

SPECIFICATION

Bis-esters of methanediol with penicillins and penicillanic acid 1,1-dioxide

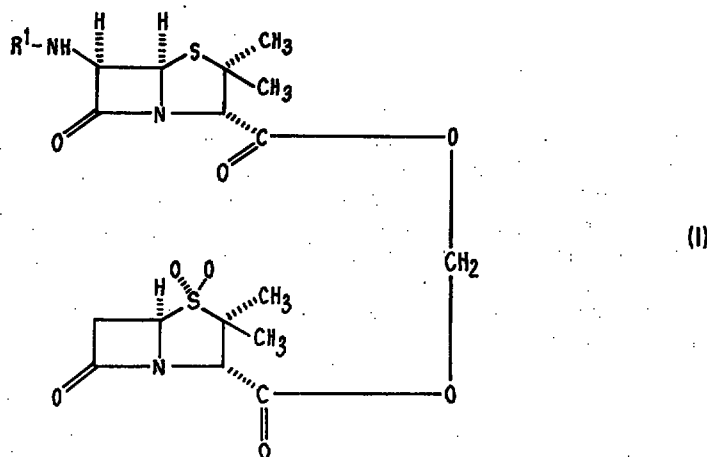
This invention relates to new chemical compounds. More particularly it relates to new chemical compounds which are of value as antibacterial agents. These new antibacterial agents are bis-esters of methanediol, in which one hydroxy group of the methanediol has been esterified with the carboxy group of a 6'-acylaminopenicillanic acid compound, and the other hydroxy group of the methanediol has been esterified with the carboxy group of penicillanic acid 1,1-dioxide.

West German Offenlegungsschrift No. 2,824,535, published December 14, 1978, and Iranian Patent No. 19,601, granted July 12, 1978, disclose penicillanic acid, 1,1-dioxide, and esters thereof readily hydrolyzable *in vivo*, as antibacterial agents and as betalactamase inhibitors. Penicillanic acid 1,1-dioxide and esters thereof readily hydrolyzable *in vivo* increase the antibacterial effectiveness of certain penicillin and cephalosporin compounds against certain bacteria.

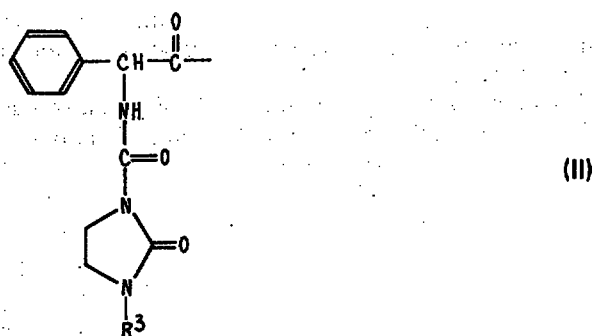
Belgian Patent No. 764,688, granted March 23, 1971, discloses: (a) certain 6'-acylaminopenicillanoyloxymethyl 6-acylaminopenicillanates; (b) certain 6'-acylaminopenicillanoyloxymethyl 6-aminopenicillanates; (c) 6'-aminopenicillanoyloxymethyl 6-aminopenicillanate; and (d) chloromethyl 6-aminopenicillanate. United States Patent No. 3,850,908 discloses chloromethyl esters of several natural, biosynthetic and semi-synthetic penicillin compounds.

The antibacterial agents of the present invention are effectively absorbed from the gastrointestinal tract of mammals, and after absorption they are transformed into a 6-acylaminopenicillanic acid and penicillanic acid 1,1-dioxide.

This invention provides new antibacterial agents of the formula



and the pharmaceutically-acceptable salts thereof, wherein R¹ is selected from 2-phenylacetyl, 2-phenoxyacetyl, 2-carboxy-2-(2-thienyl)acetyl, 2-(4-ethyl-2,3-dioxopiperazinocarbonylamino)-2-phenylacetyl and a group of the formula

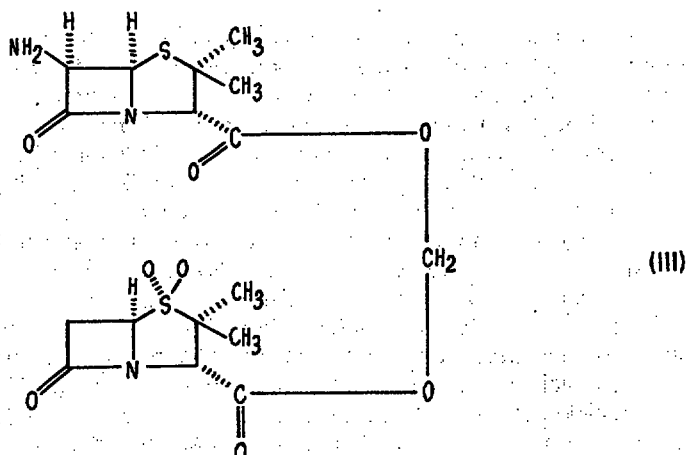


wherein R³ is selected from the group consisting of hydrogen, alkanoyl having from two to four carbons and alkylsulfonyl having from one to three carbons.

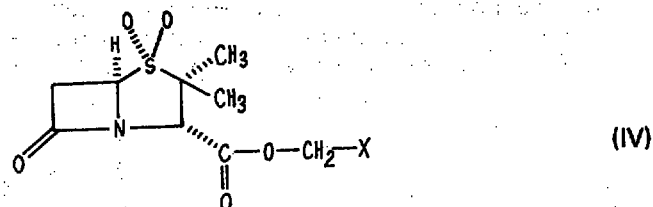
Preferred individual compounds of formula I are:

6'-(2-phenylacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide, and
6'-(2-phenoxyacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide.

The following compounds of the formula:

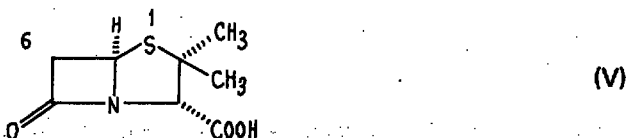


and



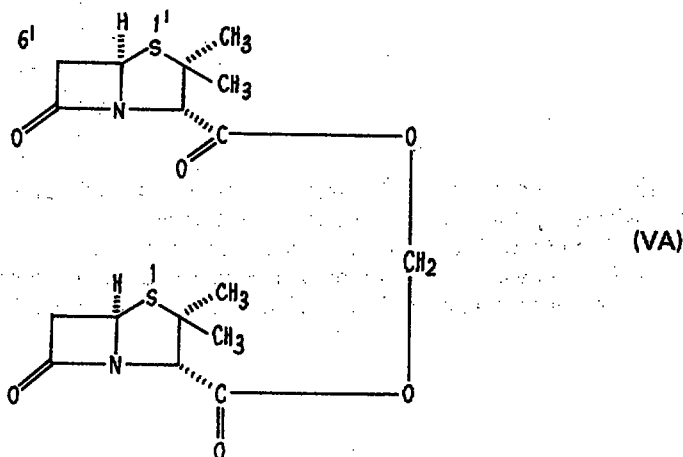
- 5 and the salts thereof, wherein X is a good leaving group are useful as intermediates in the preparation of the compounds of the invention. Examples of X are chloro, bromo, iodo, alkylsulfonyloxy having from one to four carbon atoms, benzenesulfonyloxy and toluenesulfonyloxy. Compounds of formula IV above, wherein X is selected from alkylsulfonyloxy having from 1 to 4 carbon atoms in the alkyl group, benzenesulfonyloxy and toluenesulfonyloxy from the subject of our copending Application published under the serial No. 2,081,269.

This invention relates to derivatives of penicillanic acid, which is represented by the following structural formula

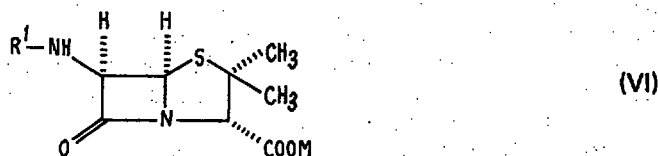


- 15 In formula V, broken line attachment of a substituent to the bicyclic nucleus indicates that the substituent is below the plane of the bicyclic nucleus. Such a substituent is said to be in the alpha-configuration. Conversely, solid line attachment of a substituent to the bicyclic nucleus indicates that the substituent is attached above the plane of the nucleus. This latter configuration is referred to as the beta-configuration.

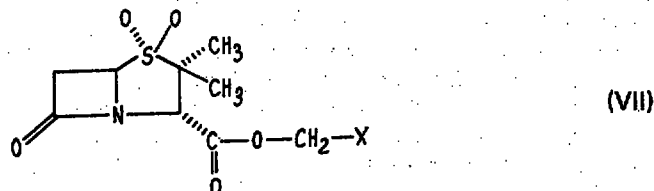
- 20 Using this system, the compounds of formulae I and III are named as derivatives of penicillanoyloxymethyl penicillate (VA), in which primed and unprimed locants are used to distinguish between the two ring systems, viz:



In one method according to the invention a compound of formula I can be prepared by reacting a carboxylate salt of the formula



with a compound of the formula



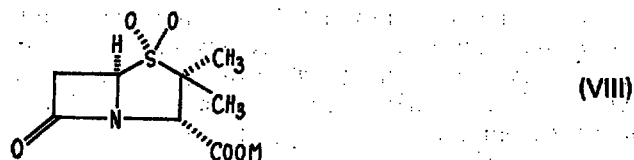
wherein R¹ and X are as previously defined, and M is a carboxylate salt forming cation. A variety of cations can be used to form the carboxylate salt in the compound of formula VI, but salts which are commonly used include: alkali metal salts, such as sodium and potassium salts; alkaline earth metal salts, such as calcium and barium salts; and tertiary amine salts, such as trimethylamine, triethylamine, tributylamine, diisopropylethylamine, *N*-methylmorpholine, *N*-methylpiperidine, *N*-methylpyrrolidine, *N,N'*-dimethylpiperazine and 1,2,3,4-tetrahydroquinoline.

The reaction between a compound of formula VI and a compound of formula VII is usually carried out by contacting the reagents in a polar, organic solvent, at a temperature in the range from about 0° to about 80°C, and preferably from 25° to 50°C. The compounds of formula VI and VII are usually contacted in substantially equimolar proportions, but an excess of either reagent, for example up to a ten-fold excess, can be used. A wide variety of solvents can be used, but it is usually advantageous to use a relatively polar solvent, since this has the effect of speeding up the reaction. Typical solvents which can be used include *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidone, dimethylsulfoxide and hexamethylphosphoramide. The reaction time varies according to a number of factors, but at about 25°C reaction times of several hours, e.g. 12 to 24 hours, are commonly used. When X is chloro or bromo, it is sometimes advantageous to add up to about one molar equivalent of an alkali metal iodide, which has the effect of speeding up the reaction.

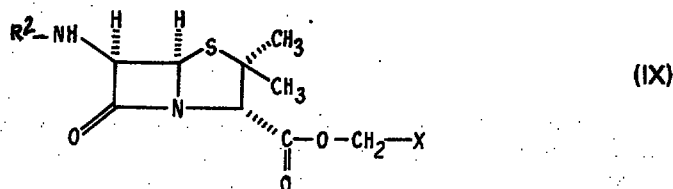
The compound of formula I is isolated in conventional fashion. When a water-miscible solvent is used, it is usually sufficient simply to dilute the reaction medium with an excess of water. The product is then extracted into a water immiscible solvent, such as ethyl acetate, and then the product is recovered by solvent evaporation. When a water immiscible solvent is used, it is usually sufficient to wash the solvent with water, and then recover the product by solvent evaporation. The compound of formula I can be purified by well-known methods, such as recrystallization or chromatography, but due regard must be given to the lability of the beta-lactam ring system.

When the group R¹ in formula VI is 2-carboxy-2-(2-thienyl)acetyl, it is usual to protect this carboxy group before the reaction with the compound of formula VII. In this case it is advantageous to start with a compound of formula VI in which the carboxy group in R¹ is in the form of a readily hydrolyzable ester, e.g. a phenyl or substituted phenyl ester. After the coupling with the compound of formula VII is complete, the free carboxy group in R¹ is liberated by mild, alkaline hydrolysis, e.g. using the technique disclosed in United States Patent No. 3,679,801.

A variation of the foregoing method of preparing a compound of formula I involves reaction of a compound of the formula



with a compound of the formula



wherein M and X are as defined previously, and R² is the group R¹, but with any free carboxy groups protected, followed if necessary by removal of any carboxy protecting group. In the compounds of formula IX, the free carboxy groups are protected with exactly the same protecting groups as described earlier for the compound of formula VI. The reaction between a compound of formula VIII and IX is carried out in exactly the same manner that is used for the reaction of a compound of formula VI with a compound of formula VII. Finally, any carboxy protecting groups are removed, and these are removed in conventional manner for the group involved.

In another method according to the invention, a compound of formula I can be prepared by acylation of the compound of formula III with an activated derivative of an acid of the formula R²—COOH, wherein R² is as previously defined, followed if necessary by removal of any carboxy protecting groups from R². This converts the moiety R²—CO into the moiety R¹—CO.

The acylation reaction is usually conducted in a reaction-inert solvent system. In a typical acylation procedure, from about 0.5 to about three molar equivalents of the activated derivative of the acid of formula R²—COOH is contacted with the compound of formula III, in a reaction-inert solvent system, at a temperature in the range from about -40 to about 30°C, and preferably from about -10 to about 10°C. The preferred ratio of activated derivative to compound of formula III is 1.0:1.0 to 1.2:1.0. Reaction-inert solvents which are commonly used in this acylation are: chlorinated hydrocarbons, such as chloroform and dichloromethane; ethers, such as diethyl ether and tetrahydrofuran; low molecular weight esters, such as ethyl acetate and butyl acetate; low molecular weight aliphatic ketones, such as acetone and methyl ethyl ketone; tertiary amides, such as *N,N*-dimethylformamide and *N*-methylpyrrolidone; acetonitrile; water; and mixtures thereof. When aqueous or partially aqueous solvent systems are used, the pH should be maintained in the range from about 4 to about 9, and preferably about 7.

An activated derivative of the acid of the formula R²—COOH which is commonly used is an acid halide, e.g. the acid chloride. In this instance it is preferable, though not essential, to carry out the acylation in the presence of an acid binder. Suitable acid binders are tertiary amines such as dialkylamines, e.g. triethylamine, *N*-methylmorpholine, *N,N*-dimethylaniline, pyridine and the like, or bicarbonates such as potassium bicarbonate or sodium bicarbonate. Buffer systems such as phosphate buffers can also be used.

Other activated derivatives of the acid of formula R²—COOH which can be used are active esters. Examples of active esters are phenyl esters, such as 4-nitrophenyl and 2,4,5-trichlorophenyl esters; thio esters, such as thiol methyl and thiol phenyl esters; and *N*-hydroxy esters, such as *N*-hydroxysuccinimide and *N*-hydroxyphthalimide esters. These active esters are prepared by methods well-known in the art. In many cases, the active ester can be replaced by the corresponding acid azide, or by the imidazole or triazole amide.

Another method for activation of the acid of formula R²—COOH involves mixed anhydride formation, i.e. mixed carboxylic-carbonic and mixed dicarboxylic anhydride formation. In the case of mixed carboxylic carbonic anhydrides, a carboxylate salt of the acid of formula R²—COOH is usually reacted with a lower-alkyl chloroformate, e.g. ethyl chloroformate; in the case of a mixed dicarboxylic anhydride, a carboxylate salt of the acid of formula R²—COOH is usually reacted with a hindered lower-alkanoyl chloride, e.g. pivaloyl chloride.

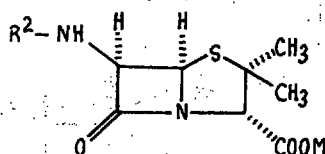
In addition to the above, the acid of formula R²—COOH can be activated by contacting the acid with a peptide coupling agent, according to standard procedures. Such agents include carbodilimides, for example dicyclohexylcarbodiimide, alkoxyacetylenes, for example methoxyacetylene and ethoxyacetylene; and *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline.

The protecting groups used to protect carboxy groups in a compound of formula R²—COOH are those conventionally used during acylation of a 6-aminopenicillanic acid derivative.

The compounds of formula VI are known antibiotics, which are prepared by the published procedures.

The compounds of formula VII are prepared from the compounds of formula VIII by reaction with a compound of formula Y—CH₂—X, wherein X and Y are each good leaving groups, e.g. chloro, bromo, iodo, alkylsulfonyloxy, benzenesulfonyloxy or toluenesulfonyloxy. The same conditions that were described previously for reaction of a compound of formula VII with a compound of formula VI are used for this reaction, except that it is preferable to use an excess of the compound of formula X—CH₂—Y (e.g. a four-fold excess).

In like manner, the compounds of formula IX are prepared by reaction of a compound of formula



(X)

with a compound of formula Y—CH₂—X, wherein R², M, Y and X are as previously defined. The conditions used are the same as those described previously for reaction of a compound of formula VIII with a compound of formula X—CH₂—Y.

The compound of formula III can be prepared by a three-step procedure which comprises: (a) conversion of 6-aminopenicillanic acid into a 6-(protected amino) penicillanic acid; (b) reaction of a salt of the 6-(protected amino)penicillanic acid with a compound of formula VII; and (c) removal of the amino protecting group. A wide variety of amino protecting groups can be used for this purpose, and typical examples are benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl and 2,2,2-trichloroethoxycarbonyl. Steps (a) and (c) are carried out in conventional fashion, and step (b) is carried out in exactly the same manner that was described previously for reaction of a compound of formula VII with a compound of formula VI.

Alternatively, the compound of formula III can be prepared by a four-step procedure which comprises (i) conversion of 6-aminopenicillanic acid into a 6-(protected amino)penicillanic acid; (ii) reaction of a salt of the 6-(protected amino)penicillanic acid with a compound of formula $X-CH_2-Y$, wherein X and Y are as previously defined; (iii) reaction of the product of step (ii) with a compound of formula VIII; and (iv) removal of the amino protecting group. A wide variety of amino protecting groups can be used for this purpose, and typical examples are benzyloxycarbonyl, 4-nitrobenzyloxy carbonyl and 2,2,2-trichloroethoxycarbonyl. Steps (i) and (iv) are carried out in conventional fashion; step (ii) is carried out in exactly the same manner that was described previously for reaction of a compound of formula VIII with a compound of formula $X-CH_2-Y$; and step (iii) is carried out in exactly the same manner that was described previously for reaction of a compound of formula VI with a compound of formula VII.

Penicillanic acid 1,1-dioxide and the salts thereof are prepared by published procedures (see West German Offenlegungsschrift 2,824,535).

Those compounds of formula I which have an acidic function, e.g. a carboxyl group, in the group R^1 will form base salts, and these base salts are to be considered within the scope and purview of this invention. The base salts are prepared by standard methods for penicillin compounds, for example by contacting the acidic and basic components in a stoichiometric ratio, in an aqueous, non-aqueous or partially aqueous medium, as appropriate. They are then recovered by filtration, by precipitation with a non-solvent followed by filtration, by evaporation of the solvent, or in the case of aqueous solutions, by lyophilization, as appropriate. Basic agents which are suitably employed in salt formation belong to both the organic and inorganic type, and they include ammonia, organic amines, alkali metal hydroxides, carbonates, bicarbonates, hydrides and alkoxides, as well as alkaline earth metal hydroxides, carbonates, hydrides and alkoxides. Representative examples of such bases are primary amines, such as n-propylamine, n-butylamine, aniline, cyclohexylamine, benzylamine, p-toluidine and octylamine; secondary amines, such as diethylamine, N-methylaniline, morpholine, pyrrolidine and piperidine; tertiary amines, such as triethylamine, N,N-dimethylaniline, N-ethylpiperidine, N-methylmorpholine and 1,5-diazabicyclo (4.3.0)non-5-ene; hydroxides, such as sodium hydroxide, potassium hydroxide, ammonium hydroxide and barium hydroxide; alkoxides, such as sodium ethoxide and potassium ethoxide; hydrides, such as calcium hydride and sodium hydride; carbonates, such as potassium carbonate and sodium carbonate; and bicarbonates, such as sodium bicarbonate and potassium bicarbonate.

When contemplating therapeutic use for a salt of an antibacterial compound of this invention, it is necessary to use a pharmaceutically-acceptable salt; however, salts other than these can be used for a variety of purposes. Such purposes include isolating and purifying particular compounds, and interconverting pharmaceutically-acceptable salts and their non-salt counterparts.

The compounds of formula I possess *in vivo* antibacterial activity in mammals, and this activity can be demonstrated by standard techniques for penicillin compounds. For example, the compound of formula I is administered to mice in which acute infections have been established by intraperitoneal inoculation with a standardized culture of a pathogenic bacterium. Infection severity is standardized such that the mice receive one to ten times the LD_{100} (LD_{100} : the minimum inoculation required to consistently kill 100 percent of control mice). At the end of the test, the activity of the compound is assessed by counting the number of survivors which have been challenged by the bacterium and also have received the compound of formula I. The compounds of formula I can be administered by both the oral (p.o) and subcutaneous (s.c.) route.

The *in vivo* activity of the antibacterial compounds of this invention makes them suitable for the control of bacterial infections in mammals, including man, by both the oral and parenteral modes of administration. The compounds are useful in the control of infections caused by susceptible bacteria in human subjects. In general, it is the substituent R^1 which determines whether a given bacterium will be susceptible to a given compound of formula I. A compound of formula I breaks down to the corresponding compound of formula VI (or free acid thereof) and penicillanic acid 1,1-dioxide after administration to a mammalian subject by both the oral and parenteral route. Penicillanic acid 1,1-dioxide then functions as a betalactamase inhibitor, and it increases the antibacterial effectiveness of the compound of formula VI (or free acid thereof). For example, when R^1 is 2-phenylacetyl or 2-phenoxyacetyl, the compounds will find use in the control of infections caused by susceptible strains of *Staphylococcus aureus*; when R^1 is 2-carboxy-2-(2-thienyl) acetyl, 2-(4-ethyl-2,3-dioxopiperazinocarbonylamino)-2-phenyl-acetyl or a group of formula II, the compounds are useful in the control of infections caused by susceptible strains of *Escherichia coli*.

In determining whether a particular strain of *Staphylococcus aureus* or *Escherichia coli* is sensitive to a particular compound of formula I, the *in vivo* test described earlier can be used.

Alternatively, the minimum inhibitory concentration (MIC) of a 1:1 mixture of the compound of formula VI (or its corresponding free acid) and the compound of formula VIII (or its corresponding free acid)

can be measured. The MIC's can be measured by the procedure recommended by the International Collaborative Study on Antibiotic Sensitivity Testing (Ericsson and Sherris, *Acta. Pathologica et Microbiologia Scandinav.*, Supp. 217, Section B: 64—68 (1971)), which employs brain heart infusion (BHI) agar and the inocular replicating device. Overnight growth tubes are diluted 100 fold for use as the standard inoculum (20,000—10,000 cells in approximately 0.002 ml. are placed on the agar surface; 20 ml. of BHI agar/dish). Twelve 2 fold dilutions of the test compound are employed, with initial concentration of the test drug being 200 mcg./ml. Single colonies are disregarded when reading plates after 18 hrs. at 37°C. The susceptibility (MIC) of the test organism is accepted as the lowest concentration of compound capable of producing complete inhibition of growth as judged by the naked eye.

When using an antibacterial compound of this invention, or a salt thereof, in a mammal, particularly man, the compound can be administered alone, or it can be mixed with other antibiotic substances and/or pharmaceutically-acceptable carriers or diluents. Said carrier or diluent is chosen on the basis of the intended mode of administration. For example, when considering the oral mode of administration, an antibacterial compound of this invention can be used in the form of tablets, capsules, lozenges, troches, powders, syrups, elixirs, aqueous solutions and suspensions, and the like, in accordance with standard pharmaceutical practice. The proportional ratio of active ingredient to carrier will naturally depend on the chemical nature, solubility and stability of the active ingredient, as well as the dosage contemplated. In the case of tablets for oral use, carriers which are commonly used include lactose, sodium citrate and salts of phosphoric acid. Various disintegrants such as starch, and lubricating agents, such as magnesium stearate, sodium lauryl sulfate and talc, are commonly used in tablets. For oral administration in capsule form, useful diluents are lactose and high molecular weight polyethylene glycols, e.g. polyethylene glycols having molecular weights of from 2000 to 4000. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents can be added. For parenteral administration, which includes intramuscular, intraperitoneal, subcutaneous, and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions are suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled to render the preparation isotonic.

As indicated earlier, the antibacterial compounds of this invention are of use in human subjects and the daily dosages to be used will not differ significantly from other, clinically-used, penicillin antibiotics. The prescribing physician will ultimately determine the appropriate dose for a given human subject, and this can be expected to vary according to the age, weight, and response of the individual patient as well as the nature and the severity of the patient's symptoms. The compounds of this invention will normally be used orally at dosages in the range from about 20 to about 100 mg. per miligram of body weight per day, and parenterally at dosages from about 10 to about 100 mg. per kilogram of body weight per day, and parenterally at dosages from about 10 to about 100 mg. per doses outside these ranges.

The following examples and preparations are provided solely for further illustration. Infrared (IR) spectra were measured as potassium bromide discs (KBr discs) and diagnostic absorption bands are reported in wave numbers (cm^{-1}). Nuclear magnetic resonance spectra (NMR) were measured at 60 MHz for solutions in deuterated chloroform (CDCl_3) or deuterated dimethyl sulfoxide ($\text{DMSO}-d_6$), and peak positions are reported in parts per million downfield from tetra-methylsilane. The following abbreviations for peak shapes are used: s, singlet; d, doublet; t, triplet; qu, quartet; m, multiplet.

Example 1

6'-(2-Phenylacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide

To a stirred solution of 1.3 g. of potassium 6-(2-phenylacetamido)penicillanate in 20 ml. of dimethyl sulfoxide was added 845 mg. of chloromethyl penicillanate 1,1-dioxide followed by a few milligrams of sodium iodide. Stirring was continued overnight at ca. 25°C, and then the reaction mixture was poured into 140 ml. of ice-water. The pH was raised to 8.5, and then the mixture was extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried (Na_2SO_4) and evaporated *in vacuo*. This afforded 600 mg. of crude material.

The crude material was chromatographed on silica gel, eluting with a 1:1 mixture of ethyl acetate and hexane, and this afforded 200 mg. of the title compound (12% yield). The IR spectrum (KBr disc) showed an absorption at 1783 cm^{-1} . The NMR spectrum (CDCl_3) showed absorptions at 7.4 (s), 6.3 (d), 5.9 (s), 5.8—5.3 (m), 4.65 (t), 4.45 (s), 3.65 (s), 3.45 (d), 1.62 (s) and 1.48—1.4 (m) ppm.

Example 2

6'-(2-phenoxyacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide

A mixture of 1.4 g. of potassium 6-(2-phenoxyacetamido)penicillanate, 845 mg. of chloromethyl

penicillanate 1,1-dioxide, 20 ml. of dimethyl sulfoxide and a few milligrams of sodium iodide was stirred at ca. 25°C overnight. The mixture was poured into 140 ml. of ice-water and the pH was adjusted to 8.5. The resultant aqueous system was extracted with ethyl acetate, and the extracts were combined, washed with water, dried (Na₂SO₄) and evaporated *in vacuo*. This afforded 660 mg. of crude material.

The crude material was chromatographed on silica gel, using a 1:1 mixture of ethyl acetate and hexane as eluant, and this afforded 230 mg. of the title product (13% yield). The IR spectrum (KBr disc) showed an absorption at 1786 cm⁻¹. The NMR spectrum (CDCl₃) showed absorptions at 7.4 (s), 5.85 (s), 5.45 (s), 5.05 (s), 4.6 (t), 4.43 (s), 4.4 (s), 3.45 (d), 1.62 (s), 1.48 (s), 1.44 (s) and 1.4 (s) ppm.

Example 3

The procedure of Example 1 is repeated, except that the potassium 6-(2-phenylacetamido)penicillanate is replaced by:

- potassium 6-(2-(4-ethyl-2,3-dioxopiperazinocarbonylamino)-2-phenylacetamido)penicillanate,
- potassium 6-(2-(2-oxoimidazolidinocarbonylamino)-2-phenylacetamido)penicillanate,
- potassium 6-(2-(3-acetyl-2-oxoimidazolidinocarbonylamino)-2-phenylacetamido)penicillanate,
- potassium 6-(2-(3-butyryl-2-oxoimidazolidinocarbonylamino)-2-phenylacetamido)penicillanate,
- potassium 6-(2-(3-methylsulfonyl-2-oxoimidazolidinocarbonylamino)-2-phenylacetamido)penicillanate and
- potassium 6-(2-(3-isopropylsulfonyl-2-oxoimidazolidinocarbonylamino)-2-phenylacetamido)penicillanate, respectively. This affords:
- 6'-(2-(4-ethyl-2,3-dioxopiperazinocarbonylamino)-2-phenylacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide,
- 6'-(2-(2-oxoimidazolidinocarbonylamino)-2-phenylacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide,
- 6'-(2-(3-acetyl-2-oxoimidazolidinocarbonylamino)-2-phenylacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide,
- 6'-(2-(3-butyryl-2-oxoimidazolidinocarbonylamino)-2-phenylacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide,
- 6'-(2-(3-methylsulfonyl-2-oxoimidazolidinocarbonylamino)-2-phenylacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide and
- 6'-(2-(3-isopropylsulfonyl-2-oxoimidazolidinocarbonylamino)-2-phenylacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide, respectively.

Example 4

- The procedure of Example 2 is repeated, except that the chloromethyl penicillanate, 1,1-dioxide used therein is replaced by an equimolar amount of:
- bromomethyl penicillanate 1,1-dioxide,
 - iodomethyl penicillanate 1,1-dioxide,
 - methylsulfonyloxymethyl penicillanate, 1,1-dioxide,
 - isobutylsulfonyloxymethyl penicillanate 1,1-dioxide,
 - benzenesulfonyloxymethyl penicillanate 1,1-dioxide, and
 - 4-toluenesulfonyloxymethyl penicillanate 1,1-dioxide, respectively. In each case, this affords 6'-(2-phenoxyacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide.

Example 5

6'-(2-Phenylacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide

- To a stirred solution of 4.62 g. of 6'-aminopenicillanoyloxymethyl penicillanate 1,1-dioxide in 25 ml. of chloroform is added 1.50 ml. of triethylamine. The mixture is cooled to 0°C, and a solution of 1.55 g. of 2-phenylacetyl chloride in 10 ml. of chloroform is added dropwise at 0°C. The resulting mixture is stirred for 5 minutes at 0°C and then for 30 minutes at 25°C. The solvent is removed by evaporation *in vacuo* and the residue is partitioned between ethyl acetate and water at pH 8. The ethyl acetate layer is removed, washed with water, dried (Na₂SO₄) and evaporated *in vacuo*, to give the title compound.

Example 6

6'-(2-Phenoxyacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide

- The title compound is prepared by acylation of 6'-aminopenicillanoyloxymethyl penicillanate 1,1-dioxide with 2-phenoxyacetyl chloride, according to the procedure of Example 5.

Example 7

6'-(2-Carboxy-2-(2-thienyl)acetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide

- The pH of a stirred suspension of 372 mg. of 2-(2-thienyl)malonic acid in 10 ml. of water and 5 ml. of tetrahydrofuran is adjusted to 6.0 by the addition of saturated sodium bicarbonate solution. To the resulting solution is added 923 mg. of 6'-aminopenicillanoyloxymethyl penicillanate 1,1-dioxide.

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The mixture is cooled to ca. 0°C, and 402 mg. of N-ethyl-N'-3-(dimethylamino)propylcarbodiimide hydrochloride is added, with stirring. Stirring is continued at ca 0°C for 5 minutes and at 25°C for 2 hours, the pH continuously being maintained between 5.8 and 6.0. At this point, the bulk of the tetrahydrofuran is removed by evaporation *in vacuo*, ethyl acetate and additional water are added and the pH is raised to 8.0. The layers are separated and the organic layer is discarded. Fresh ethyl acetate is added, and the pH is lowered to 3.0. Again the layers are separated, and the ethyl acetate layer is dried (Na₂SO₄) and evaporated *in vacuo*. This affords the title compound.

Example 8

6'-(2-(4-Ethyl-2,3-dioxopiperazinocarbonylamino)-2-phenylacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide

To a stirred mixture of 3.19 g. of 2-(4-ethyl-2,3-dioxopiperazinocarbonylamino)-2-phenylacetic acid in 50 ml. of acetone is added 1.2 ml. of N-methylmorpholine. The resulting mixture is cooled to -20°C, and a solution of 1.09 g. of ethyl chloroformate in 20 ml. of acetone is added dropwise during 10 minutes. Stirring is continued at -20°C for 60 minutes, and then a solution of 4.61 g. of 6'-aminopenicillanoyloxymethyl penicillanate 1,1-dioxide in 50 ml. of acetone is added dropwise at -20°C. Stirring is continued at -20°C for 60 minutes, at 0°C for 30 minutes and at 25°C for 30 minutes. At this point the solvent is removed by evaporation *in vacuo*, and the residue is partitioned between ethyl acetate and water at pH 2.5. The layers are separated and the aqueous layer is discarded. Fresh water is added and the pH is raised to 8.5. The layers are shaken and separated, and then the organic layer is discarded. Fresh ethyl acetate is added and the pH is again adjusted to 2.5. The layers are shaken and separated. The ethyl acetate layer is washed with water, and then it is dried. Evaporation of the ethyl acetate layer *in vacuo* affords the title compound.

Example 9

The procedure of Example 8 is repeated, except that the 2-(4-ethyl-2,3-dioxopiperazinocarbonylamino)-2-phenylacetic acid is replaced by:

- 2-(2-oxoimidazolidinocarbonylamino)-2-phenylacetic acid,
- 2-(3-acetyl-2-oxoimidazolidinocarbonylamino)-2-phenylacetic acid,
- 2-(3-butyryl-2-oxoimidazolidinocarbonylamino)-2-phenylacetic acid,
- 2-(3-methylsulfonyl-2-oxoimidazolidinocarbonylamino)-2-phenylacetic acid and
- 2-(3-isopropylsulfonyl-2-oxoimidazolidinocarbonylamino)-2-phenylacetic acid, respectively. This

affords:

- 6'-(2-[2-oxoimidazolidinocarbonylamino]-2-phenylacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide,
- 6'-(2-[3-acetyl-2-oxoimidazolidinocarbonylamino]-2-phenylacetamido)-penicillanoyloxymethyl penicillanate 1,1-dioxide,
- 6'-(2-[3-butyryl-2-oxoimidazolidinocarbonylamino]-2-phenylacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide,
- 6'-(2-[3-methylsulfonyl-2-oxoimidazolidinocarbonylamino]-2-phenylacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide and
- 6'-(2-[3-isopropylsulfonyl-2-oxoimidazolidinocarbonylamino]-2-phenylacetamido)penicillanoyloxymethyl penicillanate 1,1-dioxide, respectively.

Preparation 1

6'-Aminopenicillanoyloxymethyl penicillanate 1,1-dioxide

To a solution of 1.2 g. of 6'-(4-nitrobenzyloxycarbonylamino)penicillanoyloxymethyl penicillanate 1,1-dioxide in a mixture of 30 ml. of water and 50 ml. of tetrahydrofuran was added 1 drop of acetic acid (pH dropped to 4.5), followed by 1.2 g. of 10% palladium-on-carbon. The mixture was shaken under an atmosphere of hydrogen, at ca. 50 psig pressure, for 1.5 hours. The mixture was then filtered and the residue was washed with water and with tetrahydrofuran. The tetrahydrofuran-water, water and tetrahydrofuran solutions were combined and the pH was adjusted to 8.5. The resulting solution was extracted with ethyl acetate, and the ethyl acetate extract was dried (Na₂SO₄). The dried solution was evaporated *in vacuo* giving 600 mg. of crude material.

The crude material was chromatographed on silica gel, eluting with 3:1 ethyl acetate-hexane, which afforded 200 mg. of the title compound (23% yield). The IR spectrum (KBr disc) showed an absorption at 1783 cm⁻¹. The NMR spectrum (CDCl₃) showed absorptions at 5.9 (s), 5.5 (m), 4.63 (m), 4.5 (s), 3.5 (d), 1.7 (s), 1.6 (s), 1.5 (s) and 1.45 (s) ppm.

6'-Aminopenicillanoyloxymethyl penicillanate 1,1-dioxide will form acid-addition salts. The salts are prepared in conventional fashion, i.e. using the methods described earlier for the formation of acid-addition salts of those compounds of formula I which have an amino group as part of the group R¹.

Preparation 2

Chloromethyl penicillanate 1,1-dioxide

To a stirred solution of 24 g. of penicillanic acid 1,1-dioxide in 125 ml. of N,N-dimethylformamide was added 9.5 ml. of diisopropylethylamine, followed by 45 ml. of chloriodomethane. Stirring was

continued overnight and then reaction mixture was added to 300 ml. of water. The pH was adjusted to 8.5, and then the mixture was extracted with ethyl acetate. The extract was washed with water, followed by saturated sodium chloride solution, and then it was dried over sodium sulfate. The dried extract was concentrated to dryness *in vacuo* to give the crude product as a gum (8.9 g.).

The crude product was combined with some additional material of comparable quality, and it was chromatographed on silica gel eluting with 1:1 ethyl acetate:hexane. This afforded the title compound which showed only a single spot when assayed by thin-layer chromatography. The IR spectrum (KBr disc) showed an absorption at 1801 cm^{-1} . The NMR spectrum (CDCl_3) showed absorptions at 6.0 (d, 1H, $J=6\text{ Hz}$), 5.7 (d, 1H, $J=6\text{ Hz}$), 4.7 (t, 1H, $J=3.5\text{ Hz}$), 4.5 (s, 1H), 3.55 (d, 2H, $J=3.5\text{ Hz}$), 1.7 (s, 3H) and 1.5 (s, 3H) ppm.

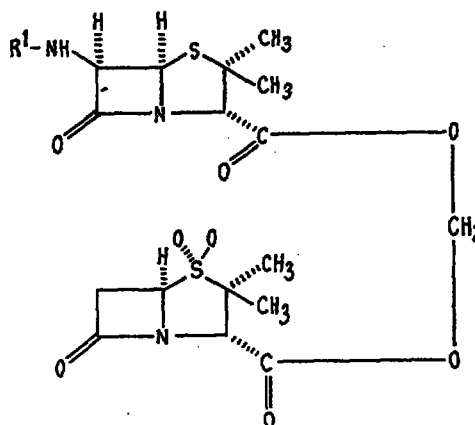
Preparation 3

The procedure of Example 25 is repeated, except that the chloriodomethane used therein is replaced by an equimolar amount of bromiodomethane, diiodomethane, di(methylsulfonyloxy)methane, di(isobutylsulfonyloxy)methane, di(benzenesulfonyloxy)methane and di(4-toluenesulfonyloxy)methane. This affords:

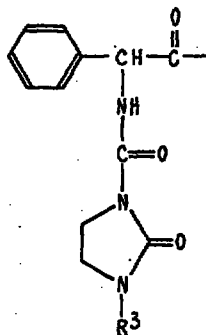
bromomethyl penicillanate 1,1-dioxide,
iodomethyl penicillanate 1,1-dioxide,
methylsulfonyloxymethyl penicillanate 1,1-dioxide,
isobutylsulfonyloxymethyl penicillanate 1,1-dioxide,
benzenesulfonyloxymethyl penicillanate 1,1-dioxide and
4-toluenesulfonyloxymethyl penicillanate 1,1-dioxide, respectively.

Claims

1. A compound of formula



and the pharmaceutically-acceptable salts thereof, wherein R^1 is selected from the group consisting of 2-phenylacetyl, 2-phenoxyacetyl, 2-carboxy-2-[2-thienyl]-acetyl, 2-(4-ethyl-2,3-dioxopiperazinocarbonylamino)-2-phenylacetyl and a group of the formula



wherein R^3 is selected from the group consisting of hydrogen, alkanoyl having from two to four carbons and alkylsulfonyl having from one to three carbons.

2. The compound according to claim 1, wherein R^1 is 2-phenylacetyl.

3. The compound according to claim 1, wherein R^1 is 2-phenoxyacetyl.

4. A pharmaceutical composition, suitable for treating a bacterial infection in a mammalian subject, which comprises a compound according to any of claims 1 to 3 together with a pharmaceutically-acceptable carrier.



continued overnight and then reaction mixture was added to 300 ml. of water. The pH was adjusted to 8.5, and then the mixture was extracted with ethyl acetate. The extract was washed with water, followed by saturated sodium chloride solution, and then it was dried over sodium sulfate. The dried extract was concentrated to dryness *in vacuo* to give the crude product as a gum (8.9 g.).

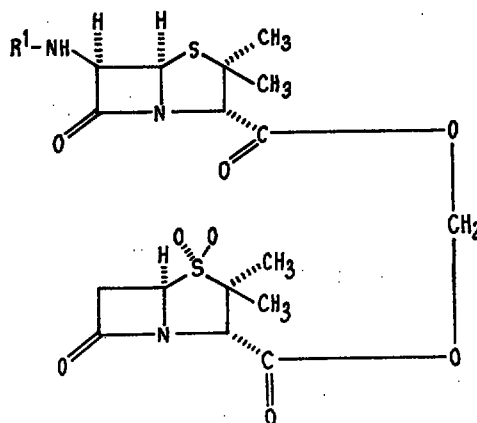
- 5 The crude product was combined with some additional material of comparable quality, and it was chromatographed on silica gel eluting with 1:1 ethyl acetate:hexane. The afforded the title compound which showed only a single spot when assayed by thin-layer chromatography. The IR spectrum (KBr disc) showed an absorption at 1801 cm^{-1} . The NMR spectrum (CDCl_3) showed absorptions at 6.0 (d, 1H, $J=6\text{ Hz}$), 5.7 (d, 1H, $J=6\text{ Hz}$), 4.7 (t, 1H, $J=3.5\text{ Hz}$), 4.5 (s, 1H), 3.55 (d, 2H, $J=3.5\text{ Hz}$), 1.7 (s, 3H) and 1.5 (s, 3H) ppm.

Preparation 3

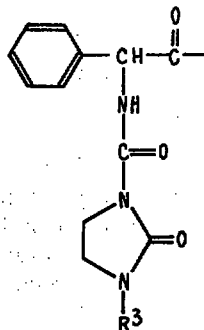
- The procedure of Example 25 is repeated, except that the chloriodomethane used therein is replaced by an equimolar amount of bromiodomethane, diiodomethane, di(methylsulfonyloxy)methane, di(isobutylsulfonyloxy)methane, di(benzenesulfonyloxy)methane and di(4-toluenesulfonyloxy)methane. This affords:
- 15 bromomethyl penicillanate 1,1-dioxide,
iodomethyl penicillanate 1,1-dioxide,
methylsulfonyloxymethyl penicillanate 1,1-dioxide,
isobutylsulfonyloxymethyl penicillanate 1,1-dioxide,
20 benzenesulfonyloxymethyl penicillanate 1,1-dioxide and
4-toluenesulfonyloxymethyl penicillanate 1,1-dioxide, respectively.

Claims

1. A compound of formula

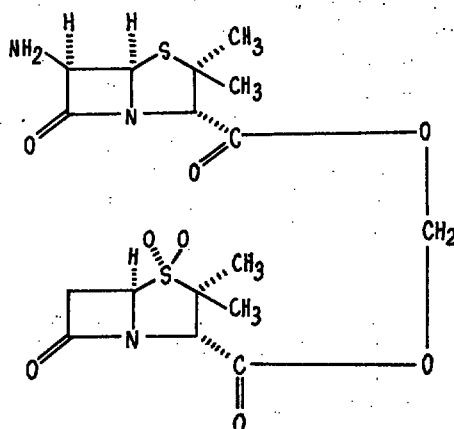


- 25 and the pharmaceutically-acceptable salts thereof, wherein R^1 is selected from the group consisting of 2-phenylacetyl, 2-phenoxyacetyl, 2-carboxy-2-[2-thienyl]-acetyl, 2-(4-ethyl-2,3-dioxopiperazinocarbonylamino)-2-phenylacetyl and a group of the formula



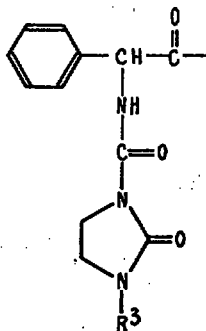
- wherein R^3 is selected from the group consisting of hydrogen, alkanoyl having from two to four carbons and alkylsulfonyl having from one to three carbons.
- 30 2. The compound according to claim 1, wherein R^1 is 2-phenylacetyl.
3. The compound according to claim 1, wherein R^1 is 2-phenoxyacetyl.
4. A pharmaceutical composition, suitable for treating a bacterial infection in a mammalian subject, which comprises a compound according to any of claims 1 to 3 together with a
35 pharmaceutically-acceptable carrier.

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

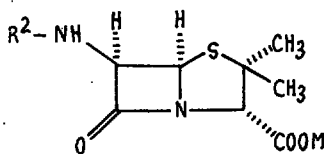


or a pharmaceutically-acceptable salt thereof, wherein

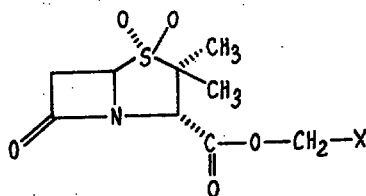
- 5 R^1 is selected from the group consisting of 2-phenylacetyl, 2-phenoxyacetyl, 2-carboxy-2-(2-thienyl)acetyl, 2-(4-ethyl-2,3-dioxopiperazinocarbonylamino)-2-phenylacetyl and a group of the formula



wherein R^3 is selected from the group consisting of hydrogen, alkanoyl having from two to four carbons and alkylsulfonyl having from one to three carbons, which comprises reacting a compound of formula



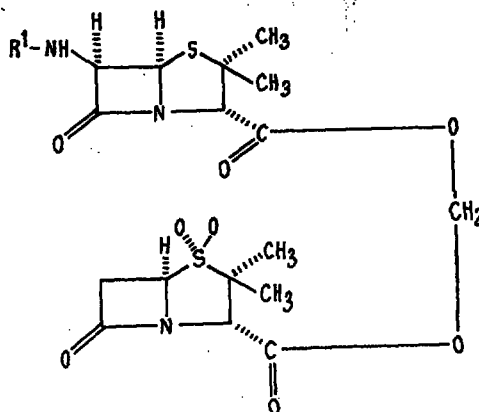
with a compound of the formula



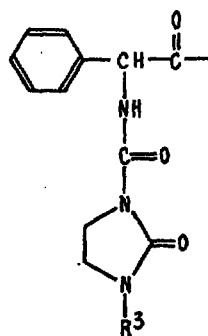
- 15 wherein R^2 is the group R^1 in which any free carboxy group has been protected, M is a carboxylate salt forming cation and X is selected from the group consisting of chloro, bromo, iodo, alkylsulfonyloxy having from one to four carbon atoms, benzenesulfonyloxy and toluenesulfonyloxy; followed, if necessary, by removal of the carboxy protecting group.



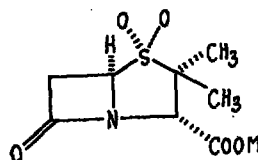
6. A process for the preparation of a compound of the formula



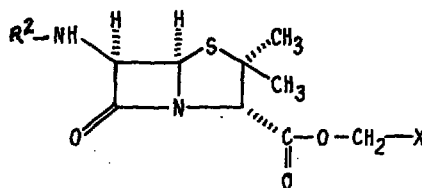
or a pharmaceutically-acceptable salt thereof, wherein R^1 is selected from the group consisting of 2-phenylacetyl, 2-phenoxyacetyl, 2-carboxy-2-[2-thienyl]acetyl, 2-(4-ethyl-2,3-dioxopiperazinocarbonylamino)-2-phenylacetyl and a group of the formula



wherein R^3 is selected from the group consisting of hydrogen, alkanoyl having from two to four carbons and alkylsulfonyl having from one to three carbons, which comprises reacting a compound of the formula



with a compound of the formula



wherein R^2 is the group R^1 in which any free carboxy group has been protected, M is a carboxylate salt forming cation and X is selected from the group consisting of chloro, bromo, iodo, alkylsulfonyloxy having from one to four carbon atoms, benzenesulfonyloxy and toluenesulfonyloxy; followed, if necessary, by removal of the carboxy protecting group.

7. A process according to either claim 5 or claim 6, wherein the reaction is carried out in a polar, organic solvent at a temperature in the range from 0 to 80°C.

8. A process according to claim 7, wherein said polar organic, solvent is selected from *N,N*-dimethylformamide, *N*-methylpyrrolidone, dimethylsulfoxide and hexamethylphosphoramide.

