyl moieties associated with said heterocyclic moieties have 1-6 carbon atoms, or $R_3$ and $R_4$ taken together with the nitrogen to which at least one is attached may form a 5-or 6-membered nitrogen-containing heterocyclic ring; $R^9$ is as defined for $R^3$ except that it may not be hydrogen; or wherein $R^1$ and $R^8$ taken together represent $C_2$-$C_{10}$ alkylidene or $C_2$-$C_{10}$ alkylidene substituted by hydroxy; $X$ is $C_2$-$C_6$ straight or branched chain alkylene; $R^2$ is hydrogen, an anionic charge or a conventional readily removable carboxyl protecting group, providing that when $R^2$ is hydrogen or a protecting group, there is also present a counter anion;
$R^{15}$ is selected from the group consisting of substituted and unsubstituted: alkyl, alkenyl and alkyndyl, having from 1-10 carbon atoms; cycloalkyl, cycloalkylalkyl and alklycycloalkyl, having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moieties; spirocycloalkyl having 3-6 carbon atoms; phenyl; aralkyl, aralkenyl and aralkynyl wherein the aryl moiety is phenyl and the aliphatic portion has 1-6 carbon atoms; heteroaryl, heteroaralkyl, heterocyclyl and heterocyclicalkyl wherein the hetero atom or atoms in the above-named heterocyclic moieties are selected from the group consisting of 1-4 oxygen, nitrogen and sulfur atoms and the alkyl moieties associated with said heterocyclic moieties have 1-6 carbon atoms; wherein the substituent or substituents relative to the above-named radicals are selected from the group consisting of: amino, mono-, di- and trialkylamino, hydroxyl, alkoxyl, mercapto, alkylthio, phenylthio, sulfamoyl, amidino, guanidino, nitro, chloro, bromo, fluoro, cyano and carboxyl; and wherein the alkyl moieties of the above-recited substituteds have 1-6 carbon atoms; and $R^{10}$ and $R^{11}$ each independently represents

(a) $C_1-C_6$ alkyl, $C_2-C_6$ alkenyl, $C_2-C_6$ alkynyl, $C_3-C_6$ cycloalkyl or cycloalkylalkyl having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moiety, said alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkylalkyl group being optionally substituted by 1-3 substituents
to which they are attached represent 4 to 6 membered
containing heterocyclic ring containing a double bond, and
and 0-2 additional heteroatoms selected from O, N and S,
said ring being attached to A through a sulfur atom,
said heterocyclic ring
said ring being optionally substituted by 1-3 substituents
independently selected from:

(4) heterocyclic, or heterocycloalkyl, wherein the heterocyclic
being optionally substituted from 0, N and S and the alkoxy groups

(5) heterocyclic, or heterocycloalkyl, wherein the heterocyclic
being optionally substituted from 0, N and S and the alkoxy groups

(6) heterocyclic, or heterocycloalkyl, wherein the heterocyclic
being optionally substituted from 0, N and S and the alkoxy groups

(7) alkoxy, carboxy, carbonyl, di-(C1-C6) alkoxy, di-(C1-C6) amido,
di-(C1-C6) alkyl, di-(C1-C6) aryl, di-(C6-C10) aryl, di-(C6-C10) alkyl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
di-(C6-C10) alkoxy, di-(C6-C10) amido, di-(C6-C10) alkyl, di-(C6-C10) aryl,
alkoxy, alkenyl, amine, C₁₋₅ alkyl, C₁₋₅ and with 1-3 halo, C₁₋₅ alkyl, carboxyl, halo, amino, C₁₋₅ alkylamino or di(C₁₋₅)alkylamino groups, hydroxy, C₁₋₅ alkoxy, C₁₋₅ alkanoyloxy, amino, C₁₋₅ alkylamino, di(C₁₋₅)-alkylamino, C₁₋₅ alkanoylamino, carboxy, C₁₋₅ alkoxy-carboxyl, halo, exo or phenyl; or wherein said heterocyclic ring

\[
\begin{align*}
& R^{10} - \sigma - R^{11} \\
\end{align*}
\]

is fused to a C₅₋₆ carbocyclic ring, a phenyl ring, a 5-6 member heterocyclic ring or a 5-6 member heteroaryl ring, all of which rings may be optionally substituted by 1-3 of the substituents referred to above for the

\[
\begin{align*}
& R^{10} - \sigma - R^{11} \\
\end{align*}
\]

ring; or a pharmaceutically acceptable salt thereof, which process comprises subjecting an intermediate of the formula

\[
\begin{align*}
& R^{15} \\
\end{align*}
\]

wherein R¹, R⁸, R¹⁵ and λ are as defined above and R²' is a conventional readily removable carboxyl group to nucleophilic displacement in an inert organic solvent and in the presence of silver ion with a sulfide reagent of the formula

\[
\begin{align*}
& R^{10} - \sigma - R^{11} \\
\end{align*}
\]

wherein R¹⁰ and R¹¹ are as defined above so as to displace the iodo group of intermediate II with the group
and form a compound of the formula

$$\text{R}^1 \quad \text{R}^8 \quad \text{R}^{10} \quad \text{R}^{11} \quad \text{R}^{15} \quad \text{S} \quad \text{S} \quad \text{N} \quad \text{COOR}^2 \quad \text{X}^{-}$$

wherein $\text{X}^{-}$ is a counter anion and $\text{R}^1$, $\text{R}^8$, $\text{R}^{10}$, $\text{R}^{11}$, $\text{R}^{15}$ and $\text{R}^{2'}$ are as defined above, and, if desired, removing the carbonyl protecting group $\text{R}^{2'}$ to give the corresponding deblocked compound of the formula I, or a pharmaceutically acceptable salt thereof.

A process for the preparation of a compound of the formula

$$\text{R}^1 \quad \text{R}^8 \quad \text{R}^{10} \quad \text{R}^{11} \quad \text{R}^{15} \quad \text{S} \quad \text{S} \quad \text{N} \quad \text{COOR}^2$$

Wherein $\text{R}^8$ is hydrogen and $\text{R}^1$ is selected from the group consisting of hydrogen; substituted and unsubstituted alkyl, alkenyl and alkynyl, having from 1-10 carbon atoms; cycloalkyl and cycloalkylalkyl, having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moieties; phenyl; aralkyl, aralkenyl and aralkynyl wherein the aryl moiety is phenyl and the aliphatic portion has 1-6 carbon
C-15 alkyl optionally substituted with hydroxy or carboxyl groups constituting said heterocyclic moieties associated with said heterocyclic moieties having 1-4 carbon atoms; wherein the substituent or substituents relative to the above-named radicals are independently selected from the following: —CH₃, —OCH₃, —OH, —SH, —COOH, —CONH₂, —COCH₃, —CO₂H, —S(O)₂CH₃, —S(O)₂CH₂CH₃, —S(O)₂CH₂CH₂CH₃, —N(H)₂, —N(CH₃)₂.
wherein, relative to the above-named substituents, the groups R³ and R⁴ are independently selected from hydrogen; alkyl, alkenyl and alkynyl, having from 1-10 carbon atoms; cycloalkyl, cycloalkylalkyl and alkylcycloalkyl, having 3-6 carbon atoms; in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moieties; phenyl; aralkyl, aralkenyl and aralkynyl wherein the aryl moiety is phenyl and the aliphatic portion has 1-6 carbon atoms; and heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl wherein the hetero atom or atoms in the above-named heterocyclic moieties are selected from the group consisting of 1-4 oxygen, nitrogen or sulfur atoms and the alkyl moieties associated with said heterocyclic moieties have 1-6 carbon atoms, or R³ and R⁴ taken together with the nitrogen to which at least one is attached may form a 5- or 6-membered nitrogen-containing heterocyclic ring; R⁹ is as defined for R³ except that it may not be hydrogen; or wherein R¹ and R⁸ taken together represent C₂-C₁₀ alkylidene or C₂-C₁₀ alkylidene substituted by hydroxy; A is C₂-C₆ straight or branched chain alkylene; R² is hydrogen, an anionic charge or a conventional readily removable carboxyl protecting group, providing that when R² is hydrogen or a protecting group, there is also present a counter anion;
R\textsuperscript{15} is selected from the group consisting of substituted and unsubstituted: alkyl, alkenyl and alkynyl, having from 1-10 carbon atoms; cycloalkyl, cycloalkylalkyl and alkylcycloalkyl, having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moieties; spirocycloalkyl having 3-6 carbon atoms; phenyl; aralkyl, aralkenyl and aralkynyl wherein the aryl moiety is phenyl and the aliphatic portion has 1-6 carbon atoms; heteroaryl, heteroaralkyl, heterocyclyl and heterocyclylalkyl wherein the hetero atom or atoms in the above-named heterocyclic moieties are selected from the group consisting of 1-4 oxygen; nitrogen and sulfur atoms and the alkyl moieties associated with said heterocyclic moieties have 1-6 carbon atoms; wherein the substituent or substituents relative to the above-named radicals are selected from the group consisting of: amino, mono-, di- and trialkylamino, hydroxyl, alkoxyl, mercapto, alkylthio, phenylthio, sulfamoyl, amidino, guanidino, nitro, chloro, bromo, fluoro, cyano and carboxy; and wherein the alkyl moieties of the above-recited substituents have 1-6 carbon atoms.

and R\textsuperscript{10} and R\textsuperscript{11} each independently represents

(a) C\textsubscript{1-6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{3-6} cycloalkyl or cycloalkylalkyl having 3-6 carbon atoms in the cycloalkyl ring and 1-6 carbon atoms in the alkyl moiety, said alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkylalkyl group being optionally substituted by 1-3 substituents
said ring being attached to A through a sulfur atom, thereby forming a sulfonium group, said heterocyclic ring being optionally substituted by 1-3 substituents independently selected from:

- $C_1$-$C_6$ alkyl optionally substituted by 1-3 hydroxy, $C_1$-$C_4$ alkoxy, carboxy, halo, amino, $C_1$-$C_6$ alkylamino or di($C_1$-$C_6$)alkylamino groups, hydroxy, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkanoyloxy, amino, $C_1$-$C_6$ alkylamino, di($C_1$-$C_6$)-alkylamino, $C_1$-$C_6$ alkanoylamino, carboxy, $C_1$-$C_6$ alkoxy-carbonyl, halo, oxo or phenyl; or wherein said heterocyclic ring

$$R^{10} \quad \overline{\quad} \quad R^{11}$$

is fused to a $C_5$-$C_6$ carbocyclic ring, a phenyl ring, a 5-6 member heterocyclic ring or a 5-6 member heteroaryl ring, all of which rings may be optionally substituted by 1-3 of the substituents referred to above for the

$$R^{10} \quad \overline{\quad} \quad R^{11}$$

ring; or a pharmaceutically acceptable salt thereof, which process comprises the steps of

1. Reacting an intermediate of the formula

$$\text{III}$$
wherein $R^1$, $R^8$, and $R^{15}$ are as defined above and $R^{2'}$ is a conventional readily removable carboxyl protecting group in an inert organic solvent with diphenyl chlorophosphate in the presence of base to give an intermediate of the formula

\[ \text{IV} \]

wherein $R^1$, $R^8$, $R^{15}$ and $R^{2'}$ are as defined above;

(2) reacting intermediate IV in an inert organic solvent and in the presence of base with a mercaptan agent of the formula

\[ \text{ES-A-OH} \]

wherein $\text{A}$ is as defined above to give an intermediate of the formula

\[ \text{V} \]

wherein $R^1$, $R^8$, $R^{15}$, $\text{A}$, and $R^{2'}$ are as defined above;

(3) reacting intermediate V in an inert organic solvent and in the presence of base with methanesulfonyl chloride or a functional acylating equivalent thereof to give an intermediate of the formula

\[ \text{VI} \]
wherein \( R^1, R^8, R^{15}, A \) and \( R^2' \) are as defined above;

(4) reacting intermediate VI in an inert organic solvent with a source of iodide ion so as to displace the methanesulfonyloxy group with an iodo group and form an intermediate of the formula

\[
\begin{align*}
&\text{II} \\
\end{align*}
\]

wherein \( R^1, R^8, R^{15}, A \) and \( R^2' \) are as defined above; and

(5) subjecting intermediate II to nucleophilic displacement in an inert organic solvent and in the presence of silver ion with a sulfide reagent of the formula

\[
\begin{align*}
&\text{II} \\
\end{align*}
\]

wherein \( R^{10} \) and \( R^{11} \) are as defined above so as to displace the iodo group of intermediate II with the group

\[
\begin{align*}
&\text{II} \\
\end{align*}
\]

and form a compound of the formula

\[
\begin{align*}
&\text{II} \\
\end{align*}
\]

wherein \( X^- \) is a counter anion and \( R^1, R^8, R^{15}, A, R^{10}, R^{11} \)
and $R^2'$ are as defined above, and, if desired, removing the carboxyl protecting group $R^2$ to give the corresponding deblocked compound of formula I, or a pharmaceutically acceptable salt thereof.

16. A process of claim 14 or 15, whereby $3\text{-}[2\text{-}(1\text{-Tetrahydrothiophenium})\text{ethylthio}]\text{-6-alpha-[1-(R)-hydroxysthyl]}\text{-4- R-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate}$ is manufactured.

17. A compound substantially as hereinbefore described with reference to any one of the examples.

18. A process substantially as hereinbefore described with reference to any one of the examples.


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END