

PATENT SPECIFICATION

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NO DRAWINGS

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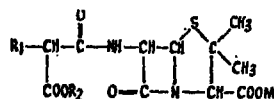
(54) PROCESS FOR PREPARING ESTERS OF α -CARBOXY-ARYLMETHYL-PENICILLINS

- (71) We, CHAS. PFIZER & Co., INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York 17, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

- It has now been found the acylation of 6-aminopenicillanic acid with a reactive derivative of an aryl substituted malonic acid proceeds readily and permits the economic preparation of valuable esters of α -carboxy arylmethylpenicillins which are valuable as orally administrable antibiotics.

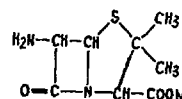
- As used throughout the following description and claims the terms "lower alkoxy" and "lower alkyl" means such groups which contain from 1 to 4 carbon atoms, and the term "lower alkylene" means a group which contains from 1 to 3 carbon atoms.

- According to the present invention there is provided a process for the preparation of penicillins of the formula

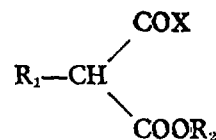


- wherein R_1 and R_2 are as hereinafter defined, M is hydrogen, sodium, potassium, or tri (lower alkyl) amine; comprising reacting a compound of the formula

[Price 25p]



with an acylating agent of the formula

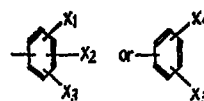


wherein X is chloro, bromo, or $-\text{OCOR}_4$ 35
 wherein R_4 is benzyl or lower alkyl; R_1 is

thienyl
 furyl
 pyridyl
 phenyl, or 40
 substituted phenyl

wherein the substituent is (lower)alkyl, chloro, bromo, (lower)alkoxy, di(lower)-alkylamino, or trifluoromethyl; and R_2 is 45

isopropylphenyl,



wherein X_1 is chloro, bromo, fluoro, lower alkyl, or lower alkoxy;

X_2 is lower alkyl or chloro;

X_3 is hydrogen or methyl; and

5 X_4 is nitro or di(lower alkyl) amino;

as indanyl and substituted derivatives thereof wherein the substituent is methyl, chloro, or bromo;

10 as tetrahydronaphthyl and substituted derivatives thereof, wherein the substituent is methyl, chloro, or bromo;

1 - (lower)alkoxy - 2,2,2 - trichloroethyl,

1 - (lower)alkoxy - 2,2,2 - trifluorethyl,

[carbo(lower)alkoxy] lower alkoxymethyl,

15 [dicarbo(lower)alkoxy] lower alkoxymethyl,

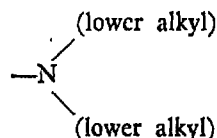
$-(CH_2)_n-NR_5R_6$,

$-CH_2-CH(CH_3)-NR_5R_6$, and

$-CH(CH_3)-CH_2-NR_5R_6$ and

$-(lower\ alkylene)-Y_1$

20 wherein m is an integer of 2 or 3; $-NR_5R_6$ is



wherein the (lower alkyl) groups may be alike or different; and $-N(lower\ alkyl)$ anilino; and

25 Y_1 is

azetidino

aziridino

pyrrolidino

piperidino

30 morpholino

thiomorpholino

N-(lower alkyl)piperazino

pyrrolo

35 imidazolo

2-imidazolino

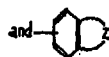
2,5-dimethylpyrrolidino

1,4,5,6-tetrahydropyrimidino

4-methylpiperidino, and

2,6-dimethylpiperidino;

40 and



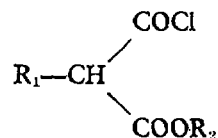
and substituted derivatives thereof, wherein Z is alkylene

45 and is $-(CH_2)_3-$ or $-(CH_2)_4-$, and wherein the substituent is methyl, chloro, or bromo;

in a reaction-inert solvent system as herein-after defined at a temperature of from

0 to 50°C. and a pH of from 5 to 8.

The invention also provides a process in 50 which the acylating agent is of the formula



In the above formula, R_1 can be phenyl and R_2 can be 2-isopropyl phenyl.

The invention further provides a process 55 in which R_1 is phenyl and R_2 is



wherein X_1 may be lower alkyl, chloro, or lower alkoxy, X_2 may be lower alkyl and X_3 may be hydrogen. 60

There is further provided a process in which R_1 is phenyl and R_2 is



wherein Z is alkylene or $-(CH_2)_3-$.

There is further provided a process in 65 which R_1 is phenyl and R_2 is



wherein X_1 may be 2-methyl, 4-chloro or 2-methoxy and X_2 may be 4-methyl or 2-methyl. 70

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 favoured from an economic standpoint. 75

By reaction-inert solvent is meant a solvent 80 which, under the condition 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. 85 However, under the proper conditions of temperature, pH, and time, the hydrolysis occurs

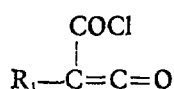
at a relatively slow rate compared to the desired N-acylation reaction. Suitable solvents for the process of this invention include methylene chloride, benzene, chloroform, dioxane, water, acetone, tetrahydrofuran, diethyl ether, and dimethyl ether. Aqueous solvent systems, including those in which an 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 favoured water immiscible solvents are methyl isobutyl ketone and ethyl acetate.

The reaction is conducted over the pH range of from 5 to 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, and 1-phenamine. It is advantageous, however, to use a tri(lower alkyl)amine, 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 0° C. to 50° C. are operative. It is, however, preferred to employ temperatures ranging from 0° to 30° C. in order to prevent degradation of the products.

The preferred form of the arylmalonic acid esters as acylating agents are the monoacid chlorides because of their relative ease of preparation compared to the preparation of the anhydrides.

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



with the alcohol R₂OH, wherein R₁ and R₂ are as defined above. The reaction is conducted on a 1:1 molar ratio at a temperature of from -70° C. to 30° C. and, desirably, in a reaction-inert solvent to permit better mix-

ing and control of the reaction. Suitable solvents are diethyl ether, dimethyl ether dioxane, methylene chloride, and chloroform.

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 0° to 80° C., according to procedures well known to those skilled in the art.

The required aryl chloro carbonyl ketenes are prepared by the reaction of an arylmalonic acid with a halogenating agent selected from PCl₃, PCl₅, POCl₃, or SOCl₂ at temperatures ranging from 0° to 50° C. for periods ranging from one hour to 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.

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 and 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 colour or 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 colour. 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 aryl malonic 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

chlorcarbonates, such as chlorobenzylcarbonate and chlorophenyl carbonate, can be used in place of the chloro(lower alkyl)carbonates.

5 The α -carboxyaryl methylpenicillin 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 2—3 and extracting the product
10 with ethyl acetate. The ethyl acetate extract is washed with water, the product extracted therefrom with 10% by weight aqueous potassium bicarbonate, then back-extracted into ethyl acetate. The ethyl acetate extracts
15 are once again extracted with water, the aqueous extract brought a 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
20 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
25 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
30 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.

35 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
40 of the aqueous phase to 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
45 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
50 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
55 choice of the base. The appropriate solvent is determined by the solubility of the desired salt.

The esters are converted by known methods to the corresponding acids as, for example, by
60 mild acid or mild alkaline or enzymatically with an esterase such as liver homogenate.

The preferred esters of this process are those wherein R_2 is indanyl, 2-isopropyl phenyl, dimethyl substituted phenyl, and
65 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
70 infection 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
75 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, certain types of clay, or in capsules alone or in mixture with the same or equivalent excipients. They may
80 also be administered orally in the form of elixirs or oral suspensions which may contain flavouring or colouring agents, or be injected parenterally; that is, for example, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form
85 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
90 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
95 solutions prior to administration may advantageously be made. Such compositions may include liquid diluents; for example, propylene glycol, diethyl carbonate, glycerol, sorbitol, buffering agents, as well as local anaesthetics and inorganic salts to afford desirable pharmacological properties.
100

The oral and parenteral dosage levels for the hereindescribed compounds are, in general, on the order of up to 200 mg./kg. and 100 mg./kg. of body weight per day, respectively.
105

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
110 and effective dosage forms of the α -carboxy aryl methyl penicillins.

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
120 parenterally into the animal, including the human body.

The following examples are provided to
125 illustrate in greater detail the manner of practicing the present invention. They are, however, not to be construed as limiting the scope thereof in any way.

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 a creased flask. The mixture is then cooled to 0° C. (still under a slow stream of nitrogen) and 2-phenyl-2-(5-indanylcarbonyl)-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 1-1/2 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 separate. The acidic aqueous layer is extracted with methylene chloride (2 x 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, 34.4 g. (99%). The crude penicillin (17 g., 0.0344 mole) in acetone (40 ml.) is cooled to 10° C. and N-ethylpiperidine (3.96 g., 0.035 mole) added. The mixture is stirred for one minute and the white crystalline salt which forms 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 slurring 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 rapidly 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, a cream-coloured foam (4.4 g.).

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

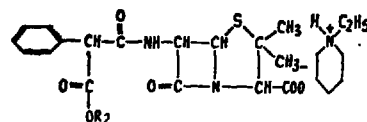
The N-ethylpiperidine salt is converted to the potassium salt as follows.

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 45° 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.).

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

The following esters of α -carboxylbenzylpenicillin are prepared as their N-ethylpiperidine salts by the procedure of Example I.



R ₂	m.p. (° C.)	
2,5-dimethylphenyl	144—150	
2,4-dimethylphenyl	142—144	
2,3-dimethylphenyl	151—153	
2,6-dimethylphenyl	150—151	115
3,4-dimethylphenyl	145—147	
3,5-dimethylphenyl	147—149	
2-chloro-4-methylphenyl	144—145	
4-chloro-2-methylphenyl	149—151	
6-chloro-2-methylphenyl	153—154	120
4-chloro-3-methylphenyl	141—142	

	R ₂	m.p. (° C.)
	2-methoxy-4-methylphenyl	150—152
	3-methoxy-2-methylphenyl	150—152
	4-indanyl	136—139
5	2-(5,6,7,8-tetrahydronaphthyl)	138—139
	1-(5,6,7,8-tetrahydronaphthyl)	136—139
	4-chloro-3,5-dimethylphenyl	140—142
	4-chloro-2,3-dimethylphenyl	144—147

EXAMPLE IV

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

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

20 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-aminopenicillanic acid, is then placed in a three-necked-indented flask equipped with a high-speed stirrer. 2-(2-Isopropylphenoxy-carbonyl)acetyl 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% by weight 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.

35 The acid solution is extracted with ethyl acetate (3×200 ml.), the combined extracts washed with water, filtered, and the filtrate extracted with 10% by weight 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.

40 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

Repetition of this procedure but at pH values of 3.0—3.3; 5—5.3; and 8.5—8.8

during the acylation step also produces the desired product. The yields, however, are lower.

EXAMPLE V

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

70 The pH of an aqueous suspension of 6-aminopenicillanic acid (10.8 g., 0.05 mole) in water (500 ml.) is adjusted to 6.4 by addition of 6N sodium hydroxide solution. To the resulting solution is added 2-(2-isopropylphenoxy-carbonyl)acetyl chloride (19 g., 0.06 mole) dropwise over a one-hour period at room temperature. The pH is held at from 6.3 to 6.5 by continuous addition of 10% by weight sodium hydroxide solution. The reaction mixture is stirred for 1.25 hours at room temperature and pH 6.3—6.5, then adjusted to pH 2 by addition of 6N hydrochloric acid. Ethyl acetate (500 ml.) is added and the mixture thoroughly stirred for five minutes. The ethyl acetate layer is separated, concentrated to about 200 ml. volume, and treated with potassium ethyl hexanoate (0.07 mole). The mixture is concentrated to small volume (about 50 ml.), fresh ethyl acetate (100 ml.) added, and the concentration repeated. This step is repeated once again, then the crystalline salt filtered, washed with ethyl acetate, and dried; yield—6.8 g. (25.4%).

EXAMPLE VI

95 Acylation of 6-aminopenicillanic acid in an aqueous emulsion

A solution of 2-phenyl-2-(2-isopropylphenoxy-carbonyl)acetyl chloride (31.6 g., 0.1 mole) in methyl isobutyl ketone (250 ml.) is added at 25° C. in one portion to a solution of 6-aminopenicillanic acid (10.8 g., 0.05 mole) in water (1000 ml.) at pH 6.4. Vigorous stirring is employed, and the pH is maintained at 6 by continuous addition of 10% by weight aqueous sodium hydroxide.

100 After six minutes, methyl isobutyl ketone (250 ml.) is added, the emulsion stirred, and adjusted to pH 2 by diluted hydrochloric acid. The solution is extracted with ethyl acetate (3×200 ml.), and the combined extracts washed with water, then dried with anhydrous sodium sulfate. The dried extract is evaporated to dryness, the residue taken up in ethyl acetate, and treated with N-ethylpiperidine (6.0 g.) to form the corresponding salt which is recovered by filtration.

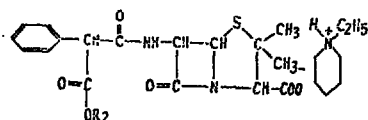
105 In like manner, the corresponding 5-indanyl - 2,4 - dimethylphenyl, 2 - methyl - 4-chlorophenyl, 3,4-dimethylphenyl and 4-indanyl esters are prepared by substituting the acid chloride of the appropriate phenyl malonic acid half esters for the isopropyl phenyl ester above.

125 Repetition of the above procedure using 2 - phenyl - 2 - (2 - isopropylphenoxy-carbonyl)acetyl chloride but at pH values of

3.5 and 8.0 produces the desired product but in lower yield.

EXAMPLE VII

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



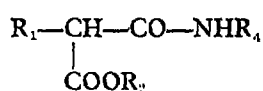
	R ₂		
10	o-dimethylaminophenyl o-diethylaminophenyl o-di-n-butylaminophenyl m-dimethylaminophenyl m-di-n-propylaminophenyl	4-chloro-2,6-dimethylphenyl 4-chloro-6-isopropyl-3-methylphenyl 4-bromo-3-isopropyl-6-methylphenyl 2-chloro-4,5-dimethylphenyl 4,6-dichloro-2-methylphenyl 5-methyl-4-indanyl	75
15	p-dimethylaminophenyl p-methylethylaminophenyl p-methylisopropylaminophenyl 2,3-diethylphenyl 2,4-diethylphenyl	1-methyl-4-indanyl 6-methyl-4-indanyl 7-methyl-4-indanyl 1 - (2,4,6 - trimethyl - 5,6,7,8 - tetrahydro-naphthyl)	80
20	2,6-diethylphenyl 2,4-di-n-propylphenyl 2,6-di-n-propylphenyl 5-ethyl-3-methylphenyl 6-ethyl-2-methylphenyl	2-methyl-5-indanyl 7-methyl-5-indanyl 4,6-dimethyl-5-indanyl 1,1-dimethyl-4-indanyl 1,1,2 - trimethyl-4-indanyl	85
25	2-ethyl-4-methylphenyl 2-methyl-6-n-propylphenyl 4-isopropyl-3-methylphenyl 2-methyl-4-sec-butylphenyl 3-methyl-4-t-butylphenyl	1,1,2,3-tetramethyl-4-indanyl 1,1,5,6-tetramethyl-4-indanyl 5,7-dimethyl-4-indanyl 5-chloro-4-indanyl 7-chloro-4-indanyl	90
30	2,3,4-trimethylphenyl 2,4,6-trimethylphenyl 3,4,5-trimethylphenyl 2,6-dimethyl-4-ethylphenyl 3,5-dimethyl-4-ethylphenyl	7-bromo-4-indanyl 6-chloro-5-indanyl 1,7-dimethyl-4-indanyl 1,1,7-trimethyl-4-indanyl 1-indanyl	95
35	4,6-dimethyl-2-ethylphenyl 2,6-diethyl-4-methylphenyl 4,5-dimethyl-2-isopropylphenyl 2,6-dichlorophenyl 3-isopropylphenyl	2-indanyl 6-methyl-5-indanyl 3-methyl-1-indanyl 5-methyl-1-indanyl 7-methyl-1-indanyl	100
40	4-isopropylphenyl 3-chloro-2-fluorophenyl 3-chloro-4-fluorophenyl 2-bromo-4-fluorophenyl 2-methoxy-4-methylphenyl	2,2-dimethyl-1-indanyl 2,3-dimethyl-1-indanyl 3,3-dimethyl-1-indanyl 2-chloro-1-indanyl 4-chloro-1-indanyl	105
45	3-methyl-4-indanyl 1-methyl-5-indanyl 2-chloro-6-methoxyphenyl 3-methoxy-2-methylphenyl 2-ethoxy-3-methylphenyl	2-bromo-1-indanyl 3-bromo-1-indanyl 1-chloro-2-indanyl 1,5,6,7,8-tetrahydronaphthyl) 2-(5,6,7,8-tetrahydronaphthyl)	110
50	2-methoxy-6-propylphenyl 6-chloro-2-methylphenyl 4-chloro-2-methylphenyl 2-chloro-5-methylphenyl 2-fluoro-4-methylphenyl	1-(3-methyl-5,6,7,8-tetrahydronaphthyl) 1-(4-methyl-5,6,7,8-tetrahydronaphthyl) 2-(1-methyl-5,6,7,8-tetrahydronaphthyl) 2-(3-methyl-5,6,7,8-tetrahydronaphthyl) 2-(4-methyl-5,6,7,8-tetrahydronaphthyl)	115
55	4-fluoro-3-methylphenyl 2-bromo-6-methylphenyl	2-(5-methyl-5,6,7,8-tetrahydronaphthyl)	120

	R_2	R_2	
5	1 - (4,4 - dimethyl - 5,6,7,8 - tetrahydro-naphthyl) 1 - (4,8 - dimethyl - 5,6,7,8 - tetrahydro-naphthyl) 2 - (1,6 - dimethyl - 5,6,7,8 - tetrahydro-naphthyl) 2-(3-bromo-1,2,3,4-tetrahydronaphthyl)	(2-imidazolino)methyl (1,4,5,6-tetrahydropyrimidino)methyl pyrrolidinomethyl piperidinomethyl morpholinomethyl thiomorpholinomethyl 2-(methylethylamino)ethyl 2-(methylbutylamino)ethyl 2-(ethylisopropylamino)ethyl 2-(ethylbutylamino)ethyl 2-(2,6-dimethylpiperidino)ethyl 2-(N-methylanilino)ethyl 2-(N-ethylanilino)ethyl 2-(N-isopropylanilino)ethyl 2-(N-n-propylanilino)ethyl 2-(N-n-butylanilino)ethyl 2-methylbutylamino-1-propyl 3-aziridino-2-propyl 3-thiomorpholino-2-propyl 2-piperidino-1-propyl 2-(N-ethyl)piperazino-1-propyl 2-di-(n-propyl)amino-1-propyl 3-(N-isopropylanilino)propyl 3-(N-ethylanilino)-2-propyl 2-(N-methylanilino)-1-propyl 3-(N-ethylanilino)propyl 1-ethoxy-2,2,2-trichloroethyl 1-butoxy-2,2,2-trichloroethyl 1-ethoxy-2,2,2-trifluoroethyl dicarbethoxyethoxymethyl 1-isopropoxy-2,2,2-trichloroethyl 1-isobutoxy-2,2,2-trichloroethyl dicarbomethoxyethoxymethyl 4-dimethylamino-2-methylphenyl 2-methyl-6-nitrophenyl 2-methyl-6-nitrophenyl 2-methyl-3-nitrophenyl 3-diisopropylaminopropyl 3-dibutylaminopropyl 3-(2-imidazolino)propyl 3-piperidinopropyl 3-pyrrolidinopropyl 3-pyrrolopropyl azetidinomethyl 3-morpholinopropyl 3-thiomorpholinopropyl 2-(1,4,5,6-tetrahydropyrimidino)ethyl 2-(N-methyl)piperazinoethyl 3-N-butylpiperazinopropyl 3-dimethylaminopropyl 3-di-(n-propyl)aminopropyl 3-aziridinopropyl 3-di-(n-propyl)amino-2-propyl 2-diethylamino-1-propyl 3-pyrrolidino-2-propyl 3-piperidino-2-propyl 3-diethylamino-2-propyl 3-morpholino-2-propyl 3-di-(n-butyl)amino-2-propyl 3-dimethylamino-2-propyl 2-pyrrolidino-1-propyl 2-di-(n-butyl)amino-1-propyl 2-thiomorpholino-1-propyl	70 75 80 85 90 95 100 105 110 115 120 125
10	1 - (2,4,7 - trimethyl - 5,6,7,8 - tetrahydro-naphthyl) 1 - (3,4,6 - trimethyl - 5,6,7,8 - tetrahydro-naphthyl) 2 - (1,5,6 - trimethyl - 5,6,7,8 - tetrahydro-naphthyl)		
15	2 - (3,4,6 - trimethyl - 5,6,7,8 - tetrahydro-naphthyl) 2 - (3,4,7 - trimethyl - 5,6,7,8 - tetrahydro-naphthyl)		
20	2 - (4,4,7 - trimethyl - 5,6,7,8 - tetrahydro-naphthyl) 2 - (5,5,8,8 - tetramethyl - 5,6,7,8 - tetrahydronaphthyl)		
25	1-(2-methyl-1,2,3,4-tetrahydronaphthyl) 1-(4-methyl-1,2,3,4-tetrahydronaphthyl) 1-(7-methyl-1,2,3,4-tetrahydronaphthyl) 1-(1,3-dimethyl-1,2,3,4-tetrahydronaphthyl) 1-(3,4-dimethyl-1,2,3,4-tetrahydronaphthyl) 1-(5,8-dimethyl-1,2,3,4-tetrahydronaphthyl)		
30	1 - (1,2,7 - trimethyl - 1,2,3,4 - tetrahydronaphthyl) 1 - (4,5,7 - trimethyl - 1,2,3,4 - tetrahydronaphthyl) 1 - (1,5,8 - trimethyl - 1,2,3,4 - tetrahydronaphthyl)		
35	2-(1-methyl-1,2,3,4-tetrahydronaphthyl) 2-(6-methyl-1,2,3,4-tetrahydronaphthyl) 2-(2,6-dimethyl-1,2,3,4-tetrahydronaphthyl) 2-(4,4-dimethyl-1,2,3,4-tetrahydronaphthyl)		
40	2 - (1,1,4,5 - tetramethyl - 1,2,3,4 - tetrahydronaphthyl) 1-(2-chloro-1,2,3,4-tetrahydronaphthyl) 1-(3-chloro-1,2,3,4-tetrahydronaphthyl) 2-(1-bromo-1,2,3,4-tetrahydronaphthyl) 1-(2-bromo-1,2,3,4-tetrahydronaphthyl)		
45	3-diethylaminopropyl 2-dimethylaminoethyl 2-dibutylaminoethyl 2-diisopropylaminoethyl 2-di-(n-propyl)aminoethyl 2-diethylaminoethyl 2-(2-imidazolino)ethyl 2-piperidinoethyl 2-pyrrolidinoethyl		
50	2-pyrroloethyl 2-imidazoloethyl 2-morpholinoethyl 2-azetidinoethyl 2-(2,5-dimethylpyrrolidino)ethyl		
55	2-aziridinoethyl 2-diisobutylaminoethyl 2-thiomorpholinoethyl 2-(4-methylpiperidino)ethyl pyrrolidinomethyl		
60	aziridinomethyl		

	R ₂	R ₂	
	2-(imidazolino)-1-propyl	3-isopropylphenyl	60
	3-(1,4,5,6-tetrahydropyrimidino)-2-propyl	2-dimethylaminoethyl	
	3-thiomorpholino-2-propyl	2-dibutylaminoethyl	
5	3-imidazolidino-2-propyl	2-(2-imidazolino)ethyl	
	2-diisopropylamino-1-propyl	2-piperidinoethyl	65
	3-(methylpropylamino)propyl	3-morpholinopropyl	
	3-(ethylisopropylamino)propyl	3-thiomorpholinopropyl	
	3-(methylethylamino)-2-propyl	2-pyrrolidinoethyl	
10	3-(ethylbutylamino)-2-propyl	2-(2-(imidazolino)ethyl	
	2-(methylethylamino)-1-propyl	2-pyrroloethyl	70
	3-imidazo-2-propyl	4-dimethylamino-2-methylphenyl	
	3-pyrrolo-2-propyl	2-diethylaminoethyl	
	3-(N-methyl)piperazino-2-propyl	2-(methylethylamino)ethyl	
15	2-morpholino-1-propyl	2-(ethylbutylamino)ethyl	
	3-(2-imidazolino)-2-propyl	2-(methylisopropylamino)ethyl	75
	3-(N-methylanilino)propyl	3-(methylpropylamino)propyl	
	3-(N-methylanilino)-2-propyl	3-(ethylisopropylamino)propyl	
	3-(N-n-butylanilino)-2-propyl	2-arizidinoethyl	
20	2-(N-n-propylanilino)-1-propyl	2-thiomorpholinoethyl	
	1-methoxy-2,2,2-trichloroethyl	2-(4-methylpiperidino)ethyl	80
	1-propoxy-2,2,2-trichloroethyl	3-(2,6-dimethylpiperidino)propyl	
	1-methoxy-2,2,2-trifluoroethyl	2-(N-ethylanilino)ethyl	
	1-butoxy-2,2,2-trifluoroethyl	2-methoxy-4-methylphenyl	
25	carbethoxyethoxymethyl	2-chloro-6-methoxyphenyl	
	1-sec-butoxy-2,2,2-trichloroethyl	2-ethoxy-3-methylphenyl	85
	1-t-butoxy-2,2,2-trichloroethyl	2-methoxy-6-propylphenyl	
	2-nitrophenyl	6-chloro-2-methylphenyl	
	3-nitrophenyl	2-chloro-5-methylphenyl	
30	4-nitrophenyl	2-chloro-4-isopropylphenyl	
	2-methyl-5-nitrophenyl	4-chloro-2,3-dimethylphenyl	90
	3-methyl-4-nitrophenyl	5-chloro-2,4-dimethylphenyl	
		4-chloro-6-isopropyl-3-methylphenyl	
		2-chloro-6-propylphenyl	
		o-dimethylaminophenyl	
35		o-di-n-butylaminophenyl	95
		m-di-n-propylaminophenyl	
		p-methylethylaminophenyl	
		p-methylisopropylaminophenyl	
		2-(N-methylanilino)ethyl	
		2-diisopropylaminoethyl	100
		3-diethylaminopropyl	
		2-(N-methyl)piperazinoethyl	
		3-(N-butyl)piperazinopropyl	
40		2-(1,4,5,6-tetrahydropyrimidino)ethyl	
		3-pyrrolopropyl	105
		3-imidazolopropyl	
		3-di-(n-propylamino)-2-propyl	
		2-diethylamino-1-propyl	
		3-pyrrolidino-2-propyl	110
		3-piperidino-2-propyl	
		3-diethylamino-2-propyl	
		3-morpholino-2-propyl	
		3-di-(n-butyl)amino-2-propyl	
		3-dimethylamino-2-propyl	
50		3-diisopropylaminopropyl	115
		3-piperidinopropyl	
		3-pyrrolidinopropyl	
		3-(1,4,5,6-tetrahydropyrimidino) propyl	
		3-(N-methylanilino)propyl	
55		3-(methylethylamino)-2-propyl	120
		3-(ethylbutylamino)-2-propyl	
		3-pyrrolo-2-propyl	
		3-(2-imidazolino)-2-propyl	
		3-imidazo-2-propyl	

EXAMPLE VIII

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



For each of the R₂ values listed, R₁=2-thienyl, 3-thienyl, 2-pyridyl, 2-furyl, and o-tolyl; and R₄=penicillanic acid residue.

	R ₂	
	1-methoxy-2,2,2-trichloroethyl	
	1-ethoxy-2,2,2-trichloroethyl	
45	1-butoxy-2,2,2-trichloroethyl	
	1-methoxy-2,2,2-trifluoroethyl	
	1-ethoxy-2,2,2-trifluoroethyl	
	2-isopropylphenyl	
	2,2-dimethylphenyl	
50	2,6-dimethylphenyl	
	2,5-diethylphenyl	
	2,4-di-n-propylphenyl	
	5-ethyl-3-methylphenyl	
	4-isopropyl-3-methylphenyl	
55	3-methyl-4-t-butylphenyl	
	2,4,6-trimethylphenyl	
	4,5-dimethyl-2-isopropylphenyl	
	2,4-dimethyl-3-ethylphenyl	
	2,6-dichlorophenyl	

	R ₂
	2-dimethylamino-1-propyl
	2-di-(n-butyl)amino-1-propyl
	2-N-methylpiperazino-1-propyl
5	2-pyrrolo-1-propyl
	2-(2-imidazolino)-1-propyl
	2-(2,5-dimethylpyrrolidino)-1-propyl
	aziridinomethyl
	piperidinomethyl
10	(2-imidazolino)methyl
	N-ethylpiperazinomethyl
	(4-methylpiperidino)methyl
	pyrrolomethyl
	3-(N-isopropylanilino)propyl
15	3-(N-methylanilino)-2-propyl
	2-(N-methylanilino)-1-propyl
	2-nitrophenyl
	3-nitrophenyl
	3-methyl-2-nitrophenyl
20	4-methyl-2-nitrophenyl
	dicarbethoxyethoxymethyl
	carbethoxyethoxymethyl
	4-indanyl
	5-indanyl
25	5-methyl-4-indanyl
	1-methyl-4-indanyl
	7-methyl-4-indanyl
	3-methyl-4-indanyl
	1-methyl-5-indanyl
30	4,6-dimethyl-5-indanyl
	1,1-dimethyl-4-indanyl
	1,1,2-trimethyl-4-indanyl
	1,1,2,3-tetramethyl-4-indanyl
	1,1,5,6-tetramethyl-4-indanyl
35	5-chloro-4-indanyl
	7-bromo-4-indanyl
	6-chloro-4-indanyl
	1,1,7-trimethyl-4-indanyl
	3-methyl-1-indanyl
40	5-methyl-1-indanyl
	7-methyl-1-indanyl
	2,2-dimethyl-1-indanyl
	3,3-dimethyl-1-indanyl
	2-chloro-1-indanyl
45	3-bromo-1-indanyl
	4-chloro-1-indanyl
	1-chloro-2-indanyl
	1-indanyl
	2-indanyl
50	2-methyl-1-indanyl
	1-methyl-1-indanyl
	2-methyl-2-indanyl
	1-(5,6,7,8-tetrahydronaphthyl)
	2-(5,6,7,8-tetrahydronaphthyl)
55	1-(2-methyl-1,2,3,4-tetrahydronaphthyl)
	1-(4-methyl-1,2,3,4-tetrahydronaphthyl)
	1-(7-methyl-1,2,3,4-tetrahydronaphthyl)
	1-(1,3-dimethyl-1,2,3,4-tetrahydronaphthyl)
	1-(2,4-dimethyl-1,2,3,4-tetrahydronaphthyl)
60	1-(5,8-dimethyl-1,2,3,4-tetrahydronaphthyl)
	1-(1,2,7-trimethyl-1,2,3,4-tetrahydronaphthyl)
	1-(4,5,7-trimethyl-1,2,3,4-tetrahydronaphthyl)
	1-(1,5,8-trimethyl-1,2,3,4-tetrahydronaphthyl)
	2-(1-methyl-1,2,3,4-tetrahydronaphthyl)
65	2-(2,6-dimethyl-1,2,3,4-tetrahydronaphthyl)

	R ₂	
	2-(4,4-dimethyl-1,2,3,4-tetrahydronaphthyl)	
	2 - (1,1,4,4 - tetramethyl - 1,2,3,4 - tetrahydronaphthyl)	
	2-(1,2,3,4-tetrahydronaphthyl)	70
	1-(3-methyl-5,6,7,8-tetrahydronaphthyl)	
	2-(1-methyl-5,6,7,8-tetrahydronaphthyl)	
	2-(4-methyl-5,6,7,8-tetrahydronaphthyl)	
	1-(4,8-dimethyl-5,6,7,8-tetrahydronaphthyl)	
	2-(1,6-dimethyl-5,6,7,8-tetrahydronaphthyl)	75
	1 - (2,4,6 - trimethyl - 5,6,7,8 - tetrahydronaphthyl)	
	2 - (1,5,6 - trimethyl - 5,6,7,8 - tetrahydronaphthyl)	
	2 - (3,4,7 - trimethyl - 5,6,7,8 - tetrahydronaphthyl)	80
	2 - (5,5,8,8 - tetramethyl - 5,6,7,8 - tetrahydronaphthyl)	

EXAMPLE IX

The following penicillins, wherein R₁ 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 R₂ values listed, are prepared by the method of Example IV from the appropriate aryl malonic acid half ester and 6-aminopenicillanic acid. For convenience only, the R₂ values are listed.

	R ₂	
	2-isopropylphenyl	95
	1-methoxy-2,2,2-trichloroethyl	
	1-ethoxy-2,2,2-trichloroethyl	
	1-methoxy-2,2,2-trifluoroethyl	
	1-butoxy-2,2,2-trifluoroethyl	100
	dicarbethoxyethoxymethyl	
	carbethoxyethoxymethyl	
	1-isopropoxy-2,2,2-trichloroethyl	
	1-t-butoxy-2,2,2-trichloroethyl	
	dicarbomethoxyethoxymethyl	105
	o-dimethylaminophenyl	
	o-diethylaminophenyl	
	o-di-n-butylaminophenyl	
	m-di-n-propylaminophenyl	
	p-methylethylaminophenyl	110
	p-methylisopropylaminophenyl	
	2,3-dimethylphenyl	
	2,5-dimethylphenyl	
	2,3-diethylphenyl	
	2,4-di-n-propylphenyl	115
	6-ethyl-2-methylphenyl	
	2-methyl-4-sec-butylphenyl	
	3-methyl-4-t-butylphenyl	
	2,3,4-trimethylphenyl	
	2,6-dimethyl-4-ethylphenyl	120
	4,6-dimethyl-2-methylphenyl	
	4,5-dimethyl-2-isopropylphenyl	
	4-butyl-5-isopropyl-2-methylphenyl	
	2,6-dichlorophenyl	
	4-dimethylamino-2-methylphenyl	125
	4-nitrophenyl	
	3-methyl-5-nitrophenyl	
	5-methyl-2-nitrophenyl	
	2-chloro-6-methoxyphenyl	

	R ₂	R ₂	
	3-methoxy-2-methylphenyl	3-(2,5-dimethylpyrrolidono)propyl	
	2-methoxy-6-propylphenyl	3-aziridinopropyl	
	4-chloro-2-methylphenyl	3-pyrrolopropyl	
5	2-bromo-6-methylphenyl	aziridinomethyl	70
	2-bromo-4-t-butylphenyl	pyrrolidinomethyl	
	2-chloro-4-isopropylphenyl	morpholinomethyl	
	2-isobutyl-4-fluorophenyl	2,4-dimethylphenyl	
	6-bromo-3,4-dimethylphenyl	2,6-dimethylphenyl	
10	4-chloro-2,3-dimethylphenyl	3,4-dimethylphenyl	75
	4-bromo-3-isopropyl-3-methylphenyl	3,5-dimethylphenyl	
	2-chloro-3,4-dimethylphenyl	(1,4,5,6-tetrahydropyrimidino)methyl pyrrolo-	
	1-(5,6,7,8-tetrahydronaphthyl)	methyl	
	2-(5,6,7,8-tetrahydronaphthyl)	3-diisopropylamino-2-propyl	
15	1-(4-methyl-5,6,7,8-tetrahydronaphthyl)	2-dimethylamino-1-propyl	80
	2-(5-methyl-5,6,7,8-tetrahydronaphthyl)	3-aziridino-2-propyl	
	1-(4,4-dimethyl-5,6,7,8-tetrahydronaphthyl)	2-(N-methylanilino)ethyl	
	2-(1,6-dimethyl-5,6,7,8-tetrahydronaphthyl)	2-(N-ethylanilino)ethyl	
20	1 - 2,4,7 - trimethyl - 5,6,7,8 - tetrahydro-	3-(N-methylanilino)propyl	85
	naphthyl)	3-(N-isopropylanilino)propyl	
	2 - (1,5,6 - trimethyl - 5,6,7,8 - tetrahydro-	3-(N-methylanilino)-2-propyl	
	naphthyl)	2-(N-methylanilino)-1-propyl	
	2 - (3,4,6 - trimethyl - 5,6,7,8 - tetrahydro-	3-(N-ethylpiperazino)-2-propyl	
	naphthyl)	3-(imidazolino)-2-propyl	
25	2 - (5,5,8,8 - tetramethyl - 5,6,7,8 - tetra-	3-(4-methylpiperidino)-2-propyl	90
	hydronaphthyl)	2-aziridino-1-propyl	
	1-(1-methyl-1,2,3,4-tetrahydronaphthyl)	2-morpholino-1-propyl	
	1-(2-chloro-1,2,3,4-tetrahydronaphthyl)	2-thiomorpholino-1-propyl	
	4-isopropylphenyl	2-imidazolo-1-propyl	
30	1-(1,2,3,4-tetrahydronaphthyl)	2-(1,4,5,6-tetrahydropyrimidino)-1-propyl	95
	2-(1,2,3,4 - tetrahydronaphthyl)	2-dipropylamino-1-propyl	
	1-indanyl	2-pyrrolo-1-propyl	
	2-chloro-1-indanyl	3-diethylaminoethyl	
	3-bromo-1-indanyl	2-piperidinoethyl	
35	4-indanyl	3-piperidinopropyl	100
	5-indanyl	2-pyrrolidinoethyl	
	5-methyl-4-indanyl	2-(1,4,5,6-tetrahydropyrimidino)ethyl	
	6-methyl-4-indanyl	3-di-(n-propylamino)-2-propyl	
	3-methyl-4-indanyl	2-diethylamino-1-propyl	
40	1-methyl-5-indanyl	3-pyrrolidino-2-propyl	105
	7-methyl-5-indanyl	3-piperidino-2-propyl	
	4,6-dimethyl-5-indanyl	3-diethylamino-2-propyl	
	1,1-dimethyl-4-indanyl	3-morpholino-2-propyl	
	1,1,2,3-tetramethyl-4-indanyl	3-di-(n-butyl)amino-2-propyl	
45	5,7-dimethyl-4-indanyl	3-dimethylamino-2-propyl	110
	7-chloro-4-indanyl	2-azetidinoethyl	
	7-bromo-4-indanyl	3-azetidino-2-propyl	
	6-chloro-5-indanyl	2-chloro-4-methylphenyl	
	1,1,7-trimethyl-4-indanyl	6-chloro-2-methylphenyl	
50	2-indanyl	2-methoxy-4-methylphenyl	115
	1-methyl-1-indanyl	4-chloro-3,5-dimethylphenyl	
	2-dimethylaminoethyl		
	3-diethylaminopropyl		
	2-piperidinoethyl		
55	3-morpholinopropyl		
	3-thiomorpholinopropyl		
	2-pyrrolidinoethyl		
	2-(2-imidazolino)ethyl		
	2-pyrroloethyl		
60	3-(N-methyl)piperazinopropyl		
	2-di-(n-propyl)aminoethyl		
	2-di-(n-butyl)aminoethyl		
	3-diisopropylaminopropyl		
	3-imidazolopropyl		
65	3-(2-imidazolinopropyl)		

EXAMPLE X

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-chlorophenyl, 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.

	R ₂	R ₂	
	1-methoxy-2,2,2-trichloroethyl	1-methyl-5-indanyl	15
	1-propoxy-2,2,2-trichloroethyl	4,6-dimethyl-5-indanyl	
	1-methoxy-2,2,2-trifluoroethyl	1,1,2,3-tetramethyl-4-indanyl	
5	1-ethoxy-2,2,2-trifluoroethyl	5,7-dimethyl-4-indanyl	
	dicarbethoxyethoxymethyl	5-chloro-4-indanyl	
	carbethoxyethoxymethyl	6-chloro-5-indanyl	70
	1-isopropoxy-2,2,2-trichloroethyl	1,7-dimethyl-4-indanyl	
	1-t-butoxy-2,2,2-trichloroethyl	1-chloro-2-indanyl	
10	dicarbomethoxyethoxymethyl	2-bromo-1-indanyl	
	2-isopropylphenyl	2-piperidinoethyl	
	o-dimethylaminophenyl	2-morpholinoethyl	75
	o-di-n-butylaminophenyl	3-thiomorpholinopropyl	
	m-di-n-propylaminophenyl	2-pyrrolidinoethyl	
15	p-methylisopropylaminophenyl	3-pyrrolopropyl	
	3,4-dimethylphenyl	2-(1,4,5,6-tetrahydropyrimidino)ethyl	
	2,4-diethylphenyl	3-di-(n-propylamino)-2-propyl	80
	2,6-di-n-propylphenyl	3-pyrrolidinopropyl	
	6-ethyl-2-methylphenyl	2-dimethylaminoethyl	
20	2-methyl-6-n-propylphenyl	2-dibutylaminoethyl	
	2-methyl-4-sec-butylphenyl	2-pyrroloethyl	
	2,3,4-trimethylphenyl	2-imidazoloethyl	85
	3,4,5-trimethylphenyl	2-(2,5-dimethylpyrrolidino)ethyl	
	2,6-dimethyl-4-ethylphenyl	2-azetidinoethyl	
25	4,6-dimethyl-2-methylphenyl	2-azetidino-1-propyl	
	4,5-dimethyl-2-isopropylphenyl	3-dimethylaminopropyl	
	2,6-dichlorophenyl	3-diisopropylaminopropyl	90
	2-nitrophenyl	3-aziridinopropyl	
	5-methyl-2-nitrophenyl	3-(N-methylpiperazino)propyl	
30	4-dimethylamino-2-methylphenyl	3-(2-imidazolino)propyl	
	3-isopropylphenyl	3-(1,4,5,6-tetrahydropyrimidino)propyl	
	2-methoxy-4-methylphenyl	pyrrolidinomethyl	95
	2-chloro-6-methoxyphenyl	thiomorpholinomethyl	
	2-ethoxy-3-methylphenyl	pyrrolomethyl	
35	4-chloro-2-methylphenyl	(imidazolino)methyl	
	4-fluoro-3-methylphenyl	piperidinomethyl	
	2-bromo-4-t-butylphenyl	2-pyrrolidino-1-propyl	100
	6-bromo-3,4-dimethylphenyl	2-morpholino-1-propyl	
	4-chloro-2,3-dimethylphenyl	2-pyrrolo-1-propyl	
40	4-chloro-6-isopropyl-3-methylphenyl	2-imidazolo-1-propyl	
	2-chloro-3,4-dimethylphenyl	3-imidazolo-2-propyl	
	1-(3-methyl-5,6,7,8-tetrahydronaphthyl)	3-(2-imidazolino)-2-propyl	105
	2-(4-methyl-5,6,7,8-tetrahydronaphthyl)	2-(methylethylamino)ethyl	
	1-(4,8-dimethyl-5,6,7,8-tetrahydronaphthyl)	2-(methylbutylamino)ethyl	
45	1 - (3,4,6 - trimethyl - 5,6,7,8 - tetrahydro-	3-(methylpropylamino)propyl	
	naphthyl)	3-(methylethylamino)-2-propyl	
	2 - (3,4,6 - trimethyl - 5,6,7,8 - tetrahydro-	2-(methylbutylamino)-1-propyl	110
	naphthyl)	2-(diethylamino)-1-propyl	
	2 - (5,5,8,8 - tetramethyl - 5,6,7,8 - tetra-	3-pyrrolidino-2-propyl	
50	hydronaphthyl)	3-piperidino-2-propyl	
	1-(5,6,7,8-tetrahydronaphthyl)	3-diethylamino-2-propyl	115
	2-(5,6,7,8-tetrahydronaphthyl)	3-morpholino-2-propyl	
	1-(1-methyl-1,2,3,4-tetrahydronaphthyl)	3-di-(n-butyl)amino-2-propyl	
	2-(3-chloro-1,2,3,4-tetrahydronaphthyl)	3-dimethylamino-2-propyl	
55	1-(1,2,3,4-tetrahydronaphthyl)	2-(2,6-dimethylpiperidino)ethyl	
	1-indanyl	3-(methylethylamino)propyl	
	2-indanyl	3-piperidinopropyl	120
	3-methyl-1-indanyl	2-(n-methylanilino)ethyl	
	1-methyl-1-indanyl	2-(n-ethylanilino)ethyl	
60	4-indanyl	3-(N-methylanilino)propyl	
	5-indanyl	3-(N-isopropylanilino)propyl	
	5-methyl-4-indanyl	3-(N-methylanilino)-2-propyl	125
	3-methyl-4-indanyl	2-(N-methylanilino)-1-propyl	

EXAMPLE XI

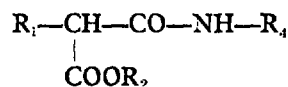
α - Carbo(2 - isopropylphenoxy)benzyl-
penicillin—Anhydride Method

- 5 A stirred solution of mono-(2-isopropyl-
phenyl)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
10 by dry chloroethylcarbonate (900 mg.). A
precipitate of triethylamine hydrochloride
forms immediately. A solution of 6-amino-
penicillanic acid (1.8 g.) in sodium bicarbonate
solution (20 ml. of 5% by weight solution)
and acetone (5 ml.) is added all at once to
15 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 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-ethyl-
piperidine 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.

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



(R₁=the penicillanic acid moiety)

35	R ₁	R ₂	R' (Cl—COOR')
	phenyl	5-indanyl	ethyl
	phenyl	4-indanyl	isobutyl
	phenyl	2-isopropylphenyl	benzyl
40	phenyl	2,4-dimethylphenyl	n-propyl
	phenyl	2,5-dimethylphenyl	methyl
	phenyl	3,4-dimethylphenyl	ethyl
	phenyl	4-chloro-2-methylphenyl	ethyl
	phenyl	2-chloro-4-methylphenyl	ethyl
45	phenyl	—CH ₂ —CH ₂ —N(n-C ₃ H ₇) ₂	n-propyl
	phenyl	—CH ₂ —CH ₂ —morpholino	n-propyl
	3-thienyl	5-indanyl	ethyl
	3-thienyl	2-isopropylphenyl	ethyl
	3-thienyl	2-methoxy-4-methylphenyl	ethyl
50	3-thienyl	2-(1,2,3,4-tetrahydronaphthyl)	benzyl
	3-thienyl	2,6-dimethylphenyl	ethyl
	3-thienyl	—CH ₂ —piperidino	ethyl
	3-thienyl	—CH ₂ —CH ₂ —CH ₂ —N—(CH ₃) ₂	ethyl
	3-thienyl	—CH ₂ —imidazolo	ethyl
55	p-chlorophenyl	5-indanyl	ethyl
	o-chlorophenyl	5-indanyl	ethyl
	p-methoxyphenyl	5-indanyl	ethyl
	p-trifluoromethylphenyl	5-indanyl	ethyl
	m-tolyl	5-indanyl	ethyl
60	p-dimethylaminophenyl	5-indanyl	ethyl
	p-dimethylaminophenyl	2-isopropylphenyl	ethyl
	p-chlorophenyl	2-isopropylphenyl	ethyl
	2-thienyl	5-indanyl	n-propyl
	2-thienyl	2,4-dimethylphenyl	n-propyl
65	2-thienyl	4-chloro-2-methylphenyl	n-propyl
	2-pyridyl	5-indanyl	ethyl
	3-pyridyl	5-indanyl	ethyl
	4-pyridyl	5-indanyl	ethyl
	2-furyl	5-indanyl	ethyl
70	4-pyridyl	—CH ₂ CH ₂ —N(n-C ₃ H ₇) ₂	benzyl
	4-pyridyl	—CH ₂ —pyrrolidino	isobutyl
	4-pyridyl	2-isopropylphenyl	ethyl
	4-pyridyl	3,4-dimethylphenyl	ethyl

EXAMPLE XII

- 75 The products of Examples III and VII—XI
are converted to the sodium and potassium
salts by the procedures of Example II.

EXAMPLE XIII

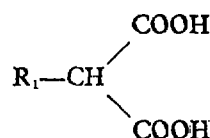
Following the procedures of Examples
I—III and VII—XI but substituting N-ethyl
piperidine by the appropriate amine produces

the following salts of the compounds described: N-methylpiperidine, triethylamine, tributylamine, N,N'-dibenzylethylenediamine, procaine, and dibenzylamine.

equimolar proportion of the desired ethyl aryl acetate in the presence of an excess (4—8 times) of sodium ethylate with continuous removal of by-product alcohol from the reaction mixture. The esters thus produced are hydrolyzed to the acid by known methods.

5 Preparation A Malonic Acids

The following aryl malonic acids not previously described in the literature are prepared by the method of Wallingford *et al.*, J. Am. Chem. Soc. 63, 2056—2059 (1964) which comprises condensing an alkyl carbonate, usually diethyl carbonate, with an



R ₁	R ₁
o-methoxyphenyl	3-pyridyl
m-methoxyphenyl	4-pyridyl
p-methoxyphenyl	o-butoxyphenyl
o-trifluoromethylphenyl*	o-dimethylaminophenyl
m-trifluoromethylphenyl	o-diethylaminophenyl
p-trifluoromethylphenyl	m-dimethylaminophenyl
o-isopropylphenyl	p-dimethylaminophenyl
3-furyl	

* The necessary o-trifluorophenylacetic acid is prepared from o-trifluorobenzonitrile by the procedure of Corse *et al.*, J. Am. Chem. Soc. 70, 2841 (1948) which comprises:

- conversion of the nitrile to o-trifluoro-methylacetophenone by a Grignard reaction with methylmagnesium iodide, followed by hydrolysis;
- reaction of the acetophenone with sulfur and morpholine at 135° C. for 16 hours, followed by treatment with glacial acetic acid and hydrochloric acid.

35 Preparation B Phenylchlorocarbonyl Ketene

(1) To phenylmalonic acid (20 g.) in ethyl ether (100 ml.) there is added phosphorous pentachloride (46 g.). A vigorous reaction occurs. The reaction mixture is refluxed for four hours, then the ether partially removed by heating on a steam bath. The reaction mixture becomes black when about half the ether is removed, and the remaining ether is removed under reduced pressure (at 100 mm.). The residue is distilled under vacuum and the fraction boiling at 75°—90° C. at 1.5—4 mm. collected. The product, a yellow liquid, is redistilled at 74° C. and 1.5 mm. It shows a strong peak in the infrared region of the spectrum at 4.69 μ .

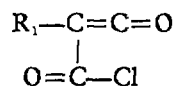
Repetition of this procedure but using 10 g. of phenylmalonic acid instead of 20 g. produces a less vigorous reaction on addition of the phosphorous pentachloride. The same product is obtained.

(2) Phosphorous pentachloride (23 g.) is added over a five-minute period to a stirred solution of phenylmalonic acid (10 g.) in ethyl ether (50 ml.) initially at a temperature of 0°—5° C. The temperature rises to 13° C. during the addition. The mixture is then re-

fluxed for five hours and allowed to stand overnight at room temperature. Removal of the ether at 20 mm. produces a dark concentrate which is vacuum distilled to give the desired product: b.p. 80°—88° C. at 1.5—2.0 mm. and 74° C. at 0.2 mm.

(3) To a stirred solution of phosphorous pentachloride (46 g.) in ethyl ether (100 ml.) there is added phenylmalonic acid (10 g.) over a two-minute period. The mixture is stirred at room temperature for four hours, then refluxed for four hours and allowed to stand overnight at room temperature. The excess phosphorous pentachloride is filtered off and the ether boiled off at atmosphere pressure. The reaction mixture gradually progresses in colour from dark yellow to red. The residue is distilled *in vacuo* to give the product: b.p. 83°—86° C. at 1.5 mm. as a yellow liquid.

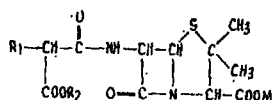
The procedure of Preparation B-3 is repeated but using the appropriate malonic acid derivative in place of phenylmalonic acid to produce the following compounds.



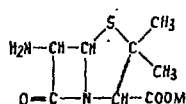
	R ₁	R ₁	
5	2-thienyl 3-thienyl 2-furyl o-tolyl m-tolyl p-tolyl o-methoxyphenyl m-methoxyphenyl p-methoxyphenyl o-trifluoromethylphenyl p-trifluoromethylphenyl m-trifluoromethylphenyl o-isopropylphenyl	3-furyl 2-pyridyl 3-pyridyl 4-pyridyl o-bromophenyl o-chlorophenyl p-chlorophenyl m-chlorophenyl o-butoxyphenyl o-dimethylaminophenyl o-diethylaminophenyl m-dimethylaminophenyl p-dimethylaminophenyl	
15	Preparation C 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 solu- tion and generally from 5 to 10 ml. per gram of ketene) there is added the alcohol R ₂ OH (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 -70° C. to -20° C. The products are re- covered by evaporation of the solvent.	n-ethylpiperazino piperidino pyrrolidino pyrrolo morpholino thiomorpholino imidazolino imidazolidino	60
20		Preparation E 2-Aminopropanols The following 2-aminopropanols having the formula	65
25		HO—CH ₂ —CH—NR ₅ R ₆ CH ₃	70
30	The esters are used without further purifica- tion in the preparation of the α-carboxy aryl- penicillin esters described herein.	wherein NR ₅ R 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 appropri- ate precursor ester of the formula	75
35	Preparation D Aminoisopropanols The following aminoisopropanols are pre- pared by the reaction 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.	H ₅ C ₂ OOC—CH—NR ₅ R ₆ CH ₃	
40	The product, if liquid, 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.	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.	80
45		HO—CH ₂ —CH—NR ₅ R ₆ CH ₃ —NR ₅ R ₆	85
50		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	90
55	H ₃ C—CH—CH ₂ —NR ₅ R ₆ OH —NR ₅ R ₆ dimethylamino diethylamino di-n-propylamino diisopropylamino di-n-butylamino 1,4,5,6-tetrahydropyrimidino		95

WHAT WE CLAIM IS:—

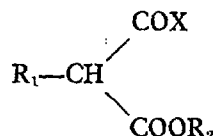
1. A process for the preparation of penicillins of the formula



5 wherein R_1 and R_2 are as hereinafter defined, M is hydrogen, sodium, potassium, or tri-(lower alkyl)amine; comprising reacting a compound of the formula



10 with an acylating agent of the formula

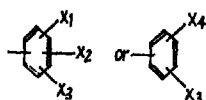


wherein X is chloro, bromo, or $-\text{OCOR}_1$, wherein R_1 is benzyl or lower alkyl; R_2 is

15 thienyl
furyl
pyridyl
phenyl, or
substituted phenyl

20 wherein the substituent is (lower)alkyl, chloro, bromo, (lower)alkoxy, di(lower)alkylamino, or trifluoromethyl; and R_2 is

isopropylphenyl,



25

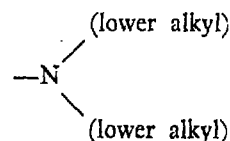
wherein X_1 is chloro, bromo, fluoro, lower alkyl, or lower alkoxy;
 X_2 is lower alkyl or chloro;
 X_3 is hydrogen or methyl; and

30 X_4 is nitro or di(lower alkyl) amino;
ac indanyl and substituted derivatives thereof, wherein the substituent is methyl, chloro, or bromo;

35 ac tetrahydronaphthyl and substituted derivatives thereof, wherein the substituent is methyl, chloro, or bromo;

1-(lower)alkoxy-2,2,2-trichloroethyl,
1-(lower)alkoxy-2,2,2-trifluoroethyl,
[carbo(lower)alkoxy] lower alkoxymethyl;
[dicarbo(lower)alkoxy] lower alkoxy- 40
methyl,
 $-(\text{CH}_2)_m-\text{NR}_5\text{R}_6$,
 $-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{NR}_5\text{R}_6$, and
 $-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{NR}_5\text{R}_6$ and
 $-(\text{lower alkylene})-\text{Y}_1$ 45

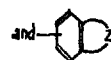
wherein m is an integer of 2 or 3; $-\text{NR}_5\text{R}_6$ is



wherein the (lower alkyl) groups may be alike or different; and $-\text{N}-(\text{lower alkyl})\text{anilino}$; and Y_1 is 50

azetidino
aziridino
pyrrolidino
piperidino
morpholino
thiomorpholino
N-(lower alkyl)piperazino
pyrrolo
imidazolo
2-imidazolino
2,5-dimethylpyrrolidino
1,4,5,6-tetrahydropyrimidino
4-methylpiperidino, and
2,6-dimethylpiperidino; 55
60
65

and



and substituted derivatives thereof, wherein Z is alkylene and is

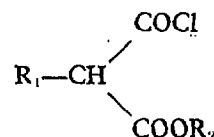


70

and wherein the substituent is methyl, chloro, or bromo;

in a reaction-inert solvent system as hereinbefore defined at a temperature of from 0 to 50° C. and a pH of from 5 to 8. 75

2. The process of claim 1, wherein the acylating agent is of the formula



3. The process of claim 2, wherein the reaction is conducted in a non-aqueous reaction-inert solvent system in the presence of a tri(lower)alkyl amine.

5 4. The process of claim 2, wherein the reaction-inert solvent system is an aqueous solvent system.

5. The process of claim 3, wherein the solvent is methylene chloride and the tri(lower)alkyl amine is triethylamine.

10 6. The process of claim 4, wherein R_1 is phenyl and R_2 is 2-isopropylphenyl.

7. The process of claim 4, wherein R_1 is phenyl and R_2 is



25

wherein X_1 is lower alkoxy, X_2 is lower alkyl, and X_3 is hydrogen.

10. The process of claim 4, wherein R_1 is phenyl and R_2 is



30

wherein Z is alkylene.

11. The process of claim 7, wherein X_1 is 2-methyl and X_2 is 4-methyl.

12. The process of claim 8, wherein X_1 is 4-chloro and X_2 is 2-methyl.

13. The process of claim 9, wherein X_1 is 2-methoxy and X_2 is 4-methyl.

14. The process of claim 10, wherein Z is $-(CH_2)_3-$.

15. A process for the preparation of penicillins as defined in claim 1, substantially as described herein.

16. Penicillins as defined in claim 1, whenever prepared by the process according to claim 1 substantially as described herein.

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wherein each of X_1 and X_2 is lower alkyl and X_3 is hydrogen.

8. The process of claim 4, wherein R_1 is phenyl and R_2 is



15



20

wherein X_1 is chloro, X_2 is lower alkyl, and X_3 is hydrogen.

9. The process of claim 4, wherein R_1 is phenyl and R_2 is

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