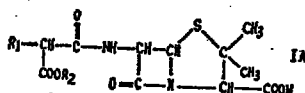
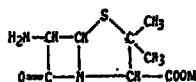


wherein the substituent is at least one of chloro, bromo, fluoro, (C_1-C_6) alkoxy, (C_1-C_6) alkyl, nitro or methylenedioxy; γ -phenylpropargyl, γ -(substituted phenyl)propargyl wherein the substituent is chloro, bromo, (C_1-C_6) alkoxy, (C_1-C_6) alkyl or nitro.

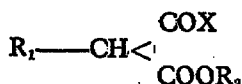
The process of this invention comprises preparing compounds of the formula



wherein M is hydrogen, sodium, potassium, or tri (C_1-C_6) alkylamine; which comprises reacting a compound of the formula



15 with an acylating agent of the formula



wherein X is chloro, bromo, or $-\text{OCOR}_4$, wherein R_4 is benzyl or (C_1-C_6) alkyl; and R_1 and R_2 are as defined above and R_2 is also

- 20 (lower alkylene) Y_1 wherein Y_1 is
 azetidino
 aziridino
 pyrrolidino
 piperidino
 25 morpholino
 thiomorpholino
 N-(C_1-C_6 alkyl)piperazino
 pyrrolo
 imidazolo
 30 2-imidazolino
 2,5-dimethylpyrrolidino
 1,4,5,6-tetrahydropyrimidino
 4-methylpiperidino, or
 2,6-dimethylpiperidino;
 35 and (lower alkylene) contains from 1 to 3 carbon atoms; and



and substituted derivatives thereof, wherein Z is $-(\text{CH}_2)_n-$ or $-(\text{CH}_2)_4-$, and wherein the substituent is methyl, chloro or bromo; in a reaction-inert solvent system at a temperature of from about 0 to 50°C. and a pH of from about 5 to 8 and when M is hydrogen, if desired forming the pharmaceutically acceptable salts thereof.

The degree of purity of the 6-aminopenicillanic acid is not critical to the success of the process. The 6-aminopenicillanic acid can be used in the pure form, the partially pure form, or in crude form such as that contained in a fermentation broth. Indeed, when using

water as solvent, fermentation broths containing 6-aminopenicillanic acid are favored from an economic standpoint.

By reaction-inert solvent is meant a solvent which, under the conditions of the process, does not enter into any appreciable reaction with either the reactants or the products. Aqueous and non-aqueous solvents can be used. The use of water as solvent does, of course, result in some hydrolysis of the acid chloride reactant. However, under the proper conditions of temperature, pH, and time, the hydrolysis occurs at a relatively slow rate compared to the desired N-acylation reaction. Suitable solvents for the process of this invention include methylene chloride, benzene, chloroform, dioxane, water, acetone, tetrahydrofuran, diethyl ether, and dimethyl ether. Aqueous solvent systems, including those in which an emulsion is formed, e.g., water-water immiscible solvent, can also be used. Solvents which readily form emulsions with water include those water immiscible solvents such as benzene, n-butanol, methylene chloride, chloroform, methyl isobutyl ketone, and lower alkyl acetates (e.g., ethyl acetate). The favored water immiscible solvents are methyl isobutyl ketone and ethyl acetate.

DETAILED DESCRIPTION OF THE INVENTION

The reaction is conducted over the pH range of from about 5 to about 8 and, preferably, over the pH range of 6 to 7. The pH is maintained at about the neutral point by the addition of a suitable acid acceptor such as an alkali metal or alkaline earth metal hydroxide. Alternatively, and preferably, the pH is maintained by the expedient of employing a salt of 6-aminopenicillanic acid with an organic base. Any organic base which forms a salt with 6-aminopenicillanic acid can be used. Suitable organic bases are tri(lower)alkylamines, dibenzylamine, N,N'-dibenzylethylenediamine, N-(lower)alkyl piperidines, N-(lower)alkyl morpholines, N-benzyl- β -phenethylamine, N,N' - bis-dehydroabietylamine, dehydrobietylamine, and 1-phenamine. It is advantageous, however, to use a tri(lower)alkylamine, preferably triethylamine, as the organic base. Such bases have the advantage of forming a salt with 6-aminopenicillanic acid which is soluble in many of the above-named solvents. They are particularly useful when using a non-aqueous solvent system such as methylene chloride.

The reaction can be conducted over a wide range of temperature. Temperatures of from about 0° to about 50°C. are operative. It is, however, preferred to employ temperatures ranging from about 0° to about 30°C. in order to prevent degradation of the products.

The preferred form of the arylmalonic acid esters used as acylating agents is the mono-acid chlorides because of their relative ease of

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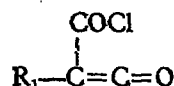
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preparation compared to the preparation of the anhydrides.

- 5 The arylmalonic acid monoester reactants are conveniently prepared by reaction of the appropriate aryl chloro carbonyl ketene



- 10 with the proper alcohol R_2OH , wherein R_1 and R_2 are as defined above. The reaction is conducted on a 1:1 molar ratio at a temperature of from about -70°C . to about 30°C . and, desirably, in a reaction-inert solvent to permit better mixing and control of the reaction. Suitable solvents are diethyl ether, dimethyl ether, dioxane, methylene chloride and chloroform.

- 15 The reaction mixture is then treated with water and a base, e.g., sodium bicarbonate, added. The reaction mixture, if below the freezing point of water, is warmed to at least 0°C . either before or after addition of the water and base. Sufficient base, generally two to three equivalents, is added in order to neutralize the by-product hydrogen chloride, and to form the salt of the arylmalonic acid monoester. The mixture is stirred for about one-half hour then the organic solvent removed under reduced pressure below 35°C . The remaining solution is extracted with ether, cooled to 10° – 15°C . and adjusted to about pH 2. The acid solution is extracted with a suitable solvent, e.g., methylene chloride, the extract dried and the solvent then removed under reduced pressure.

- 35 The arylmalonic acid monoesters thus produced are converted to their mono acid chloride derivatives by treatment with excess thionyl chloride, usually in the presence of a reaction-inert solvent such as benzene, diethyl ether, or methylene chloride at a temperature of from about 0° to 80°C ., according to procedures well known to those skilled in the art.

- 40 The required aryl chloro carbonyl ketenes are prepared by the reaction of an arylmalonic acid with a halogenating agent selected from the groups consisting of PCl_5 , PCl_3 , POCl_3 , and SOCl_2 at temperatures ranging from about 0° to about 50°C . for periods ranging from about one hour to about ten hours. The reaction is conducted in the presence of a solvent system, preferably a reaction-inert solvent system. Suitable solvents are dialkyl ethers; e.g., diethyl ether, dipropyl ether, mono- and dimethyl ethers of ethylene glycol and propylene glycol, methylene chloride and chloroform.

- 55 The reaction period is, of course, dependent upon the reaction temperature and the nature of the reactants. However, for a given combination of reactants, the lower temperatures require longer reaction periods than do higher temperatures.

The molar proportions of reactants; i.e., arylmalonic acid to halogenating agent, can vary widely, e.g., up to 1:10 or higher but, for satisfactory yields, should be at least stoichiometric. In actual practice, the stoichiometric ratio of reactants is preferred.

The reactants may be added all at once or separately. If separately, the order of addition is not critical. However, it appears that the reaction is smoother and subject to fewer side reactions, as evidenced by the color of the reaction mixture, particularly upon distillation, when the arylmalonic acid is added to the halogenating agent. The reaction mixture, under such conditions, generally progresses from a yellow to a red color. The reaction mixture on reverse addition; i.e., the addition of halogenating agent to the arylmalonic acid, progresses from yellow to black.

The arylhalocarbonyl ketene products are isolated from the reaction by distillation *in vacuo*. Because of their great reactivity, they are generally stored under a nitrogen atmosphere at low temperatures and in the absence of light.

Acid anhydride derivatives of the arylmalonic acid half esters are prepared by reaction of the half esters with a chloro(lower alkyl)carbonate in the presence of an acid acceptor such as pyridine or a tri(lower alkyl)amine. Such reactions are described in the J. Am. Chem. Soc. 75, 637–9 (1953) and J. Org. Chem. 22, 248 (1957). As will be obvious to those skilled in the art, other chlorocarbonates, such as chlorobenzylcarbonate and chlorophenyl carbonate, can be used in place of the chloro(lower alkyl)carbonates.

The α -carboxyarylpenicillin esters are isolated by conventional methods known to those skilled in the art. A typical method, for example, when using water as solvent, comprises adjusting the pH of the reaction mixture to about 2–3 and extracting the product with ethyl acetate. The ethyl acetate extract is washed with water, the product extracted therefrom with 10 percent aqueous potassium bicarbonate, then back-extracted into ethyl acetate. The ethyl acetate extracts are once again extracted with water, the aqueous extract brought to pH of 2–3, then re-extracted with ethyl acetate. The product is recovered by removal of the volatiles. Alternatively, the product is isolated as an alkali metal or amine salt by addition of the proper base, inorganic or organic, to the dry ethyl acetate extract.

When using an aqueous emulsion as solvent, it is expedient to isolate the product by extracting the reaction, after adjustment to pH 2, with a suitable water immiscible solvent. Ethyl acetate is especially useful. The extract is then dried and evaporated to dryness. The product is converted to an amine or alkali metal salt by adding the appropriate base; e.g., N-ethylpiperidine or potassium ethyl

hexanoate to a solution of the ester product in a suitable solvent such as ethyl acetate.

A further method which is of value when the acylation reaction is conducted in a non-aqueous solvent medium; e.g., in methylene chloride, comprises adding water to the reaction mixture and then adjusting the pH of the aqueous phase to about 2—3. The aqueous phase is separated, extracted with the non-aqueous solvent, and the combined non-aqueous solvent layers dried. The products are precipitated from the non-aqueous solvent by the addition of a suitable organic base such as N-ethylpiperidine or by the addition of sodium or potassium 2-ethyl hexanoate as their corresponding salts. Alternatively, the non-aqueous solvent, after drying, is removed by distillation at a lower temperature, the residue taken up in a suitable solvent, and the product precipitated therefrom by addition of an appropriate base. This alternative procedure affords greater latitude as regards choice of the base. The appropriate solvent is determined by the solubility of the desired salt.

The novel esters of the present invention are converted by known methods to the corresponding acids as, for example, by mild alkaline hydrolysis or enzymatically with an esterase such as liver homogenate.

The preferred esters of this process are those wherein R₂ is indanyl, 2-isopropyl phenyl, dimethyl substituted phenyl, and chloro substituted tolyl. Such esters as well as the remaining esters within the ambit of this invention are effective antibiotics both *in vivo* and *in vitro*. They are, for example, remarkably effective in treating a variety of susceptible gram-positive and gram-negative infections in animals, including man. For this purpose, the pure materials or mixtures thereof with other antibiotics can be employed. They may be administered alone or in combination with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch, milk sugar, or certain types of clay, or in capsules alone or in admixture with the same or equivalent excipients. They may also be administered orally in the form of elixirs or oral suspensions which may contain flavoring or coloring agents, or be injected parenterally; that is, for example, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may be either aqueous such as water, isotonic saline, isotonic dextrose, Ringer's solution, or non-aqueous such as fatty oils of vegetable origin (cotton seed, peanut oil, corn, sesame), or other non-aqueous vehicles which will not interfere with the therapeutic efficiency of the preparation and

are non-toxic in the volume or proportion used (glycerol, propylene glycol, sorbitol). Additionally, compositions suitable for extemporaneous preparation of solutions prior to administration may advantageously be made. Such compositions may include liquid diluents for example, propylene glycol, diethyl carbonate, glycerol or sorbital; buffering agents, as well as local anesthetics and inorganic salts to afford desirable pharmacological properties.

The oral and parenteral dosage levels for the herein described compounds are, in general, of the order of up to 200 mg./kg. and 100 mg./kg. of body weight per day, respectively.

Many of the penicillin ester compounds of this invention exhibit improved absorption on oral administration over that produced by the corresponding free acid or alkali metal salt forms. They, therefore, represent convenient and effective dosage forms of the α -carboxy-arylmethylpenicillins.

Additionally, many of the esters described herein, although inactive or of relatively low activity against gram-negative organisms *per se* are metabolized to the parent acid; i.e., α -carboxybenzylpenicillin when injected parenterally into the animal, including the human body.

The antimicrobial spectra of several esters of α -carboxybenzyl penicillin and that of the acid against *Staphylococcus aureus* 5 and *Escherichia coli* 266 are presented in Table I. The tests were run under standardized conditions in which nutrient broth containing various concentrations of the test material was seeded with the particular organism specified, and the minimum growth (MIC) at which growth of each organism failed to occur was observed and recorded. The test materials have the following formula and were tested as their sodium or potassium salts. Benzylpenicillin (K salt) when thus tested gave values of 0.156 > 100 vs. *S. aureus* and *E. coli*, respectively.

Table II presents *in vivo* data for several compounds of this invention in mice (PO=oral and SQ=subcutaneous routes of administration).

The values are obtained under standardized conditions. The procedure comprises production of an acute experimental *E. coli* 266 infection in mice by the intraperitoneal inoculation of the mice with a standardized 10⁻⁸ *E. coli* 266 culture suspended in 5 percent hog gastric mucin. The test compounds, in the form of their sodium or potassium salts, are administered to the infected mice by a multiple dosing regimen in which the first dose is given 0.5 hour after inoculation and is repeated 4, 24 and 48 hours later. The percent of mice surviving are then determined.

The LD₁₀₀ of *E. coli* 266 (the lowest concentration required to produce 100 percent mortality in mice) is 10⁻⁷. Control animals receive inocula of 10⁻⁵, 10⁻⁶ and 10⁻⁷ as a check on possible variation in virulence which can occur.

TABLE I
In Vitro Spectra

R ₂	<i>S. aureus</i>	<i>E. coli</i>
2-(N-methylanilino)ethyl	0.39	100
2-N-methyl-N-formylaminoethyl	0.78	50
2-N-methyl-N-acetylaminoethyl	0.78	50
2-N-ethyl-N-formylaminoethyl	0.195	100
2-N-ethyl-N-acetylaminoethyl	0.195	25
2-N-isopropyl-N-formylaminoethyl	0.195	25
2-N-isopropyl-N-acetylaminoethyl	0.049	25
2-N-(n-butyl)-N-formylaminoethyl	0.195	25
2-N-(n-butyl)-N-acetylaminoethyl	0.024	>200
3-N-(isopropyl)-N-formylaminopropyl	0.098	12.5
3-N-(isopropyl)-N-acetylaminoethyl	0.39	50
2-N-methyl-N-carbomethoxyaminoethyl	0.98	25
2-N-methyl-N-carbo(isobutoxy)aminoethyl	1.56	100
2-N-ethyl-N-carbomethoxyaminoethyl	0.78	50
2-N-ethyl-N-carbo(isobutoxy)aminoethyl	1.56	50
2-N-(n-butyl)-N-carbomethoxyaminoethyl	0.39	25
3-N-formylaminopropyl	0.78	50
3-N-acetylaminoethyl	0.39	25
3-N-carbo(isobutoxy)aminopropyl	6.25	100
3-N-isopropyl-N-carbo(isobutoxy)aminopropyl	0.195	25
3-(1-ethylpiperidyl)	0.78	3.12
3-(1-benzylpiperidyl)	0.19	3.12
H	1.25	3.12
4-(2-carboxyvinyl)phenyl	0.39	50
2-t-butyl-4-methoxyphenyl	0.098	12.5
2-biphenyl	0.012	1.56
2-carbomethoxymethylphenyl	0.392	6.25

TABLE I (Continued)

R ₂	S. aureus	E. coli
4-carboxymethylphenyl	0.049	6.25
4-(2-carboxyethyl)phenyl	1.56	50
4-(2-carbomethoxyethyl)phenyl	0.195	3.125
2-methoxy-4-(2-carboxyvinyl)phenyl	1.56	25
2-methoxy-4-(2-carbomethoxyvinyl)phenyl	1.56	25
4-(2-carboxy-2-carbobenzoxaminoethyl)phenyl	0.39	100
4-acetamidophenyl	0.78	50
4-carbomethoxymethylphenyl	1.56	12.5
2-methoxy-4-formylphenyl	0.195	12.5

TABLE II

In vivo Data vs. E. coli in Mice

R ₂	P.O.		S.Q.	
	200 mg./kg.	100	200 mg./kg.	100
2-N-methyl-N-formylaminoethyl	10	0	80	90
2-N-methyl-N-acetylaminoethyl	40	40	90	70
2-N-ethyl-N-formylaminoethyl	0	0	100	70
2-N-ethyl-N-acetylaminoethyl			90	20 ^(e)
2-N-isopropyl-N-formylaminoethyl			80	60 ^(e)
2-N-isopropyl-N-methylaminoethyl			80	10 ^(e)

TABLE II (Continued)

R ₂	% Survivors			
	PO (mg./kg.)		SQ (mg./kg.)	
	200	100	200	100
2-t-butyl-4-methoxyphenyl	100	80	100	100
2-biphenyl	100	100	100	80(e)
2-carbomethoxymethylphenyl	70	20	90	90(e)
4-carbomethoxymethylphenyl	80	0	90	50(e)
4-(2-carbomethoxyethyl)phenyl	50	0	80	70
4-carbomethoxymethylphenyl	90	30	100	100
4-(carboethoxyethyl)phenyl	80	0	90	50
2-hydroxymethylphenyl	60	20	60	10(e)
2-methoxy-4-formylphenyl	10	0	100	60
4-carbomethoxymethylphenyl	90	30	100	100
R ₂	P.O.		S.Q.	
	200 mg./kg. 100		200 mg./kg. 100	
2-N-(n-butyl)-N-formylaminoethyl			70	0(e)
2-N-(n-butyl)-N-acetylaminoethyl			90	0(e)
3-N-(isopropyl)-N-formylaminopropyl			70	10(e)
3-N-(isopropyl)-N-acetylaminoethyl	10	0(e)	100	90(e)
2-N-methyl-N-carbomethoxyaminoethyl	10	0(e)	100	0(e)
2-N-methyl-N-carbo(isobutyl)aminoethyl	0	0(e)	70	0(e)
2-N-ethyl-N-carbomethoxyaminoethyl	20	0(e)	60	10(e)
2-N-ethyl-N-carbo(isobutoxy)aminoethyl	10	10	80	0
2-N-(n-butyl)-N-carbomethoxyaminoethyl	0	0(e)	80	0(e)
3-N-formylaminopropyl	0	0(e)	70	0(e)
3-N-acetylaminoethyl	0	0(e)	70	20(e)
3-N-carbo(isobutoxy)aminopropyl	0	10(e)	100	50(e)

TABLE II (Continued)

R ₂	P.O.		S.Q.	
	200 mg./kg.	100	200 mg./kg.	100
3-N-isopropyl-N-carbo(isobutoxy)aminopropyl	0	0 ^(c)	70 ^(c)	0 ^(c)
2-N,N-dibenzylaminoethyl	80	0 ^(c)	70	0 ^(c)
2-N-methyl-N-benzylethyl	0	0 ^(c)	60	20 ^(c)
3-(1-ethylpiperidyl)	10	100	0 ^(c)	40 ^(c)
2-(1-benzylpiperidyl)	60	90	0 ^(c)	50 ^(c)

(a)150 mg./kg.

(b)75 mg./kg.

(c)50 mg./kg.

The following examples are provided to illustrate in greater detail the manner of practicing the present invention.

5

Example I

N - Ethylpiperidine Salt of α - [carbo(5-indanyloxy)]benzylpenicillin

A mixture of 6-aminopenicillanic acid (17.3 g., 0.08 mole) in methylene chloride (125 ml.) and triethylamine (16.2 g., 0.16 mole) is well stirred at room temperature for two hours under a nitrogen atmosphere in an indented round-bottom flask. The mixture is then cooled to 0°C. (still under a slow stream of nitrogen) and 2 - phenyl - 2 - (5 - indanyloxycarbonyl)acetyl chloride (21.9 g., 0.07 mole) in methylene chloride (30 ml.) added from a dropping funnel as rapidly as possible while maintaining the exothermic reaction temperature below +15°C. with an ice bath. The ice bath is removed and the mixture stirred vigorously for 1½ hours. Water (135 ml.) is then added and the mixture stirred well for an additional two minutes. The pH (8.8) is adjusted to 2 by addition of 6N-HCl (15 ml.). The mixture is stirred vigorously for ten minutes and the organic layer separated. The acidic aqueous layer is extracted with methylene chloride (2×67 ml.), the methylene chloride layers combined, dried over magnesium sulfate, filtered, and concentrated to dryness under reduced pressure below 35°C. The light yellowish foam obtained is dried to give the crude penicillin derivative, 34.4 g. (99%). The crude penicillin derivative (17 g., 0.0344 mole) in acetone (40 ml.) is cooled to 10°C. and N-ethylpiperidine (3.96 g., 0.1035 mole) added. The mixture is stirred for one minutes and the white crystalline salt which forms is recovered by filtration, washed with acetone, and dried. The salt is obtained in 86% yield (17.9 g.); m.p. 143—145°C. (dec.).

It is purified further by slurrying in acetone (10 g./100 ml.) at 40°C., cooling to room temperature, filtering and drying. An 80% recovery of the salt is realized; m.p. 149—151°C. (dec.).

It is converted to the potassium salt as follows. To a suspension of the N-ethylpiperidine salt (5 g., 8.2 mM.) in ethyl acetate (75 ml.) is added potassium ethyl hexanoate (1.93 g., 10.6 mM.) at room temperature. The mixture is then heated at 45°C. for two minutes, allowed to cool to room temperature, then cooled to 0°C. in an ice bath. The potassium salt is recovered by filtration, washed with ethyl acetate and dried; 4.2 g., (96.1%); m.p. 198—199°C. (dec.). The sodium salt, prepared in like manner from sodium ethylhexanoate, melts at 182—184°C. (dec.).

Example II

N - Ethylpiperidine Salt of α - [carbo(2-isopropylphenoxy)]benzylpenicillin

A mixture of 6-aminopenicillanic acid (3.74 g., 17.3 mM.), methylene chloride (50 ml.) and triethylamine (3.5 g., 35 mM.) is vigorously stirred at room temperature under nitrogen for 1.5 hours, then cooled to 0°C. A solution of 2 - phenyl - 2 - (2 - isopropylphenoxy)carbonyl)acetyl chloride (4.3 g., 14.4 mM.) in methylene chloride (5 ml.) is added and the reaction mixture stirred at room temperature for one hour. Water (20 ml.) is then added, the mixture stirred for two minutes, cooled to 10°C., then adjusted to pH 2 by addition of 6N hydrochloric acid. The mixture is stirred for five minutes, after which the methylene chloride layer is separated, dried, and evaporated to dryness to give the crude penicillin derivative, a cream-colored foam (4.4 g.).

The crude penicillin derivative (550 mg., 1.12 mM.) in ethyl acetate (1 ml. at room temperature is treated with N-ethylpiperidine

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(147 mg.), stirred for two minutes, then cooled to 0°C., filtered and dried to give the salt; 625 mg. (92%); m.p. 139—140°C. The overall yield of the amine salt, based upon the acid chloride reactant, is 84.2%.

5 The N-ethylpiperidine salt is converted to the potassium salt as follows.

10 Benzene (100 ml.) is placed in a 250 ml. three-necked flask and 50 ml. of benzene distilled off. The N-ethylpiperidine salt (3 g., 5 mM.) is added to the refluxing benzene which is then cooled to room temperature. Potassium ethyl hexanoate (3.2 ml. of a 26% acetone solution) is added and the mixture heated to 450°C. for three minutes. It is allowed to cool to room temperature, then chilled to 0°C., filtered and dried. Yield = 2.1 g. (78%); m.p. 180—182°C. (dec.).

20 The sodium salt is produced in like manner by substitution of sodium ethylhexanoate for potassium ethylhexanoate; m.p. 170—172°C. (dec.) from isopropanol or ethyl acetate.

Example III

25 This example illustrates the preparation of α -[carbo(2-isopropylphenoxy)]benzylpenicillin from a 6-aminopenicillanic acid containing fermentation broth.

30 A fermentation broth containing 6-aminopenicillanic acid is prepared according to the procedure of Example I of U.S. Patent 3,239,427, issued March 8, 1966, which comprises the enzymatic hydrolysis of benzylpenicillin by *Proteus rettgeri*.

35 The broth (1.5 liters) is treated with calcium chloride (0.5 g.) and diatomaceous earth (3 g.) at room temperature for ten minutes, then filtered. The clarified broth (1 liter), containing 5.4 g. (0.024 mole) of 6-amino-

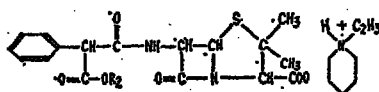
penicillanic acid, is then placed in a three-necked-indented flask equipped with a high-speed stirrer. 2-(2-isopropylphenoxy)carbonyl chloride (10 g., 0.0315 mole) is then added dropwise at room temperature over a one-hour period. The pH is maintained between 6.3—6.5 by the continuous addition of 10% aqueous potassium hydroxide. The mixture is stirred for an additional hour at room temperature and pH 6.3—6.5, then adjusted to pH 2.0 by 6N hydrochloric acid.

The acid solution is extracted with ethyl acetate (3×200 ml.), the combined extracts washed with water, filtered, and the filtrate extracted with 10% aqueous potassium bicarbonate (500 ml.). The aqueous layer is separated, saturated with potassium chloride, and back-extracted with ethyl acetate (2×200 ml.). The combined ethyl acetate extracts are extracted with water (3×100 ml.), the water extracts combined and acidified to pH 2 by 6N hydrochloric acid. The precipitate which forms is extracted with ethyl acetate (2×75 ml.), the extract dried with anhydrous sodium sulfate, filtered, then evaporated to dryness under reduced pressure at 35°C.

The residue (5.4 g.), an oily appearing foam, is dissolved in ethyl acetate (10 ml.) and N-ethylpiperidine (1.13 g., 0.01 mole) added at room temperature. A crystalline product immediately separates. The mixture is chilled then filtered, and the product washed with ethyl acetate and dried. Yield = 5.85 g. (40%); m.p. 146—148°C. (dec.).

Example IV

The following compounds are prepared by the procedure of Example II from the appropriate arylmalonic acid half esters as their N-ethylpiperidine salts.

R₂R₂

3-biphenyl

4-(carbo-n-butoxy)methylphenyl

4-biphenyl

4-(2-carboxyethyl)phenyl

2-chloro-3-biphenyl

4-(2-carbomethoxyethyl)phenyl

2-bromo-4-biphenyl

4-(2-carbethoxyethyl)phenyl

2-nitro-4-biphenyl

2-chloro-3-(2-carboxyethyl)phenyl

2-dimethylamino-5-biphenyl

2,4-dimethyl-6-(carboxymethyl)-phenyl

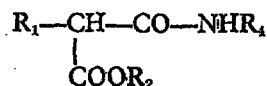
2-carbomethoxymethylphenyl

R ₂	R ₂
4-(2-carboxyvinyl)phenyl	2-N-(n-butyl)-N-formylaminoethyl
2-methoxy-4-(2-carboxyvinyl)-phenyl	2-N-(n-butyl)-N-acetylaminoethyl
2-methoxy-4-(2-carbomethoxyvinyl)phenyl	3-N-(isopropyl)-N-formylamino-propyl
2,5-dimethyl-4-(2-carboxyvinyl)-phenyl	3-N-(isopropyl)-N-acetylamino-propyl
2,6-dimethoxy-4-(2-carboxyvinyl)phenyl	2-N-methyl-N-carbomethoxy-aminoethyl
2-chloro-3-(2-carboxyvinyl)-phenyl	2-N-methyl-N-carbo(isobutoxy)-aminoethyl
2-(2-carboxyvinyl)-6-nitro-4-biphenyl	2-N-ethyl-N-carbomethoxyaminoethyl
3-methyl-4-(2-carboxyethyl)-phenyl	2-N-ethyl-N-carbo(isobutoxy)-aminoethyl
4-t-butyl-2-biphenyl	2-N-(n-butyl)-N-carbomethoxy-aminoethyl
3-methoxy-2-biphenyl	3-N-formylaminopropyl
2-t-butyl-4-biphenyl	3-N-acetylaminoethyl
2-methyl-4-biphenyl	3-N-carbo(isobutoxy)aminopropyl
2-isopropyl-4-methoxyphenyl	3-N-isopropyl-N-carbo(isobutoxy)-aminopropyl
2-t-butyl-4,5-dimethoxyphenyl	
2-t-butyl-4-ethoxyphenyl	γ-phenylpropargyl
4-dimethylamino-3-isopropoxyphenyl	γ-(p-tolyl)propargyl
5-dimethylamino-2-isopropylphenyl	γ-(3,4-dimethoxyphenyl)propargyl
2-N-methyl-N-formylaminoethyl	γ-(4-chlorophenyl)propargyl
2-N-methyl-N-acetylaminoethyl	γ-(2-chlorophenyl)propargyl
2-N-ethyl-N-formylaminoethyl	γ-(4-methoxyphenyl)propargyl
2-N-ethyl-N-acetylaminoethyl	γ-(4-nitrophenyl)propargyl
2-N-isopropyl-N-formylaminoethyl	2-N-methyl-N-carbo(isopropoxy)-aminoethyl
2-N-isopropyl-N-acetylaminoethyl	2-N-ethyl-N-carbo(isopropoxy)-aminoethyl
2-N,N-dibenzylaminoethyl	γ-(4-nitrophenyl)allyl

R ₂	R ₂
3-N,N-dibenzylaminopropyl	γ-(4-isopropoxy-3-methoxyphenyl)allyl
2-N-methyl-N-benzylaminoethyl	γ-(3-fluorophenyl)allyl
3,-N,N-dibenzylamino-2-propyl	γ-(2,6-dichlorophenyl)allyl
2-N,N-dibenzylamino-1-propyl	γ-(2,4,5-trichlorophenyl)-allyl
2-N-(n-butyl)-N-benzylaminoethyl	γ-(3-bromophenyl)allyl
2-N-(n-butyl)-N-butyrylaminoethyl	γ-(2-methylphenyl)allyl
3-N-methyl-N-propionylamino-propyl	γ-(4-methylphenyl)allyl
2-N-carbomethoxyaminoethyl	γ-(2-chloro-4-methylphenyl)-allyl
2-N-benzyl-N-carbomethoxy-aminoethyl	γ-(4-isopropylphenyl)allyl
3-N-benzyl-N-carbo(isopropoxy-)aminopropyl	γ-(2,4,6-trimethylphenyl)-allyl
2-N-carbobutoxyaminoethyl	γ-(2,5-dimethyl-4-methoxyphenyl)-allyl
2-N-benzyl-N-acetylaminethyl	γ-(3-methoxy-4-ethoxyphenyl)-allyl
3-piperidyl	γ-(3-chloro-4-methoxyphenyl)-allyl
3-(1-methylpiperidyl)	γ-(3-methyl-6-nitrophenyl)allyl
3-(1-ethylpiperidyl)	γ-(2-nitro-4-chlorophenyl)allyl
3-(1-isopropylpiperidyl)	γ-(3-nitro-5-bromophenyl)allyl
3-(1-n-butylpiperidyl)	γ-(2,6-dinitrophenyl)allyl
3-(1-benzylpiperidyl)	γ-(2-ethoxy-5-nitrophenyl)allyl
γ-phenylallyl	γ-(4-n-butoxyphenyl)allyl
γ-(4-chlorophenyl)allyl	γ-(2,4-xylyl)propargyl
γ-(2-methoxyphenyl)allyl	γ-(m-tolyl)propargyl
γ-(4-methoxyphenyl)allyl	γ-(3-chlorophenyl)propargyl
γ-(3,4-methylenedioxyphenyl)-allyl	γ-(3-methoxyphenyl)propargyl
γ-(3,4-dimethoxyphenyl)allyl	γ-(3-nitrophenyl)propargyl
γ-(2-nitrophenyl)allyl	

Example V

The following compounds are prepared by the procedure of Example I from the appropriate aryl malonic acid half esters and 6-aminopenicillanic acid.



- 5 For each of the R_2 values listed, R_1 =2-thienyl, 3-thienyl, 2-pyridyl, 2-furyl, and o-tolyl; and R_4 =penicillanic acid residue.

R_2	R_2
2-biphenyl	2-methoxy-4-(2-carbomethoxyvinyl)-phenyl
3-biphenyl	2,6-dimethoxy-4-(2-carboxyvinyl)-phenyl
4-biphenyl	2-chloro-3-(2-carboxyvinyl)-phenyl
2-chloro-3-biphenyl	2-(2-carboxyvinyl)-6-nitro-4-biphenyl
2-bromo-4-biphenyl	3-methyl-4-(2-carboxyethyl)-phenyl
2-nitro-4-biphenyl	2,4-dimethyl-6-(carboxymethyl)-phenyl
2-dimethylamino-5-biphenyl	4-t-butyl-2-biphenyl
2-t-butyl-4-methoxyphenyl	3-methoxy-2-biphenyl
4-carbomethoxymethylphenyl	2-methyl-4-biphenyl
2-carbomethoxymethylphenyl	2-isopropyl-4-methoxyphenyl
4-(carbo-n-butoxy)methylphenyl	2-t-butyl-4,5-dimethoxyphenyl
4-(2-carboxyethyl)phenyl	4-dimethylamino-3-isopropoxy-phenyl
4-(2-carbomethoxyethyl)phenyl	5-dimethylamino-2-isopropyl-phenyl
4-carbomethoxymethylphenyl	2-N-methyl-N-formylaminoethyl
2-chloro-3-(2-carboxyethyl)-phenyl	2-N-methyl-N-acetylaminomethyl
2,4-dimethyl-6-(carboxymethyl)-phenyl	γ -(3,4-dimethoxyphenyl)allyl
4-(2-carboxyvinyl)phenyl	γ -(4-nitrophenyl)allyl
2-methoxy-4-(2-carboxyvinyl)-phenyl	γ -(3-fluorophenyl)allyl
2-N-isopropyl-N-formylaminoethyl	γ -(2,6-dichlorophenyl)allyl
2-N-(n-butyl)-N-acetylaminomethyl	γ -(3-bromophenyl)allyl
3-N-(isopropyl)-N-formylaminopropyl	γ -(2-methylphenyl)allyl
3-N-(isopropyl)-N-acetylaminopropyl	

R_2	R_2
2-N-methyl-N-carbomethoxy-aminopropyl	γ -(4-methylphenyl)allyl
2-N-methyl-N-carbo(isobutoxy)-aminoethyl	γ -(2-chloro-4-methylphenyl)-allyl
2-N-ethyl-N-carbo(isobutoxy)-aminoethyl	γ -(4-isopropylphenyl)allyl
2-N-(n-butyl)-N-carbomethoxy-aminoethyl	γ -(2,5-dimethyl-4-methoxyphenyl)-allyl
3-N-formylaminopropyl	γ -(3-methoxy-4-ethoxyphenyl)-allyl
3-N-acetylaminopropyl	γ -(3-chloro-4-methoxyphenyl)-allyl
3-N-carbo(isobutoxy)amino-propyl	γ -(3-methyl-6-nitrophenyl)-allyl
3-N-isopropyl-N-carbo(isobutoxy)-aminopropyl	γ -(2-nitro-4-chlorophenyl)-allyl
2-N,N-dibenzylaminoethyl	γ -(3-nitro-5-bromophenyl)allyl
3-N-methyl-N-benzylaminopropyl	γ -(2-ethoxy-5-nitrophenyl)-allyl
3-piperidyl	γ -(4-n-butoxyphenyl)allyl
3-(1-ethylpiperidyl)	γ -phenylpropargyl
3-(1-butylpiperidyl)	γ -(p-tolyl)propargyl
3-(1-benzylpiperidyl)	γ -(3,4-dimethoxyphenyl)propargyl
γ -phenylallyl	γ -(4-chlorophenyl)propargyl
γ -(4-chlorophenyl)allyl	γ -(4-methoxyphenyl)propargyl
γ -(2-methoxyphenyl)allyl	γ -(4-nitrophenyl)propargyl
γ -(4-methoxyphenyl)allyl	
γ -(3,4-methylenedioxyphenyl)allyl	

Example VI

5 The following penicillins, wherein R_1 is 3-furyl, 3-pyridyl, 4-pyridyl, p-tolyl, o-methoxyphenyl, p-methoxyphenyl, p-trifluoromethylphenyl, p-chlorophenyl, o-dimethylaminophenyl, and p-dimethylaminophenyl for

each of the R_2 values listed, are prepared by the method of Example III from the appropriate aryl malonic acid half ester and 6-aminopenicillanic acid. For convenience, only the R_2 values are listed.

R ₂	R ₂
3-biphenyl	2,4-dimethyl-6-(carboxymethyl)-phenyl
4-biphenyl	4-t-butyl-2-biphenyl
2-chloro-3-biphenyl	3-methoxy-2-biphenyl
2-bromo-4-biphenyl	2-methyl-4-biphenyl
2-nitro-4-biphenyl	2-isopropyl-4-methoxyphenyl
2-dimethylamino-5-biphenyl	4-dimethylamino-3-isopropoxyphenyl
4-(carbo-n-butoxy)methylphenyl	5-dimethylamino-2-isopropylphenyl
4-(2-carboxyethyl)phenyl	2-N-methyl-N-formylaminoethyl
4-carbomethoxymethylphenyl	2-N-methyl-N-acetylaminomethyl
4-(2-carboethoxyethyl)phenyl	2-N-(n-butyl)-N-formylaminoethyl
2-chloro-3-(2-carboxyethyl)phenyl	2-N-(n-butyl)-N-acetylaminomethyl
4-(2-carboxyvinyl)phenyl	3-N-(isopropyl)-N-acetylaminopropyl
2-methoxy-4-(2-carbomethoxyvinyl)phenyl	2-N-methyl-N-carbomethoxyaminoethyl
2,5-dimethyl-4-(2-carboxyvinyl)phenyl	2-N-methyl-N-carbo(isobutyloxy)-aminoethyl
2,6-dimethoxy-4-(2-carboxyvinyl)phenyl	2-N-(n-butyl)-N-carbomethoxyaminoethyl
2-chloro-3-(2-carboxyvinyl)phenyl	3-N-acetylaminopropyl
3-methyl-4-(2-carboxyethyl)-phenyl	γ-(4-chlorophenyl)allyl
3-N-carbo(isobutoxy)aminopropyl	γ-(2-methoxyphenyl)allyl
3-N-isopropyl-N-carbo(isobutoxy)-aminopropyl	γ-(3,4-methylenedioxyphe-nyl)-allyl
2-N,N-dibenzylaminoethyl	γ-(3,4-dimethoxyphenyl)allyl
2-N-methyl-N-benzylaminoethyl	γ-(4-nitrophenyl)allyl
3-N-butyl-N-benzylaminopropyl	γ-(3-fluorophenyl)allyl
3-N,N-dibenzylamino-2-propyl	γ-(2,4,5-trichlorophenyl)allyl
2-N-benzyl-N-acetylaminomethyl	γ-(3-bromophenyl)allyl
3-piperidyl	γ-(2-methylphenyl)(allyl)
3-(1-methylpiperidyl)	γ-(2-chloro-4-methylphenyl)allyl
3-(1-isopropylpiperidyl)	γ-(3-chloro-4-methoxyphenyl)allyl

R ₂	R ₂
3-(1-benzylpiperidyl)	γ-(2-nitro-4-chlorophenyl)allyl
γ-phenylallyl	γ-(phenylpropargyl)
γ-(4-n-butoxyphenyl)allyl	γ-(4-chlorophenyl)propargyl
γ-(p-tolyl)propargyl	γ-(4-nitrophenyl)propargyl
γ-(4-methoxyphenyl)propargyl	

Example VII

Following the procedure of Example II, the α-carboxy aryl penicillin esters, wherein the aryl group, R₁, for each of the R₂ values given, is m-tolyl, m-methoxyphenyl, m-trifluoromethylphenyl, o-isopropylphenyl, o-chloro-

phenyl, o-bromophenyl, m-bromophenyl, m-chlorophenyl, o-butoxyphenyl, o-butylphenyl, o-diethylaminophenyl, p-di-(n-propyl)aminophenyl, o-dibutylaminophenyl, and m-dimethylaminophenyl, are prepared from the appropriate reactants.

10

R ₂	R ₂
4-biphenyl	2-chloro-3-biphenyl
2-bromo-4-biphenyl	2-nitro-4-biphenyl
2-dimethylamino-5-biphenyl	2-N-(n-butyl)-N-carbomethoxy-aminoethyl
4-(carbo-n-butoxy)methylphenyl	3-N-acetylaminopropyl
4-(2-carbomethoxyethyl)-phenyl	3-N-isopropyl-N-carbo(isobutoxy)-aminopropyl
4-carbomethoxymethylphenyl	2-N-methyl-N-benzylaminoethyl
2-chloro-3-(2-carboxyethyl)phenyl	3-N,N-dibenzylaminopropyl
2-methoxy-4-(2-carbomethoxy-vinyl)phenyl	3-piperidyl
2,5-dimethyl-4-(2-carboxy-vinyl)phenyl	3-(1-isopropylpiperidyl)
2-chloro-3-(2-carboxyvinyl)-phenyl	3-(1-benzylpiperidyl)
3-methyl-4-(2-carboxyethyl)-phenyl	γ-phenylallyl
2,4-dimethyl-6-(carboxymethyl)-phenyl	γ-(4-chlorophenyl)allyl
3-methoxy-2-biphenyl	γ-(4-methoxyphenyl)allyl
2-methyl-4-biphenyl	γ-(3,4-methylenedioxyphenyl)-allyl
2-isopropyl-4-methoxyphenyl	γ-(4-nitrophenyl)allyl
4-dimethylamino-3-isopropoxy-phenyl	γ-(3-fluorophenyl)allyl
	γ-(3-bromophenyl)allyl
	γ-phenylpropargyl
	γ-(p-tolyl)propargyl

R ₂	R ₂
5-dimethylamino-2-isopropyl-phenyl	γ-(2-chlorophenyl)propargyl
2-N-methyl-N-formylaminoethyl	γ-(3-methoxyphenyl)propargyl
2-N-ethyl-N-acetylaminoethyl	γ-(3-nitrophenyl)propargyl
2-N-isopropyl-N-formylaminoethyl	
ethyl	
2-N-(n-butyl)-N-acetylamino-ethyl	
3-N-(isopropyl)-N-acetyl-aminopropyl	
2-N-methyl-N-carbomethoxy-aminoethyl	

Example VIII

α - Carbo(2 - isopropylphenoxy)benzylpenicillin — Anhydride Method

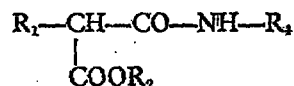
- 5 A stirred solution of mono - (2 - isopropylphenyl)phenylmalonate (2.5 g.) in dry acetone (10 ml.) is cooled to 0°C. in an ice bath. Anhydrous triethylamine (1.27 g.) is added dropwise over a 15-minute period, followed by
- 10 dry chloroethylcarbonate (900 mg.). A precipitate of triethylamine hydrochloride forms immediately. A solution of 6-aminopenicillanic acid (1.8 g.) in sodium bicarbonate solution (20 ml. of 5% solution) and acetone (5 ml.)
- 15 is added all at once to the mixed anhydride. The mixture is stirred at 0°C. for one-half hour, then extracted with ether (3×50 ml.) and acidified to pH 1.0 with concentrated hydrochloric acid. The acid solution is extracted with ethyl acetate (3×50 ml.), the
- 20

extracts combined, back-washed with water, saturated salt solution, and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gives the product as a yellow oil; 940 mg. (21.6%).

It is converted to the crystalline N-ethylpiperidine salt by dissolving in ethyl acetate (1 ml.) and adding a slight excess of N-ethylpiperidine. The salt is collected, washed with ethyl acetate, and dried.

Example IX

In like manner, the following penicillins are prepared from the appropriate reactants.



(R₃ = the penicillanic acid moiety.)

R ₁	R ₂	R ¹ (in Cl-COOR')
phenyl	2-biphenyl	ethyl
phenyl	3-biphenyl	ethyl
phenyl	4-biphenyl	ethyl
phenyl	2-methyl-4-biphenyl	ethyl
phenyl	3-methoxy-2-biphenyl	ethyl
phenyl	2-nitro-4-biphenyl	ethyl
phenyl	2-t-butyl-4-methoxyphenyl	methyl
phenyl	4-(2-carbomethoxyethyl)phenyl	methyl

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R ₁	R ₂	R ¹ (in Cl-COOR')
phenyl	2-methoxy-4-(2-carbomethoxy-vinyl)phenyl	methyl
3-thienyl	2-biphenyl	methyl
p-chlorophenyl	2-biphenyl	methyl
p-methoxyphenyl	2-biphenyl	methyl
4-pyridyl	2-biphenyl	methyl
3-thienyl	2-t-butyl-4-methoxyphenyl	methyl
p-chlorophenyl	2-t-butyl-4-methoxyphenyl	methyl
p-methoxyphenyl	2-t-butyl-4-methoxyphenyl	methyl
4-pyridyl	2-t-butyl-4-methoxyphenyl	methyl
p-dimethylamino-phenyl	2-t-butyl-4-methoxyphenyl	methyl
phenyl	2-N,N-dibenzylaminoethyl	ethyl
phenyl	3-(1-benzylpiperidyl)	ethyl
phenyl	3-N-acetylaminopropyl	ethyl
phenyl	2-N-methyl-N-benzylaminoethyl	ethyl
phenyl	γ-phenylallyl	methyl
phenyl	γ-phenylpropargyl	methyl
phenyl	γ-(3,4-methylenedioxyphenyl)-allyl	methyl

Example X

α - Carbo(2 - Biphenyloxy)Benzylpenicillin Potassium Salt

- 5 α - Carbo(2 - biphenyloxy)phenyl Acetic Acid
 Phenyl malonic acid (90.0 g., 0.5 mole), o-phenylphenol (85 g., 0.5 mole), N,N-dimethylformamide (0.8 ml.), isopropyl ether (725 ml.) and thionyl chloride (59.5 g., 0.5 mole) are
 10 combined, stirred and heated to reflux on a steam bath for two hours. The mixture is cooled to room temperature then washed with water (3×50 ml.) and extracted with saturated aqueous sodium bicarbonate solution
 15 (3×100 ml.). The combined aqueous extracts are washed with ether (2×25 ml.) then acidified to pH 30 with 6N hydrochloric acid and extracted again with ether (3×50 ml.). The ether extracts are washed with water (2×15 ml.) followed by saturated aqueous salt solution (2×15 ml.) then dried over anhydrous sodium sulfate and evaporated to dryness to give 90.3 g of α - carbo - (2 - biphenyloxy)-phenyl acetic acid.

Acid Chloride of α - Carbo(2 - biphenyloxy)-phenyl Acetic Acid

A dry flask fitted with a condenser and drying tube is charged with α - carbo(2 - biphenyloxy)phenyl acetic acid (45.0 g., 0.135 mole), methylene chloride (450 ml.), anhydrous N,N-dimethylformamide (0.1 ml.) and thionyl chloride (16.66 g., 0.140 mole) and the mixture refluxed for three hours. The methylene chloride solvent is removed under reduced pressure then an additional 200 ml. of solvent added and the evaporation repeated to leave a yellow oil (48.0 g.).

α - Carbo(2 - biphenyloxy)benzylpenicillin

A slurry of 6-aminopenicillanic acid (29.16 g., 0.135 mole) in methylene chloride (800 ml.) is rapidly stirred while triethylamine (27.27 g. 0.27 mole) is added at room temperature. The mixture is filtered after two hours of stirring, cooled to 5°C. and the acid chloride of α - carbo(2 - biphenyloxy)phenyl acetic acid (48.0 g., 0.135 mole) in methylene

- chloride (200 ml.) added at such a rate that the temperature did not rise above 10°C. The mixture was then stirred for one hour, diluted with water (400 ml.) adjusted to pH 2.0 and thoroughly agitated. The methylene chloride phase is separated, dried over sodium sulfate and evaporated to dryness. The residue is taken up in ethyl acetate (300 ml.), the solution washed with water (3×150 ml.) and extracted with saturated aqueous sodium bicarbonate (3×150 ml.). The aqueous extract is washed with ethyl acetate then acidified to pH 2.0 in the presence of fresh ethyl acetate (300 ml.).
- The suspension is thoroughly mixed, the ethyl acetate phase separated and washed successively with water (3×150 ml.) and saturated brine (3×150 ml.). It is then dried (anhydrous sodium sulfate) and evaporated to dryness under reduced pressure.
- The residue is dissolved in ethyl acetate (400 ml.) and N-ethylpiperidine (12.0 g.) added. The mixture is seeded and allowed to

stand overnight. The product is filtered washed with ethyl acetate and air dried; 37.5 g., m.p. 131—133°C. (dec.).

It is converted to the potassium salt by adding potassium 2-ethyl hexanoate (16 ml. of an ethyl acetate solution containing 0.283 g./ml.) to a slurry of the N-ethylpiperidine salt (10 g.) in dry benzene (100 ml.). The mixture clears, is heated to 45°C. in a steam bath, seeded and held at room temperature. The product is filtered off and washed with ether (5.97 g.).

Example XI

The above procedures are repeated but using the following phenol derivatives in place of o-phenylphenol:

butylated hydroxyanisole
4-carbomethoxyethylphenol
4-carbomethoxymethylphenol
4-carbomethoxymethylphenol*

The following esters are thus produced as their N-ethylpiperidine salts (NEP):

Penicillins (as NEP salt)	M.P. (°C.)
α -carbo(2-t-butyl-4-methoxyphenoxy)benzylpenicillin	148—52 (dec.)
α -carbo(4-carbomethoxyethylphenoxy)benzylpenicillin	94—96.5 (dec.)
α -carbo(4-carbomethoxymethylphenoxy)benzylpenicillin	104—06 (dec.)
α -carbo(4-carbomethoxymethylphenoxy)benzylpenicillin	89—92 (dec.)

They are converted to their sodium or potassium salts as described above using sodium or potassium 2-ethyl-hexanoate.

50 PREPARATION A Esters of Arylcarboxy Ketenes — General Preparation Method

To a solution of the appropriate aryl halo-carbonyl ketene (0.1 mole) in methylene chloride (sufficient to provide a clear solution and generally from about 5 to 10 ml. per gram of ketene) there is added the proper alcohol R₂OH (0.1 mole). The reaction mixture is maintained under an atmosphere of nitrogen and stirred for a period of from 20 minutes to three hours, care being taken to exclude moisture. The temperature may range from about -70°C. to about -20°C.

Water (200 ml.) is then added to the reaction mixture followed by three equivalents of sodium bicarbonate. The mixture is warmed to 0°C. and stirred for a half-hour to form a heavy emulsion. The methylene chloride is removed under reduced pressure below 35°C. and the remaining aqueous solution extracted with ether. The ether extract is back-washed

with water (made alkaline to pH 8 with sodium bicarbonate), dried with anhydrous sodium sulfate, and evaporated to give unreacted alcohol.

The basic aqueous solution is cooled to 10°C., adjusted to pH 2.0 with dilute hydrochloric acid then extracted with methylene chloride. The extract is dried with anhydrous sodium sulfate and evaporated to dryness to leave the malonic acid half ester.

The esters are used without further purification in the preparation of the α -carboxy-arylpenicillin esters described herein.

PREPARATION B Acid Chlorides of Arylmalonic Acid Half-Esters General Preparation Method

A solution of the malonic acid half-ester in methylene chloride (approximately 10 ml. per gram of ester) and thionyl chloride (1 equivalent) is gently refluxed for three hours. The methylene chloride solvent and other volatiles are then removed by evaporation under reduced pressure. Phosphorus oxychloride rather than thionyl chloride is used to prepare the half-ester of malonic acid with this phenol derivative.

duced pressure to leave the acid chloride product. The acid chlorides are used without further purification.

REFERENCE PREPARATION C

Aminoisopropanols

The following aminoisopropanols are prepared by the reduction of propylene oxide with the appropriate amine. The procedure in general comprises reacting the propylene oxide with an aqueous solution of the amine in a 1.0 to 1.4 molar ratio in a sealed tube. The sealed tube is shaken and allowed to stand overnight, then heated to 80°C. for six hours, then at 95°C. for four hours. The tube is then cooled, the contents removed, and the aminoisopropanol salted out with potassium carbonate.

The product, if fluid, is separated, dried with solid potassium hydroxide, then distilled under reduced pressure. The product, if solid, is filtered off and recrystallized from a suitable solvent.

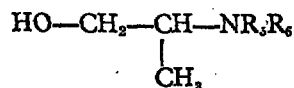


dimethylamino
diethylamino
di-n-propylamino
diisopropylamino
di-n-butylamino
1,4,5,6-tetrahydropyrimidino
n-ethylpiperazino
piperidino
pyrrolidino
pyrrolo
morpholino
thiomorpholino
imidazolino
imidazolidino

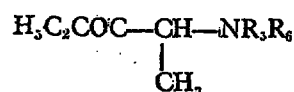
REFERENCE PREPARATION D

2-Aminopropanols

The following 2-aminopropanols having the formula



wherein NR_5R_6 represents a di(lower alkyl)-amino or a heterocyclic group, are prepared by the procedure of Moffett, Org. Syn., Coll. Vol. IV, p. 834 which comprises lithium aluminum hydride reduction of the appropriate precursor ester of the formula



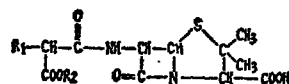
said esters being prepared as described by Moffett, Org. Syn. Coll. Vol. IV, p. 466 by reaction of the desired amine with ethyl α -bromopropionate.



di(n-propyl)amino
di(n-butyl)amino
diisopropylamino
1,4,5,6-tetrahydropyrimidino
N-methylpiperazino
N-n-butylpiperazino
piperidino
morpholino
thiomorpholino
pyrrolo
imidazolino
imidazolidino

WHAT WE CLAIM IS:—

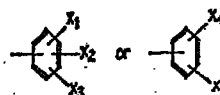
1. Compounds of the formula



and the pharmaceutically acceptable salts thereof wherein R_1 is

thienyl
furyl
pyridyl
phenyl, or
substituted phenyl

wherein the substituent is (C_1-C_6) alkyl, chloro, bromo, (C_1-C_6) alkoxy, $\text{di}(\text{C}_1-\text{C}_6)$ -alkylamino, or trifluoromethyl; and R_2 is



wherein X_1 is chloro, bromo, fluoro, (C_1-C_6) -alkyl, or (C_1-C_6) alkoxy;

X_2 is (C_1-C_6) alkyl or chloro;

X_3 is phenyl, carboxyvinyl, $\text{carbo}(\text{C}_1-\text{C}_6)$ -alkoxyvinyl, hydrogen, $\text{carboxy}(\text{C}_1-\text{C}_6)$ alkyl or $\text{carbo}(\text{C}_1-\text{C}_6)$ alkoxy (C_1-C_6) alkyl;

and X_4 is nitro or $\text{di}(\text{C}_1-\text{C}_6)$ alkylamino;

or R_2 is mono-substituted phenyl wherein the substituent is phenyl, carboxyvinyl, $\text{carbo}(\text{C}_1-\text{C}_6)$ alkoxyvinyl, $\text{carbo}(\text{C}_1-\text{C}_6)$ alkoxy (C_1-C_6) alkyl or $\text{carboxy}(\text{C}_1-\text{C}_6)$ alkyl;

R_2 also is

3-[1-(R_3 -substituted)piperidyl],

$-(\text{CH}_2)_m-\text{NR}_5\text{R}_6$,

$-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{NR}_5\text{R}_6$,

$-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{NR}_5\text{R}_6$, biphenyl, or

(C_1-C_6) alkynyl wherein m is an integer from 2 to 3;

R_5 is hydrogen, (C_1-C_6) alkyl or benzyl;

and R_6 is (C_1-C_6) alkyl, (C_1-C_6) alkanoyl,

benzyl, phenyl or $\text{carbo}(\text{C}_1-\text{C}_6)$ alkoxy;

with the proviso that when R_5 is hydrogen R_6

is $\text{carbo}(\text{C}_1-\text{C}_6)$ alkoxy and when R_5 is

(C_1-C_6) alkyl, R_6 may not be (C_1-C_6) alkyl;

and γ -phenylallyl, γ -(substituted phenyl)allyl



* C L M S *

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1,290,177

19

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duced pressure to leave the acid chloride pro-
duct. The acid chlorides are used without fur-
ther purification.

REFERENCE PREPARATION C

Aminoisopropanols

- 5 The following aminoisopropanols are pre-
pared by the reduction of propylene oxide
with the appropriate amine. The procedure
in general comprises reacting the propylene
oxide with an aqueous solution of the amine
in a 1.0 to 1.4 molar ratio in a sealed tube.
The sealed tube is shaken and allowed to
stand overnight, then heated to 80°C. for six
hours, then at 95°C. for four hours. The tube
is then cooled, the contents removed, and the
aminoisopropanol salted out with potassium
carbonate.

- 10 The product, if fluid, is separated, dried
with solid potassium hydroxide, then distilled
under reduced pressure. The product, if solid,
is filtered off and recrystallized from a suit-
able solvent.

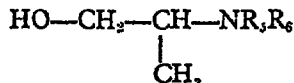
NR₃R₄

- 25 dimethylamino
diethylamino
di-n-propylamino
diisopropylamino
di-n-butylamino
30 1,4,5,6-tetrahydropyrimidino
n-ethylpiperazino
piperidino
pyrrolidino
pyrrolo
35 morpholino
thiomorpholino
imidazolino
imidazolidino

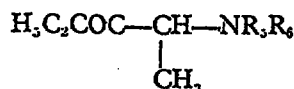
REFERENCE PREPARATION D

2-Aminopropanols

- 40 The following 2-aminopropanols having the
formula



- wherein NR₃R₄ represents a di(lower alkyl)-
amino or a heterocyclic group, are prepared
by the procedure of Moffett, Org. Syn., Coll.
Vol. IV, p. 834 which comprises lithium alu-
minum hydride reduction of the appropriate
precursor ester of the formula



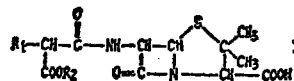
- 50 said esters being prepared as described by
Moffett, Org. Syn. Coll. Vol. IV, p. 466 by
reaction of the desired amine with ethyl α-
bromopropionate.

--NR₃R₄

- di(n-propyl)amino 55
di(n-butyl)amino
diisopropylamino
1,4,5,6-tetrahydropyrimidino
N-methylpiperazino
N-n-butylpiperazino 60
piperidino
morpholino
thiomorpholino
pyrrolo
imidazolino 65
imidazolidino

WHAT WE CLAIM IS:—

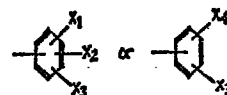
1. Compounds of the formula



- and the pharmaceutically acceptable salts 70
thereof wherein R₁ is

- thienyl
furyl
pyridyl
phenyl, or 75
substituted phenyl

- wherein the substituent is (C₁—C₆)alkyl,
chloro, bromo, (C₁—C₆)alkoxy, di(C₁—C₆)-
alkylamino, or trifluoromethyl;
and R₂ is 80



- wherein X₁ is chloro, bromo, fluoro, (C₁—C₆)-
alkyl, or (C₁—C₆)alkoxy;
X₂ is (C₁—C₆)alkyl or chloro;
X₃ is phenyl, carboxyvinyl, carbo(C₁—C₆)-
alkoxyvinyl, hydrogen, carboxy(C₁—C₆)alkyl 85
or carbo(C₁—C₆)alkoxy(C₁—C₆)alkyl;
and X₄ is nitro or di(C₁—C₆ alkyl)amino;
or R₂ is mono-substituted phenyl wherein the
substituent is phenyl, carboxyvinyl, carbo- 90
(C₁—C₆)alkoxyvinyl, carbo(C₁—C₆)alkoxy-
(C₁—C₆)alkyl or carboxy (C₁—C₆)alkyl;
R₂ also is

- 3-[1-(R₃-substituted)piperidyl],
—(CH₂)_m—NR₃R₄, 95
—CH₂—CH(CH₃)—NR₃R₄,
—CH(CH₃)—CH₂—NR₃R₄, biphenyl, or
(C₁—C₆)alkynyl wherein m is an integer from
2 to 3;
R₃ is hydrogen, (C₁—C₆)alkyl or benzyl;
and R₄ is (C₁—C₆)alkyl, (C₁—C₆)alkanoyl,
benzyl, phenyl or carbo(C₁—C₆)alkoxy;
with the proviso that when R₃ is hydrogen R₄
is carbo(C₁—C₆)alkoxy and when R₃ is 100
(C₁—C₆)alkyl, R₄ may not be (C₁—C₆)alkyl;
and γ-phenylallyl, γ-(substituted phenyl)allyl 105



wherein the substituent is at least one of chloro, bromo, fluoro, (C₁-C₆)alkoxy, (C₁-C₆)alkyl, nitro or methylenedioxy; γ -phenylpropargyl, γ -(substituted phenyl)propargyl wherein the substituent is chloro, bromo, (C₁-C₆)alkoxy, (C₁-C₆)alkyl or nitro.

2. The compounds of claim 1, wherein R₁ is p-chlorophenyl, R₂ is alkynyl, and the pharmaceutically-acceptable salts thereof.

3. The compounds of claim 1, wherein R₁ is phenyl, R₂ is γ -phenylpropargyl, and the pharmaceutically-acceptable salts thereof.

4. The compounds of claim 1, wherein R₁ is phenyl, R₂ is γ -phenylallyl, and the pharmaceutically-acceptable salts thereof.

5. The compounds of claim 2, wherein R₁ is p-chlorophenyl, R₂ is propargyl, and the pharmaceutically-acceptable salts thereof.

6. The compounds of claim 1, wherein R₁ is phenyl and R₂ is substituted phenyl wherein at least one substituent is phenyl and the pharmaceutically-acceptable salts thereof.

7. The compounds of claim 1, wherein R₁ is phenyl and R₂ is substituted phenyl wherein at least one substituent is carbo(C₁-C₆)alkoxy(C₁-C₆)alkyl and the pharmaceutically-acceptable salts thereof.

8. The compounds of claim 1, wherein R₁ is phenyl and R₂ is 2-t-butyl-4-methoxyphenyl and the pharmaceutically-acceptable salts thereof.

9. The compound of claim 6, wherein R₁ is phenyl and R₂ is 2-biphenyl and the pharmaceutically-acceptable salts thereof.

10. The compound of claim 7, wherein R₁ is phenyl and R₂ is 2-carbomethoxymethylphenyl and the pharmaceutically-acceptable salts thereof.

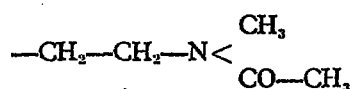
11. α - [Carbo(4 - carbomethoxymethylphenoxy)]benzylpenicillin.

12. The compounds of claim 1, wherein R₁ is phenyl and R₂ is -CH₂-CH₂-NR₅R₆ wherein R₅ is (C₁-C₆)alkyl and R₆ is (C₁-C₆)alkanoyl and the pharmaceutically-acceptable salts thereof.

13. The compound of claim 1, wherein R₁ is phenyl and R₂ is 3-(1-benzylpiperidyl) and the pharmaceutically-acceptable salts thereof.

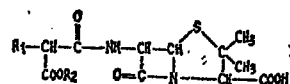
14. The compound of claim 1, wherein R₁ is phenyl and R₂ is -CH₂-CH₂-NR₅R₆ wherein each of R₅ and R₆ is benzyl and the pharmaceutically-acceptable salts thereof.

15. The compound of claim 12, wherein R₁ is phenyl and R₂ is



and the pharmaceutically-acceptable salts thereof.

16. A process for preparing penicillins of the formula



and the pharmaceutically acceptable salts thereof wherein R₁ and R₂ are as defined in claim 1 and R₂ is also (lower alkylene) Y₁ wherein

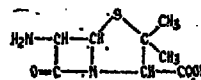
Y₁ is

azetidino
aziridino
pyrrolidino
piperidino
morpholino
thiomorpholino
N-(C₁-C₆ alkyl)piperazino
pyrrolo
imidazolo
2-imidazolino
2,5-dimethylpyrrolidino
1,4,5,6-tetrahydropyrimidino
4-methylpiperidino, or
2,6-dimethylpiperidino;

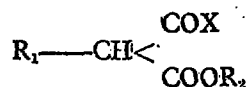
and (lower alkylene) contains from 1 to 3 carbon atoms; and



and substituted derivatives thereof, wherein Z is -(CH₂)₃- or -(CH₂)₄-, and wherein the substituent is methyl, chloro or bromo; which comprises reacting a compound of the formula



wherein M is hydrogen, sodium, potassium, or tri(C₁-C₆ alkyl)amine; with an acylating agent of the formula



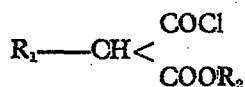
wherein X is chloro, bromo, or -OCOR₁ wherein R₁ is benzyl or (C₁-C₆)alkyl; and R₁ and R₂ are as defined above in a reaction-inert solvent system at a temperature of from about 0 to 50°C. and a pH of from about 5 to 8.

17. The process of acylating agent

18. Compound prepared by
19. The process of preparing compound described.

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17. The process of claim 16, wherein the acylating agent is of the formula



STEVENS, HEWLETT & PERKINS,
Chartered Patent Agents,
5, Quality Court,
Chancery Lane,
London, W.C.2.

18. Compounds of Formula I whenever prepared by the process as herein described.

Reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949, to patent No. 1,133,886.

19. The process according to claim 16 of preparing compounds of Formula I as herein described.

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