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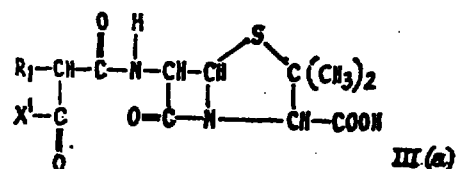
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(71) We, PFIZER INC., formerly known as Chas. Pfizer & Co., Inc., a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York 17, State of New York, United States of America, do hereby 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:—

The use of ketenes as acetylating agents is well known in the art. The acylation of amino groups by means of simple or mixed acid anhydrides, acid halides, acid azides, β -thiolacetones, acylated enols and carboxylic acids with carbodiimides is also known in the art (Sheehan, U.S. Patent 3,159,617, December 1, 1964). However, the introduction of α -carboxyl arylacetyl groups into 6-aminopenicillanic acid has, up until now, been limited to the use of a simple or mixed anhydride, an acid halide of an arylmalonic acid or an aryl malonic acid ester as acylating agent (U.S. Patent 3,142,673, British Patent 1,004,670).

The novel arylcarboxy and arylcarbothiolic ketene esters of Application No. 2985/69 (Serial No. 1,243,209) are especially valuable as agents for the acylation of amines with production of esters of α -carbothiolic and α -carboxy- α -arylacetyl amines. They are particularly useful for the acylation of amines such as 6-aminopenicillanic acid for the production of known and novel anti-bacterial agents. Prior art methods for introducing α -carboxy arylacetyl groups into amino compounds such as 6-aminopenicillanic acid have made use of acid anhydrides, mixed or simple, or acid halides of aryl malonic acids. The use of the prior acylating agents requires extreme caution during reaction and recovery steps in order to obtain satisfactory yields and avoid decarboxylation of the carboxy group. The acylating agents of this invention on the other hand react smoothly and rapidly with

The new penicillins of this invention have the general formula

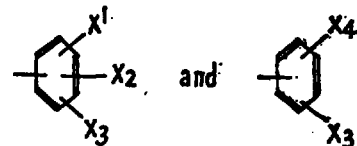


wherein R_1 is

thienyl,
furyl,
pyridyl,
phenyl,
or substituted phenyl wherein the substituent is (lower)alkyl, chloro, bromo, (lower)alkoxy, di(lower)alkylamino or trifluoromethyl;

X' is —OR₂ or —SR, wherein R₂ is

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
 X_4 is nitro, di(lower alkyl) amino);

furyl,
quinolyl,
methyl substituted quinolyl,
phenazinyl,
phenazinyl,

9,10-anthraquinonyl,
phenanthrenequinonyl,
anthracenyl,
phenanthryl,
5 (1,3-benzodioxolyl),
3-(2-methyl-4-pyronyl),
3-(4-pyronyl) or
(N-methyl)pyridyl:



10 (wherein Y₂ is:

—CH=CH—O—,
—CH=CH—S—,
—CH₂—CH₂—S—,
—CH=N—CH=CH—,
15 —C(O)—CH=CH—C(O)— or
—C(O)—C(O)—CH=CH—);



(wherein Z' is lower alkylene and is —CH₂—
and —CH₂—, or substituted derivatives
20 thereof wherein the substituent is methyl,
chloro or bromo)

substituted benzyl, with the proviso that R₁
cannot be thienyl or furyl when X' is sub-
stituted benzyl

25 (wherein the substituent is:

chloro,
bromo,
fluoro,
lower alkyl,
30 lower alkoxy,
lower alkanoyl,
carbo(lower)alkoxy, when R₁ is other than
phenyl nitro, and
di(lower)alkylamino),
35 phthalimidomethyl,
benzohydryl,
trityl,
cholesteryl,
alkenyl having up to 8 carbon atoms,
40 alkynyl having up to 8 carbon atom,
cycloalkyl or
(lower alkyl) substituted cycloalkyl having
from 3 to 7 carbon atoms in the cycloalkyl
moiety,
45 bicyclo [4.4.0] decyl,
thujyl,
fenchyl,
isofenchyl,
7-adamantanyl,
50 (2-pyrrolidono)methyl,
(4-imidazolyl)methyl,
1-indanylmethyl,

2-indanylmethyl,
[2,2 - di - (lower alkyl) - 1,3 - dioxolon-
4 - yl]methyl,
furylmethyl,
pyridylmethyl,

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

ac tetrahydronaphthyl and substituted deri-
vatives thereof wherein the substituent is
methyl, chloro or bromo;

1 - (lower)alkoxy - 2,2,2 - trichloroethyl
when R₁ is pyridyl,

1 - (lower)alkoxy - 2,2,2 - trifluoroethyl,
when R₁ is other than phenyl,

[carbo(lower)alkoxy] lower alkoxymethyl,
[di - carbo(lower)alkoxy] lower alkoxy-
methyl,

—CH₂—CH₂—NR₃R₆,

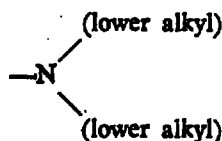
—CH₂—CH₂—CH₂—NR₃R₆,

—CH₂—CH(CH₃)—NR₃R₆ or

—CH(CH₃)—CH₂—NR₃R₆, or

—(lower alkylene)—Y₁

wherein —NR₃R₆ is —NH(lower alkanoyl),



wherein the (lower alkyl) groups may be alike
or different; and —N(lower alkyl)anilino; and
Y₁ is:

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

wherein each of lower alkoxy, lower alkyl or
lower alkanoyl have from 1 to 4 carbon atoms,
and (lower alkylene) contains from 1 to 3
carbon atoms; and R₁ is hydrogen, phenyl,
mono-, di-, or tri-substituted phenyl wherein
the substituent is at least one of chloro,
bromo, fluoro, lower alkyl, lower alkoxy or
trifluoromethyl, with the proviso that only one
of the positions, ortho to the thio group of
the phenyl moiety be substituted; wherein each
of lower alkyl and lower alkoxy contain from
1 to 4 carbon atoms, with the proviso that
when R₁ is thienyl, furyl, phenyl, or substi-
tuted phenyl, R₂ cannot be substituted phenyl.

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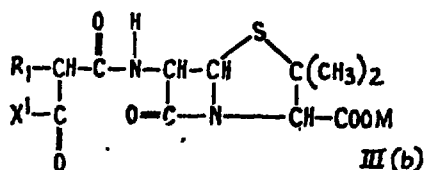
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Of the lower alkyl, lower alkoxy, lower alkanoyl and carbo(lower) alkoxy groups those having from one to four carbon atoms in the alkyl, alkoxy and alkanoyl moieties are preferred since the reactants bearing such groups are more readily available than are those required for such groups having a greater number of carbon atoms.

Also included within the scope of this invention are the pharmaceutically acceptable salts of the compounds of Formula III in which one or both acid groups are involved in salt formation. Salts such as the sodium, potassium, calcium, magnesium, ammonium and substituted ammonium salts, e.g., procaine, dibenzylamine, N,N'-dibenzylethylenediamine, N,N'-bis(dehydroabietyl)ethylenediamine, 1-phenamine, N-ethylpiperidine, N-benzyl-β-phenethylamine, trialkylamines, including triethylamine, as well as salts with other amines which have been used to form salts with benzyl-penicillin are useful for the preparation of pharmaceutically elegant compositions of these valuable antibiotics.

Also included within the scope of the invention is a process for preparing acyl penicillins of the formula:



wherein M is hydrogen, sodium, potassium or tri-(lower alkyl)amine,

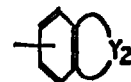
wherein R₁ is

thienyl,
furyl,
pyridyl,
phenyl,
or substituted phenyl wherein the substituent is (lower)alkyl, chloro, bromo, (lower)-alkoxy, di(lower)alkylamino or trifluoromethyl;

40 X' is —OR₂ or —SR, wherein R₂ is

hydrogen or sodium
phenyl or
substituted phenyl wherein the substituent is at least one of chloro, bromo, fluoro,
45 lower alkyl, lower alkoxy, lower alkanoyl, carbo(lower)alkoxy, nitro, or di(lower)alkyl-amino;
furyl,
quinolyl,
50 methyl substituted quinolyl,
phenazinyl,
9,10-anthraquinonyl,
phenanthrenequinonyl,
anthracenyl,
55 phenanthryl,

(1,3-benzodioxolyl),
3-(2-methyl-4-pyronyl),
3-(4-pyronyl) or
(N-methyl)pyridyl:



(wherein Y₂ is:

—CH=CH—O—,
—CH=CH—S—,
—CH₂—CH₂—S—,
—CH=N—CH=CH—,
—CH=CH—CH=CH—,
—C(O)=CH=CH—C(O)— or
—C(O)—C(O)—CH=CH—);



(wherein Z' is lower alkylene and is —CH₂— and —(CH₂)₄—, or substituted derivatives thereof wherein the substituent is methyl, chloro or bromo);

benzyl,
substituted benzyl,
(wherein the substituent is:

chloro,
bromo,
fluoro,
lower alkyl,
lower alkoxy,
lower alkanoyl,
carbo(lower)alkoxy,
nitro, and
di(lower)alkylamino);
85 phthalimidomethyl,
benzohydryl,
trityl,
cholesteryl,
alkenyl having up to 8 carbon atoms,
alkynyl having up to 8 carbon atoms,
cycloalkyl or
(lower alkyl) substituted cycloalkyl having
from 3 to 7 carbon atoms in the cycloalkyl
moiety,
95 bicyclo [4.4.0] decyl,
thujyl,
fenchyl,
isofenchyl,
7-adamtanyl,
(2-pyrrolidono)methyl,
(4-imidazolyl)methyl,
1-indanylmethyl,
2-indanylmethyl,
[2,2 - di - (lower alkyl) - 1,3 - dioxolon - 4 -
105 yl]methyl,
furylmethyl,
pyridylmethyl,

The acylation of 6-aminopenicillanic acid is conducted at a temperature of from about -70°C . to about 50°C . and preferably at a temperature of from about 0°C . to about 30°C . The reaction period is generally from a few minutes up to about 5 hours. A reaction-

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inert solvent such as ethyl acetate, dioxane, tetrahydrofuran, methyl isobutyl ketone, chloroform or methylene chloride is generally used to facilitate stirring and temperature control. It has been found especially convenient to first form the arylcarboxy or arylcarbothiol ketene ester as described above and to use the reaction mixture, without isolation of the ketene ester, directly in the amine acylation reaction. In such instances an organic base, i.e. a tertiary amine such as triethylamine or other trialkylamine, preferably a tri(lower alkyl)amine, is used to remove the hydrogen halide produced in formation of the ketene ester. From a practical standpoint, the 6-aminopenicillanic acid is used as its triethylamine salt. For this reason, methylene chloride is a preferred solvent since the triethylamine salt is readily soluble therein. The sodium or potassium salts of 6-amino-penicillanic acid can also be used but the preferred salt is the triethylamine salt because of its greater solubility in the solvent systems used. An excess of the amine to be acylated can, of course, be used as acid acceptor but is generally avoided, not only for economic reasons but also to prevent possible ammonolysis of the ester group. The reaction is desirably conducted under an atmosphere of nitrogen.

5 The N-acylation reaction can also be conducted in neutral or alkaline aqueous solution by taking advantage of the slower rate of reaction of the arylcarboxy or arylcarbothiol ketene esters with water at neutral or alkaline pH levels relative to the rate of reaction with the amino group. The reaction is conducted at temperatures ranging from just above the freezing point of the aqueous system to about 50° C. and preferably at from 0° C. to about 20° C. To permit attainment of low temperatures and to facilitate reaction, it is advantageous to employ a mixed solvent system, i.e. water plus a water miscible reaction-inert organic solvent such as dioxane or tetrahydrofuran. The ketene ester is, of course, desirably used as a solution in the same reaction-inert solvent and is preferably added to the aqueous solution of the 6-aminopenicillanic acid.

10 The acylated products are isolated by conventional methods. A typical method, for example, comprises evaporating the reaction mixture to dryness under reduced pressure, dissolving the residue in citrate buffer (pH 5.5) and extracting the product therefrom with chloroform. The chloroform extracts are washed with citrate buffer (pH 5.5), dried with anhydrous sodium sulfate and evaporated to dryness. In another method, which is of value for the isolation of acylation products poorly soluble in methylene chloride, or chloroform, the above method is followed but using n-butanol as extracting solvent in place of chloroform. The product remaining after removal of the n-butanol solvent by evaporation

15 is triturated with ether to produce an amorphous solid.

20 In still another method, essentially a variation of the above methods, saturated sodium bicarbonate (or potassium bicarbonate) is used in place of the citrate buffer. This method, of course, produces the sodium (or potassium) salt of the acylation product. If necessary, to obtain a solid product, the salt is triturated with ether.

25 In yet another method, the residue remaining after removal of the volatiles from the reaction mixture is taken up in water at pH of from about 2.3 to 2.9, usually about pH 2.7, and the free acid form of the acylation product extracted from the acid solution with chloroform, ether, n-butanol or other suitable solvent. The chloroform, ether or n-butanol extract is then washed with aqueous acid (pH 2.3—2.9) and the product recovered by lyophilization or by conversion to a solvent-insoluble salt as by neutralization with an n-butanol solution of sodium or potassium 2-ethyl-hexanoate.

30 The esters are converted by known methods to the corresponding acids; for example, when R₂ or R₁ is benzyl or a substituted benzyl group, its removal is accomplished by catalytic hydrogenation in a reaction-inert solvent such as water, ethanol, dioxane, at pH of from about 5 to about 9 and at about atmospheric pressure and ambient temperature. Favored catalysts are platinum, rhodium, nickel and palladium. When R₂ or R₁ is other than benzyl or substituted benzyl its removal is effected by mild acid treatment or enzymatically with an esterase such as liver homogenate. In addition formation of the corresponding acids or salt thereof i.e., when R₂ or R₁ is hydrogen or sodium, can be accomplished by hydrolysis of the ester compounds with aqueous sodium carbonate.

35 When preparation of the free acid form of the herein described penicillins is desired, the preferred ester groups are those wherein R₂ or R₁ is trityl, t-butyl, and β -di-isopropyl-aminoethyl. These groups are readily removed by mild acid treatment resulting in satisfactory yields of the desired acid forms of the penicillins.

40 The valuable products of this invention are remarkably effective in treating a number 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, certain types of clay, etc., or in capsules alone or in admixture with the same or equivalent excipients.

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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) and 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, sorbitol, etc.; buffering agents, as well as local anaesthetics

and inorganic salts to afford desirable pharmacological properties.

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

The antimicrobial spectra of several esters of α -carboxybenzyl penicillins against *Staphylococcus aureus* and *Escherichia coli* are presented below. 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 *Escherichia coli*, respectively.

TABLE I — In Vitro Spectra

R ₁	<i>S. aureus</i>	<i>E. coli</i>
1-naphthyl	0.39	6.25
5-(1,3-benzodioxolyl)	3.12	25
2-naphthyl	1.56	12.5
6-quinolyl	1.56	50
3-(2-methyl-4-pyronyl)	0.78	50
H	1.25	3.12
phenyl	3.12	25
o-methylphenyl	0.78	12.5
m-methylphenyl	0.78	6.25
p-methylphenyl	0.39	6.25
o-ethylphenyl	0.39	25
o-isopropylphenyl	0.39	12.5
o-formylphenol	1.56	25
o-acetylphenyl	50	>200
p-acetylphenyl	25	>200
o-nitrophenyl	25	>200
2,3-dimethylphenyl	0.78	50
3,4-dimethylphenyl	0.78	25
2,3-dimethoxyphenyl	1.56	50

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R ₁	<i>S. aureus</i>	<i>E. coli</i>
2-chloro-5-methylphenyl	3.12	3.12
4-chloro-3-methylphenyl	1.56	1.56
2-chloro-3,5-dimethylphenyl	1.56	1.56
2-chloro-3,4-dimethylphenyl	1.56	3.12
2-chloro-4,5-dimethylphenyl	0.39	0.39
4-chloro-2,3-dimethylphenyl	0.19	0.19
4-chloro-2,5-dimethylphenyl	0.19	0.39
4-chloro-2,6-dimethylphenyl	0.19	0.19
2,4-dichloro-6-methylphenyl	0.39	0.39
2,4-dichloro-3,5-dimethylphenyl	1.56	3.12
4,5-dichloro-2,3-dimethylphenyl	0.04	0.09
4-chloro-2-nitrophenyl	25	>200
1-(1,2,3,4-tetrahydronaphthyl)	0.39	12.5
2-(1,4-naphthoquinonyl)	12.5	>200
4-indanyl	0.39	6.25
5-indanyl	0.39	6.25
5-quinolyl	1.56	50
8-quinolyl	1.56	50
methyl	0.625	50
ethyl	1.25	>100
n-propyl	6.25	>200
n-butyl	50	>200
sec-butyl	3.12	>200
2-methylpropyl	3.12	>100
hexyl	>200	—
octyl	>200	>200
decyl	>200	>200
tetradecyl	>200	>200
2-cyanoethyl	1.9	6.25
2-methoxyethyl	3.12	>100

R_2	<i>S. aureus</i>	<i>E. coli</i>
2-acetoxyethyl	3.12	>200
1-(1-carbethoxy)ethyl	100	>200
2-(1,2,3-tricarbethoxy)propyl	1.56	200
2-chloroethyl	50	>200
2,2,2-trichloroethyl	100	>200
2,2,2-trifluoroethyl	1.56	25
2-(2-trifluoromethyl)propyl	0.78	200
1-ethoxy-2,2,2-trifluoroethyl	0.78	50
1-ethoxy-2,2,2-trichloroethyl	0.78	12.5
1-isopropoxy-2,2,2-trichloroethyl	1.56	100
1-butoxy-2,2,2-trichloroethyl	0.39	50
carbethoxy ethoxy methyl	25	100
dicarbethoxy ethoxy methyl	1.56	50
1-(2,3-dibutyryloxy)propyl	>500	>200
3-oxobutyl	50	>200
1,1-dimethyl acetonyl	>200	>200
2-nitrobutyl	100	>200
2-dimethylaminoethyl	1.56	50
2-diethylaminoethyl	0.78	12.5
2-di(n-propyl)aminoethyl	0.78	6.25
2-di(isopropyl)aminoethyl	1.56	100
2-di(n-butyl)aminoethyl	0.78	12.5
3-dimethylaminopropyl	0.78	25
3-di(n-propyl)amino-2-propyl	0.39	3.12
2-pyrrolidinoethyl	0.78	6.25
2-(2-imidazolino)ethyl	1.56	50
2-(2,5-dimethylpyrrolidino)ethyl	1.56	12.5
2-(4-methylpiperidino)ethyl	0.19	6.25
3-(pyrrolidino)propyl	0.19	12.5
3-piperidinopropyl	1.56	12.5
3-morpholinopropyl	1.56	6.25

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<i>R₁</i>	<i>S. aureus</i>	<i>E. coli</i>
3-pyrrolidino-2-propyl	0.39	3.12
3-piperidino-2-propyl	0.39	1.56
2-aziridinoethyl	50	
2-pyrrolidino-1-propyl	0.78	6.25
2-azetidinoethyl	3.12	100
2-piperidino-1-propyl	0.78	6.25
2-(2,6-dimethyl piperidino)ethyl	1.56	12.5
2-morpholino-1-propyl	3.12	50
2-di(n-propylamino)-1-propyl	1.56	6.25
2-(N-methylanilino)ethyl	0.39	100
3-di(n-propylamino)propyl	0.19	12.5
3-dimethylamino-2-propyl	1.56	25
3-morpholino-2-propyl	1.56	6.25
isopropyl	6.25	>200
t-butyl	1.56	100
crotyl		>200
2-imidazoloethyl	1.56	50
[2,2-dimethyl-1,3-dioxolon-4-yl]methyl	0.39	50
benzohydryl	0.78	12.5
2-carbethoxyethyl	100	>200
4-quinolyl	3.12	>200
2-(4-methylquinolyl)	3.12	100
1-butyne-4-yl	3.12	>200
trityl	1.56	25
phthalimidomethyl	0.78	12.5
2-pyridylmethyl	1.56	25
4-pyridylmethyl	0.39	25
pyrrolidonomethyl	0.19	25
propargyl	0.78	25
4-imidazolylmethyl	1.56	100
p-methoxyphenyl	0.19	12.5

R_2	<i>S. aureus</i>	<i>E. coli</i>
p-methoxyphenyl (NEP salt)(*)	0.39	3.12
6-chloro-2-methylphenyl	0.39	25
6-chloro-2-methylphenyl (NEP salt)	0.04	6.25
4-chloro-2-methylphenyl	0.78	50
4-chloro-2-methylphenyl (NEP salt)	0.09	3.12
4-chloro-3,5-dimethylphenyl	1.56	25
4-chloro-3,5-dimethylphenyl (NEP salt)	0.39	3.12
4-chloro-2,3,5-trimethylphenyl	0.045	6.25
1,1-dimethyl-2,2,2-trifluoroethyl	0.19	50
m-fluorophenyl	0.78	12.5
4-chloro-2,6-dinitrophenyl	1.56	200
6-chloro-2,4-dinitrophenyl	3.12	200
2,4-dimethylphenyl	0.39	6.25
2,5-dimethylphenyl (NEP salt)	0.04	3.12
3,5-dimethylphenyl	0.78	6.25
3,5-dimethylphenyl (NEP salt)	0.09	3.12
2,4-dimethylphenyl	0.09	3.12
2,4-dimethylphenyl (NEP salt)	0.04	3.12
2,6-dimethylphenyl	0.39	25
2,6-dimethylphenyl (NEP salt)	0.01	12.5
m-ethylphenyl	1.56	3.12
m-ethylphenyl (NEP salt)	0.39	3.12
methoxyphenyl	3.12	25
p-methoxyphenyl	3.12	12.5
4,6-dibromo-2-methylphenyl	0.19	6.25
2,6-dibromophenyl	3.12	25
2-methoxy-4-methylphenyl	0.039	12.5
2-methoxy-4-methylphenyl (NEP salt)	0.04	3.12
4-chloro-2,3-diethylphenyl	0.19	25
2-methyl-3-methoxyphenyl	0.39	12.5
2-methyl-3-methoxyphenyl (NEP salt)	0.09	6.25
4-(α,α -dimethylbenzyl)phenyl	0.78	25

<i>E. coli</i>	<i>R₂</i>	<i>S. aureus</i>	<i>E. coli</i>
3.12	5-ethyl-3-methylphenyl	0.39	12.5
25	4-(1-indanyl)phenyl	0.78	50
6.25	2,4-(dicyclopent-2-enyl)phenyl	0.005	12.5
50	p-fluorophenyl	1.56	50
3.12	p-carbomethoxyphenyl	0.78	12.5
25	p-carbo-n-propoxyphenyl	0.78	12.5
3.12	2-(5,6,7,8-tetrahydronaphthyl)	0.39	3.12
6.25	2-(5,6,7,8-tetrahydronaphthyl) (NEP salt)	0.04	1.56
50	p-carbo-n-octyloxyphenyl	0.39	50
12.5	m-dimethylaminophenyl	0.78	12.5
10	p-dimethylaminophenyl	1.56	12.5
10	o-propylphenyl	0.19	25
6.25	p-propylphenyl	0.39	12.5
3.12	2,4-dibromophenyl	1.16	25
6.25	3-(N-methylanilino)ethyl	0.19	25
3.12	7-adamantanyl	0.09	50
1.12	2-isopropoxyethyl	1.56	200
1.12	2-piperidinoethyl	0.78	3.12
	2-morpholinoethyl	1.56	6.25
.5	3-(N-methylanilino)-2-propyl (NEP salt)	0.09	25
.12	3-(N-ethylanilino)-2-propyl (NEP salt)	0.09	25
.12	2-(N-ethylanilino)ethyl (NEP salt)	0.04	12.5
	1-methoxy-2,2,2-trichloroethyl	100	>200
5	dicarbomethoxyethoxymethyl	6.25	50
25	o-ethoxyphenyl (NEP salt)	1.16	6.25
	2-n-butoxyethyl	0.39	50
5	2-isopropoxyethyl	1.56	>200
12	m-acetylphenyl	6.25	12.5
	2-isopropylmercaptoethyl	3.12	200
5	5-indanyl (TEA salt)(^b)	0.05	6.25

R_2	<i>S. aureus</i>	<i>E. coli</i>
5-indanyl (morpholine salt)	0.05	1.56

The *in vitro* spectra of esters of α -carbothiolic benzylpenicillin are given below.

R_2		
phenyl	6.25	25
p-chlorophenyl	3.12	25
o-isopropylphenyl	6.25	100
(for R_1 = p-chlorophenyl and R_2 = 2-naphthyl)	1.56	200

(*) NEP = N-ethylpiperidine

(b) TEA = triethylamine

- 5 Table II presents *in vivo* data for representative 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 incubation of the mice with a standardized (10⁻⁵) *E. coli* 266 culture suspended in 5% 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% 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.

15

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3. coli

1.56

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25

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20

TABLE II

In vivo Data vs. E. coli 266 in Mice of
 α -Carboxybenzylpenicillin esters of Formula III(b)
wherein R_1 is phenyl

R_1	% Survivors			
	PO (mg./kg)		SQ (Mg./kg.)	
	200	100	200	100
carbethoxyethoxymethyl	0	20	0	10
dicarbethoxyethoxymethyl	30	0	60	40
1-ethoxy-2,2,2-trichloroethyl	90	60	70	70
1-isopropoxy-2,2,2-trichloroethyl	20	20	40	30
1-butoxy-2,2,2-trichloroethyl	10	20	0	10
1-naphthyl	30	20	30	0
2-naphthyl	40	0	50	10
5-indanyl	100	60	70	60
5-indanyl (TEA salt)	100	70	100	100
4-indanyl	80	50	80	40
5-quinolyl	10	0	50	30
6-quinolyl	20	20	10	20
5-(1,3-benzodioxolyl)	30	20	30	50
m-methylphenyl	70	30	80	70
p-methylphenyl	30	20	20	20
o-methylphenyl	30	0	0	10
o-ethylphenyl	20	10	10	0
o-isopropylphenyl	90	60	50	50
2,3-dimethylphenyl	80	10	80	60
3,4-dimethylphenyl	80	30	50	20
4-methoxyphenyl	20	10	40	30
2,6-dimethoxyphenyl	10	0	0	20
m-fluorophenyl	70	20	50	20
2-chloro-6-methylphenyl	30	10	40	30
4-chloro-2-methylphenyl	40	0	20	30
2-chloro-5-methylphenyl	0	0	30	10

R ₂	% Survivors			
	PO (mg./kg.)		SQ (Mg./kg.)	
	200	100	200	100
4-chloro-3-methylphenyl	70	10	60	30
2-chloro-3,4-dimethylphenyl	20	20	30	0
4-chloro-3-methylphenyl	70	10	60	30
2-chloro-3,4-dimethylphenyl	20	20	30	0
4-chloro-3,5-dimethylphenyl	60	10	60	30
4-chloro-2,3-dimethylphenyl	90	60	90	60
4-chloro-2,6-dimethylphenyl	10	10	30	10
2-chloro-4,5-dimethylphenyl	20	20	70	10
4-chloro-2,5-dimethylphenyl	0	0	10	0
2,4-dichloro-6-methylphenyl	10	10	10	20
2,4-dichloro-3,5-dimethylphenyl	50	10	70	50
4-chloro-2,3,5-trimethylphenyl	60	50	80	40
4-chloro-2,6-dinitrophenyl	10	0	20	0
2-(5,6,7,8-tetrahydronaphthyl)	60	40	60	50
phenyl	0	0	10	0
2-dimethylaminoethyl	0	0	10(*)	10(*)
2-diethylaminoethyl	0	0	10	10
2-di(n-propyl)aminoethyl	20	10	90	80
2-di(isopropyl)aminoethyl	0	0	40	0
2-di(n-butyl)aminoethyl	0	10	90	80
3-dimethylaminopropyl	0	0	30	10
3-di(n-propyl)amino-2-propyl	20	0	70	30
2-pyrrolidinoethyl	10	10	80	60
2-(2-imidazolino)ethyl	0	0	40	10(*)
2-piperidinoethyl	10	10	80	60
2-morpholinoethyl	0	0	30	0
2-(2,5-dimethylpyrrolidino)ethyl	0	0	60	50
2-(4-methylpiperidino)ethyl	30	0	60	50

s
(Mg./kg.)

100

30

0

30

0

30

60

10

10

0

20

50

40

0

50

0

10(%)

10

80

0

80

10

30

50

10(%)

0

0

0

0

0

R₂

% Survivors

PO (mg./kg.) SQ (mg./kg.)

200 100 200 100

3-(pyrrolidino)propyl

0 0 80 20

3-piperidinopropyl

0 0 100 80

3-morpholinopropyl

0 0 80 70

3-pyrrolidino-2-propyl

0 0 70 50

3-piperidino-2-propyl

0 0 90 40

2-pyrrolidino-1-propyl

10 0 80 70

2-azetidinoethyl

10 0 0 0

2-piperidino-1-propyl

80 70

2-(2,6-dimethyl piperidino)ethyl

10 0 100 80

2-morpholino-1-propyl

10 30 40 20

2-di-(n-propylamino)-1-propyl

0 10 90 60

2-(N-methylanilino)ethyl

40 0 80 10

3-di(n-propylamino)propyl

0 0 80 90

3-dimethylamino-2-propyl

0 0 20 20

3-morpholino-2-propyl

0 10 70 20

2-formamidoethyl

20 0 20 10

H

— 0 — 70

2-chloroethyl

10 0 10 0

2-imidazoloethyl

0 0 40 0

p-acetylphenyl

0 0 10 0

2-acetoxyethyl

0 0 0 10

[2,2-dimethyl-1,3-dioxolon-4-yl)methyl

0 0 30 10

benzohydryl

0 0 50 10

acetonyl methyl

10 0 0 10

2-nitrobutyl

10 0 0 0

5-indanyl (TEA salt)

100 70 100 100

2-(1,4-naphthoquinonyl)

0 0 20 0

2-(4-methylquinolyl)

0 0 30 0

R ₂	% Survivors			
	PO (mg./kg.)		SQ (mg./kg.)	
	200	100	200	100
phthalimidomethyl	20	10	30	0
2,3-dimethoxyphenyl	10	0	0	20
2-pyridylmethyl	0	0	10	0
4-pyridylmethyl	0	0	40	20
2-formylphenyl	0	0	80	0
3-(2-methyl-4-pyronyl)	0	0	30	0
propargyl	0	0	100	30
1-ethoxy-2,2,2-trichloroethyl	70	0	70	20
4-imidazolylmethyl	20	10	30	10
5-indanyl (NEP salt)	100	70	100	100
o-isopropylphenyl	80	50	40	20
o-ethylphenyl (NEP salt)	20	10	10	0
(1,2,3-tricarbethoxy)-2-propyl	0	10	10	0
1,1-dimethyl-2,2,2-trifluoroethyl	20	0	60	20
2,2,2-trifluoroethyl	10	0	20	0
6-chloro-2,4-dinitrophenyl	0	0	30	0
2,5-dimethylphenyl	80	70	90	60
3,5-dimethylphenyl	80	60	80	30
2,4-dimethylphenyl	90	20	80	50
2,6-dimethylphenyl	20	0	70	50
m-ethylphenyl	90	60	100	70
m-ethoxyphenyl	0	0	10	0
p-ethoxyphenol	60	10	70	50
4,6-dibromo-2-methylphenyl	0	0	10	0
2,6-dibromophenyl	0	10	60	40
2-methoxy-4-methylphenyl	100	50	100	50
2-methyl-3-methoxyphenyl	30	0	40	30
5-ethyl-3-methylphenyl	40	0	30	10
4-(1-indanyl)phenyl	20	10	10	20

R ₂	% Survivors			
	PO (mg./kg.)		SQ (mg./kg.)	
	200	100	200	100
2,4-(dicyclopent-2-enyl)phenyl	70	10	60	30
p-fluorophenyl	0	0	60	10
p-carbomethoxyphenyl	0	0	80	20
p-carbo-n-propoxyphenyl	0	0	60	20
2-(5,6,7,8-tetrahydronaphthyl)	100	60	50	30
2-(5,6,7,8-tetrahydronaphthyl) (NEP salt)		42		19
p-carbo-n-octyloxyphenyl	20	0	40	0
m-dimethylaminophenyl	60	50	70	40
p-dimethylaminophenyl	70	0	80	80
p-propylphenyl	80	20	80	80
2,4-dibromophenyl	60	30	50	30
2-(N-methylanilino)ethyl	70	40	50	0
3-(N-methylanilino)-2-propyl (NEP salt)		135		87
3-(N-ethylanilino)-2-propyl (NEP salt)		100		50
2-(N-ethylanilino)ethyl		60		50
1-methoxy-2,2,2-trichloroethyl	0	10	0	0
dicarbomethoxyethoxymethyl	0	0	40	20
o-ethoxyphenyl		25		37
2-n-butoxyethyl	90	0	70	60
2-isopropoxyethyl	0	0	40	30
m-acetylphenyl	10	0	60	20
2-isopropylmercaptoethyl	0	0	20	0
5-indanyl (morpholine salt)	100	70	100	100

For the compound of Formula III wherein R₁ is phenyl, X¹ = SR₂, the following *in vivo* data is presented:

R ₇	% Survivors			
	PO (Mg./kg.)		SQ (Mg./kg.)	
	200	100	200	100
phenyl	0	0	60	20
p-chlorophenyl	0	20	60	0
o-isopropylphenyl	10	0	30	10
(a) 150 mg./kg.				
(b) 75 mg./kg.				
(c) 50 mg./kg.				

isopropyl

t-butyl

2-cyanide

2-methyl

2-chloro

crotyl

2-imino

p-acetyl

2-acetyl

2-acetyl

2-pyridyl

[2,6-dichloro

benzyl

2-methyl

2-methyl

2-methyl

3-methyl

3-methyl

Infra-red and Chromatographic Data of α -Carboxybenzyl-penicillin Esters of Formula III(b) wherein R_1 is phenyl

1g./kg.)

100

20

n

10

R_1	I.R.	R_f
isopropyl	3.05, 5.61, 5.75, 5.92, 6.0, 6.25 6.55—6.6	
t-butyl	3.05, 5.61, 5.74, 5.82, 5.97, 6.07	0.2(*)
2-cyanoethyl*	2.98, 4.45, 5.58, 5.68, 5.73, 6.23	
2-methoxyethyl	3.0, 5.58, 5.72, 5.78, 5.91	0.45(b)
2-chloroethyl		0.6(b)
crotyl	3.05, 5.61, 5.73, 5.80, 5.95, 6.25	0.9(b)
2-imidazoloethyl	3.0, 3.2—3.26, 3.83, 3.99, 5.62, 5.72, 5.78 (sh), 5.97	0(b)
p-acetylphenyl*	3.05, 5.63, 5.71, 5.95, 6.25	0.35(b)
2-acetoxyethyl*	3.05, 5.61, 5.75, 5.80, 5.95, 6.00, 6.24	0.3(b)
2-acetylphenyl	2.98, 5.63, 5.73, 5.95, 6.0, 6.25	0.8(b)
2-piperidinoethyl*	3.0, 5.65, 5.76, 5.98, 6.25	0.05(b)
[2,2-dimethyl-1,3-dioxolon-4-yl]-methyl	3.05, 5.61, 5.71, 5.75, 5.91, 6.06, 6.25	0.45(b)
benzohydryl*	3.05, 5.62, 5.75, 5.78, 5.95, 6.25	0.95(b)
2-dimethylaminoethyl*	3.0, 5.63, 5.70, 5.75, 5.84, 5.95, 6.25	0(b)
2-pyrrolidinoethyl*	3.0, 5.66, 5.76, 5.98, 5.97	0(b)
2,2,2-trichloroethyl*	3.37, 5.5, 5.73 (sh), 5.92, 6.25, 6.66, 6.89	0.6(b)
3-oxybutyl acetonylmethyl	3.36, 4.08, 4.32, 5.13, 5.21, 5.25, 5.33, 5.37, 5.63 (sh), 5.8, 5.97, 6.06, 6.25, 6.67, 6.89	0.6(b)
2-nitrobutyl	3.35, 3.4 (sh), 3.45 (sh), 4.1, 4.3, 5.13, 5.23, 5.27, 5.35, 5.45, 5.75, 6.06, 6.25, 6.45, 6.78, 6.92	0.6(b)
2-carbethoxyethyl*	3.36, 5.78, 5.97, 6.25, 6.62, 6.78, 7.09	0.6(b)
1,1-dimethylacetonyl*	3.35, 5.14, 5.63, 5.8, 6.02, 6.26, 6.55, 6.69	0.6(b)
2-diethylaminoethyl	3.0, 5.63, 5.78, 5.95	0(b)

R ₂	I.R.	R _f
2-pyridylmethyl	3.05, 5.65, 5.78, 6.0, 6.10, 6.3	0 ^(b)
o-nitrophenyl*	3.08, 3.35, 4.33, 5.25, 5.39, 5.63, 5.97, 6.23, 6.27, 6.62, 6.78, 6.99	0.9 ^(b)
4-chloro-2-nitrophenyl*	3.34, 5.43, 5.49, 5.67, 5.85, 5.97, 6.09, 6.21, 6.29, 6.56, 6.80, 6.89, 7.1	0.9 ^(b)
4-pyridylmethyl	2.97, 5.58—5.70, 5.92, 6.55	0 ^(b)
3-dimethylaminopropyl	2.87, 5.6, 5.72, 5.92, 5.98, 6.5 (Br)	0.6 ^(b)
2-naphthyl	3.05, 5.65, 5.71, 5.77, 5.97, 6.15, 6.25	0.95 ^(b)
pyrrolidonomethyl		0.05 ^(b)
2-di-n-propylaminoethyl	3.0, 4.18, 6.0, 5.73, 5.97, 6.19, 6.25	0 ^(b)
2-di-n-butylaminoethyl	3.0, 5.66—5.79, 5.97, 6.25	0 ^(b)
2-diisopropylaminoethyl		0 ^(b)
2-(2,5-dimethylpyrrolidino)-ethyl		
2-formylphenyl*	2.95, 3.35, 4.1, 5.7, 5.86, 5.95, 6.2, 6.65, 6.8, 7.15	0.85 ^(b)
3-(2-methyl-4-pyrronyl) propargyl		
2-aziridinoethyl	2.9, 3.35, 5.7, 4.0, 5.65, 5.7, 6.05, 6.27, 6.7, 6.83, 6.95, 7.15, 7.25	0 ^(b)
1-ethoxy-2,2,2-trichloroethyl		
3-di-n-propylamino-2-propyl	2.98—3.00, 5.68 (Br), 5.83, 6.01, 6.25	0 ^(b)
2-(4-methylpiperidino)ethyl		
3-pyrrolidino-2-propyl	3.0 (Br, W), 5.66, 5.73, 5.80, 6.0, 6.25	
3-piperidino-2-propyl	3.0 (Br, W), 5.66, 5.72, 5.83, 5.99, 6.27	
3-pyrrolidinopropyl*	3.05 (Br, W), 5.63, 3.75, 5.97, 6.25	0 ^(b)

R _f	R ₁	I.R.	R _f
0 ^(b)	1-(2,3-dibutyryloxy) propyl*	2.95, 3.35, 4.05, 5.73, 5.95, 6.0, 6.2, 6.75, 6.85, 7.2	0.75 ^(b)
0.9 ^(b)	4-imidazolymethyl*	2.7, 2.95, 3.35, 4.05, 4.25, 5.6, 5.75, 5.95, 6.2, 6.75, 6.85, 7.2	0.7 ^(b)
0.9 ^(b)	5-(1,3-benzodioxolyl)*	2.95, 3.45, 5.6, 5.9, 6.15, 6.6, 6.7, 6.8	0 ^(c)
0 ^(b)	5-(1,3-benzodioxolyl) (NEP salt)		0.9 ^(a)
0.6 ^(b)	5-indanyl*	3.36, 3.51, 5.63, 5.97, 6.21, 6.63, 6.71, (Potassium salt) 6.78, 7.14	
0.95 ^(b)	5-indanyl*	2.95, 3.35, 5.55, 5.7, 5.9, 6.2, 6.7, 6.8, 6.9, 7.15	1.0 ^(c)
0.05 ^(b)	5-indanyl* (TEA salt)	2.95, 3.35, 5.62, 5.95, 6.20, 6.72, 6.85 7.15	
0 ^(b)	5-indanyl (Morpholine salt)	2.95, 3.4, 3.45, 4.1 (W), 5.6, 5.73, 5.9 (Sh.), 5.95, 6.2, 6.72, 6.85, 7.25	
0 ^(b)	5-indanyl* (NEP salt)	2.95, 4.5, 5.6, 5.7, 5.92, 6.18	
0.85 ^(b)	6-quinolyl*	2.95, 3.35, 4.0, 5.55 (Sh), 5.65, 5.95, 6.10, 6.20, 6.60, 6.75, 7.25	
	5-quinolyl		0.75 ^(b)
0 ^(b)	4-quinolyl*	2.95, 3.05, 3.35, 5.60, 5.80, 5.95, 6.07, 6.25, 6.68, 6.85, 7.35	0.75 ^(b)
	2-(1,4-naphthoquinolyl)*	2.9, 3.35, 5.7, 6.0, 6.25, 6.3, 6.50, 6.80, 7.1	1.0 ^(c)
	2-(4-methyl-quinolyl)		
0 ^(b)	1-butyn-4-yl		
	3-piperidinopropyl		0 ^(b)
	3-morpholinopropyl	2.92, 4 (Br, W), 5.6, 5.7, 5.75, 5.87, 5.92, 6.17, 6.5	0 ^(b)
	3-morpholino-2-propyl	2.9, 5.6 (W), 5.12, 5.92, 6.05, 6.22	0 ^(b)
	3-dimethylamino-2-propyl	2.9, 5.57, 5.70, 5.85, 5.92, 6.2, 6.6	0 ^(b)
	2-pyrrolidino-1-propyl	3.05 (Br), 5.66—5.75 (Br), 5.81, 5.95, 6.23	0 ^(b)
	2-azetidinoethyl		0 ^(b)
	trityl*	2.95, 3.35, 5.1, 5.5, 5.7, 5.9, 6.1, 6.25, 6.5, 6.65, 6.85, 7.15	

R ₂	I.R.	R _f
1-ethoxy-2,2,2-trifluoroethyl*	2.95, 3.35, 5.55, 5.9, 6.2, 6.45, 6.85 7.15	
phthalimidomethyl*	2.95, 3.35, 5.55, 5.70, 5.90, 6.20, 6.60, 6.80, 7.15	
2,3-dimethoxyphenyl*	2.95, 3.35, 3.50, 5.65, 5.9, 6.2, 6.25 6.65, 6.70, 7.15	0.8 ^(b)
3-di-n-propylamino-propyl*	3.5 (Br), 5.63, 5.77, 5.97, 6.20	
m-tolyl*	3.05, 5.65, 5.72, 5.97, 6.22, 6.32	0.95 ^(d)
o-isopropylphenyl*	3.05, 5.65, 5.75, 5.97, 6.27, 6.65	0.8 ^(d)
o-isopropylphenyl (Potassium salt)	3.0, 5.65, 5.72, 5.93, 6.23	
1-naphthyl*	2.95, 3.35, 5.55, 5.70, 5.90, 6.20, 6.30, 6.65, 6.80, 7.15	0.95 ^(d)
4-indanyl*	2.95, 3.35, 5.55, 5.70, 5.90, 6.20, 6.27, 6.67, 6.80, 7.15	
4-indanyl (NEP salt)	2.95, 3.10, 3.35, 5.60, 5.90, 6.17, 6.45, 6.75, 7.15	0.9 ^(d)
p-tolyl*	2.95, 3.35, 5.59, 5.70, 5.9, 6.20, 6.65, 6.85, 7.15	
o-ethylphenyl*	2.95, 3.35, 5.60, 5.72, 5.92, 6.24, 6.55, 6.70, 6.85, 7.15	0.75 ^(d)
o-ethylphenyl (NEP salt)	2.97, 4.5 (Br), 5.6, 5.7, 5.93, 6.20	0.95 ^(b)
o-tolyl*	2.95, 3.35, 5.60, 5.70, 5.92, 6.20, 6.30, 6.68, 6.85, 7.15	0.75 ^(d)
o-tolyl* (NEP salt)	2.95, 3.35, 4.5 (Br), 5.6, 5.69, 5.92, 6.15	0.95 ^(b)
(1,2,3-tricarboethoxy)-2-propyl*	3.0 (Br), 5.65, 5.8, 6.0, 6.2, 6.28	0.95 ^(d)
2-piperidino-1-propyl	2.92, 5.6, 5.68, 5.82, 5.95, 6.2	0 ^(d)
2-(2,6-dimethyl-piperidino)ethyl	2.9, 5.6, 5.7, 5.87, 5.93, 6.20	0 ^(d)
2-morpholino-1-propyl	2.9—2.95, 5.62, 5.70, 5.85, 5.97, 6.23	0 ^(d)
2-di-n-propyl-amino-1-propyl	2.95, 4 (Br), 5.62, 5.72, 5.9 (Sh), 5.95, 6.20	0 ^(d)
2-(N-methylanilino)ethyl	2.97, 4.0 (Br), 5.6, 5.72, 5.87 (Sh), 5.95, 6.23	1.0 ^(d)
3,4-dimethylphenyl	3.0, 5.62, 5.7 (Sh), 5.9, 5.95, 6.24	1.0 ^(d)

R ₁	R ₂	I.R.	R ₁
	3,4-dimethylphenyl (NEP salt)	2.90, 3.10, 3.35, 4.20, 5.60, 5.90, 6.20, 6.42, 6.65, 6.85, 7.15	0.9(d)
	2,3-dimethylphenyl	2.95, 5.6 (Br), 5.87, 5.95, 6.23	0.9(d)
	2,3-dimethylphenyl (NEP salt)	2.95, 3.10, 3.35, 5.62, 5.90, 6.20, 6.45, 6.65, 6.77, 6.85, 7.15	0.9(d)
	p-methoxyphenyl*	2.95, 3.35, 3.50, 4.10, 5.60, 5.70, 5.9, 6.20, 6.65, 6.85, 6.92, 7.15	0.95(d)
0.95(d)	p-methoxyphenyl* (NEP salt)	3.0, 4.5 (Br), 5.65, 5.75, 5.95, 6.22	0.85(d)
0.8(d)	6-chloro-2-methylphenyl*	2.95, 3.35, 5.55, 5.90, 6.20, 6.65, 6.80, 7.15	0.95(d)
	6-chloro-2-methylphenyl (NEP salt)	2.95, 3.15, 3.40, 4.45, 5.65, 5.92, 6.23, 6.45, 6.67, 6.85, 7.15	0.9(d)
0.95(d)	4-chloro-2-methylphenyl*	2.95, 3.35, 5.69, 5.90, 6.10, 6.20, 6.45, 6.72, 6.92, 7.2	0.95(d)
	4-chloro-2-methylphenyl (NEP salt)	2.90, 4.2 (Br), 5.62, 5.92, 6.13, 6.20, 6.40	0.9(d)
	2-chloro-3,4-dimethyl- phenyl*	2.95, 3.35, 5.55, 5.9, 6.23, 6.65, 6.77, 6.80, 7.15	0.9(d)
	2-chloro-5-methylphenyl*	2.95, 3.35, 5.60, 5.9, 6.25, 6.45, 6.70, 6.90, 7.15	0.9(d)
0.75(d)	2-chloro-5-methylphenyl (NEP salt)	2.95, 4.2 (Br), 5.62, 5.97, 6.40	
0.95(b)	4-chloro-2,5- dimethylphenyl	2.95, 3.35, 5.60, 5.90, 6.20, 6.65, 6.85, 7.15	0.95(d)
0.75(d)	4-chloro-3,5-dimethyl phenyl*	2.95, 3.35, 5.60, 5.90, 6.10, 6.20, 6.50, 6.80, 7.15	1.0(d)
0.95(b)	4-chloro-3,5-dimethyl- phenyl (NEP salt)	2.95, 3.15, 3.35, 4.25, 5.65, 5.95, 6.25, 6.40, 6.48, 6.65, 6.77, 6.88, 7.15	
0.95(d)	4-chloro-2,3-dimethyl- phenyl*	2.95, 3.35, 5.60, 5.9, 6.20, 6.65, 6.80, 7.15	
0(d)	4-chloro-2,3-dimethyl- phenyl (NEP salt)	2.95, 3.10, 3.40, 5.65, 5.90, 6.20, 6.45, 6.65, 6.85, 7.15	
0(d)	4-chloro-2,6-dimethyl- phenyl*	2.95, 3.37, 5.60, 5.90, 6.23, 6.30, 6.65, 6.80, 7.20	
0(d)	2-chloro-4,5-dimethyl- phenyl*	2.95, 3.37, 5.60, 5.90, 6.25, 6.45, 6.68, 6.87, 7.20	
1.0(d)			
1.0(d)			

R ₂	I.R.	R _f
2,4-dichloro-6-methylphenyl*	2.95, 3.37, 5.60, 5.90, 6.25, 6.45, 6.65, 6.82, 7.15	0.9 ^(d)
2,4-dichloro-3,5-dimethylphenyl*	2.95, 3.37, 5.60, 5.95, 6.25, 6.65, 6.85, 9.2	0.85 ^(d)
4-chloro-2,3,5-trimethylphenyl*	2.95, 3.40, 5.62, 5.93, 6.10, 6.20, 6.65, 6.85, 7.2	0.75 ^(d)
1-n-butoxy-2,2,2-trichloroethyl		1.0 ^(e)
dicarbethoxyethoxymethyl		0.75 ^(d)
carbethoxyethoxymethyl		1.0 ^(d)
1,1-dimethyl-2,2,2-trifluoroethyl		
2,2,2-trifluoroethyl		
m-fluorophenyl	3.0 (Br), 5.63, 5.70, 5.88 (Sh), 5.95, 6.23	
4-chloro-2,6-dinitrophenyl	3.0 (Br), 5.61, 5.66, 5.95, 6.12, 6.19, 6.23	
6-chloro-2,4-dinitrophenyl	3.0 (Br), 5.62, 5.97, 6.0, 6.25	
2,5-dimethylphenyl	3.0, 5.63, 5.71, 5.90, 5.95, 6.17	0.95 ^(d)
2,5-dimethylphenyl (NEP salt)	2.95, 4.5 (Br), 5.6, 5.7, 5.92, 6.3	0.95 ^(d)
3,5-dimethylphenyl*	2.98, 5.63, 5.73, 5.91, 6.16, 6.25	0.9 ^(d)
3,5-dimethylphenyl (NEP salt)*	2.90, 3.10, 3.35, 4.15, 5.60, 5.95, 6.15, 6.25, 6.65, 6.85, 7.15	
2,4-dimethylphenyl	2.95, 5.62, 5.72, 5.91, 5.95, 6.22	0.95 ^(d)
2,4-dimethylphenyl* (NEP salt)	2.97, 4.3 (Br), 5.6, 5.7, 5.93, 6.17	0.95 ^(d)
2,6-dimethylphenyl	2.95, 5.63, 5.73, 5.91, 6.22	0.95 ^(d)
2,6-dimethylphenyl (NEP salt)	2.95, 3.10, 3.35, 5.32, 5.65, 5.95, 6.20, 6.45, 6.70, 6.90, 7.15	0.9 ^(d)
m-ethylphenyl	2.95, 5.63, 5.71, 5.91, 5.96, 6.22	0.95 ^(d)
m-ethylphenyl (NEP salt)	3.0, 4.5, 5.65, 5.74, 5.96, 6.23	0.8 ^(d)

m-ct

p-ct

4,6-met

2,6

2-r ph

2-r ph

4-ph

2

P

2

F

A

1

R _f	R ₂	I.R.	R _f
0.9 ^(d)	m-ethoxyphenyl	3.0, 5.63, 5.71, 5.91, 5.95, 6.21, 6.26	0.95 ^(d)
0.85 ^(d)	p-ethoxyphenyl	2.95, 5.63 (Br), 5.71, 5.91, 5.95, 6.15, 6.25	0.95 ^(d)
0.75 ^(d)	4,6-dibromo-2-methyl-methylphenyl	3.0, 5.63, 5.70, 5.92, 5.97, 6.25	0.95 ^(d)
1.0 ^(e)	2,6-dibromophenyl	3.0, 5.63, 5.66, 5.95, (Br), 6.25	0.95 ^(d)
0.75 ^(d)	2-methoxy-4-methyl-phenyl*	2.97, 3.40, 5.60, 5.70 (Sh), 5.92, 6.23, 6.65, 6.83, 7.20	0.9 ^(d)
1.0 ^(d)	2-methoxy-4-methyl-phenyl (NEP salt)	2.95, 3.15, 3.40, 5.65, 5.90, 6.25, 6.47, 6.62, 6.87, 7.15	
	4-chloro-2,3-diethyl-phenyl*	2.95, 3.35, 5.60, 5.90, 6.10, 6.23, 6.50, 6.80, 7.20	0.9 ^(d)
	2-methyl-3-methoxy-phenyl*	2.97, 3.40, 5.62, 5.70 (Sh), 5.92, 6.20, 6.30, 6.80, 6.95, 7.15	0.9 ^(d)
	2-methyl-3-methoxy-phenyl (NEP salt)	2.95, 3.10, 3.40, 5.65, 5.90, 6.20, 6.27, 6.45, 6.65, 6.77, 6.85, 7.15	
	4(α,α-dimethylbenzyl)-phenyl*	2.95, 3.35, 5.60, 5.70 (Sh), 6.92, 6.23, 6.65, 6.90, 7.15	0.95 ^(d)
	5-ethyl-3-methylphenyl*	2.97, 3.40, 5.60, 5.70 (Sh), 5.92, 6.15, 6.27, 6.65, 6.85, 7.15	0.95 ^(d)
0.95 ^(d)	4-(1-indanyl)phenyl*	2.95, 3.35, 5.60, 5.70, 5.90, 6.20, 6.45, 6.65, 6.85, 7.15	0.95 ^(d)
0.95 ^(d)	2,4-(dicylopent-2-enyl)-phenyl*	2.95, 3.37, 5.8, 5.70, 5.92, 6.23, 6.65, 6.85, 7.15	0.95 ^(d)
0.9 ^(d)	p-fluorophenyl*	2.95, 3.35, 5.10, 5.61, 5.65 (Sh), 5.90, 6.23, 6.45, 6.65, 6.85, 7.20	0.95 ^(d)
	p-carbomethoxyphenyl*	2.95, 3.35, 5.60, 5.75, 6.25, 6.65, 6.92, 7.15	0.95 ^(d)
0.95 ^(d)	p-carbo-n-propoxyphenyl*	2.95, 3.25, 5.60, 5.80, 6.20, 6.65, 6.80, 7.15	0.95 ^(d)
0.95 ^(d)	2-(5,6,7,8-tetrahydro-naphthyl)*	2.95, 3.40, 5.60, 5.73, 5.93, 6.18, 6.70, 6.90, 7.15	0.95 ^(d)
0.9 ^(d)	2-(5,6,7,8-tetrahydro-naphthyl) (NEP salt)	2.85, 3.05, 3.35, 5.60, 5.90, 6.15, 6.40, 6.62, 6.85, 7.10	
0.95 ^(d)	p-carbo-n-octyloxyphenyl*	2.95, 3.35, 5.60, 5.80, 5.92, 6.10, 6.20, 6.65, 6.82, 7.20	0.9 ^(d)
0.8 ^(d)	m-dimethylaminophenyl	3.0 (Br), 5.63, 5.73, 5.95, 6.22	

R ₂	I.R.	R _f
p-dimethylaminophenyl	3.0, 5.63, 5.75, 5.97 (Br), 6.22	
o-propylphenyl*	3.35, 5.6, 5.85, 5.95, 6.10, 6.20, 6.35, 6.65, 6.87, 7.15	
p-propylphenyl*	2.95, 3.37, 5.60, 5.70, 5.90, 6.20, 6.65, 6.85, 7.20	0.95 ^(d)
2,4-dibromophenyl*	2.95, 3.40, 3.50, 5.60, 5.80, 6.10, 6.25, 6.65, 6.80, 7.10	0.95 ^(d)
p-t-butylphenyl		0.95 ^(d)
2-(N-methylanilino)ethyl* (NEP salt)	3.0 (Br), 5.63, 5.78, 5.9—6.1 (Br), 6.25	0.9 ^(d)
2-(N-methylanilino)ethyl* (NEP salt)	2.98, 4.5 (Br), 5.62, 5.76, 5.95, 6.25	0.85 ^(d)
3-(N-methylanilino)-2- propyl* (NEP salt)	3.0 (Br), 4.1 (Br), NH ₂ +, 5.65, 5.84, 6.0, 6.25	0.95 ^(d)
3-(N-ethylanilino)-2- propyl* (NEP salt)	3.0, 5.63, 5.81, 5.97, 6.25	0.95 ^(d)
2-(N-ethylanilino)ethyl (NEP salt)	2.98, 4.4—4.5 (Br) NH ₂ +, 5.62, 5.77, 5.90, 6.25	0.8 ^(d)
o-ethoxyphenyl	2.95, 3.10, 3.35, 5.60, 5.90, 6.20, 6.45, 6.65, 6.75, 6.90, 7.15	
2-n-butoxyethyl	3.01, 5.61, 5.7—5.8, 5.95, 7.7 (Br), 8.1 (Br), 8.85	
2-isopropoxyethyl*	2.98, 5.59, 5.74, 5.92, 7.3 (Br), 8.7, 8.85	
m-acetylphenyl*		
2-ethoxyethyl*	3.0, 5.60, 7.56, 6.95, 6.24, 8.89	
8-quinolyl*	2.95, 3.35, 4.05, 5.65, 5.95, 6.1, 6.2, 6.3, 6.65, 6.77, 7.25	
2-isopropylmercaptoethyl		
5-quinolyl		0.75
methyl	3.05 (Br, W), 5.60, 5.64, 5.79, 5.95, 6.25	0.6 ^(b)

R_f 0.95^(a)0.95^(d)0.95^(a)0.9^(a)0.85^(d)0.95^(d)0.95^(d)0.8^(a)

0.75

0.6^(b) R_s

I.R.

 R_f

ethyl	3.05 (Br, W), 5.61, 5.73, 5.81, 5.92	0.6 ^(b)
n-hexyl	3.05 (Br, W), 5.61, 5.77, 5.80, 5.95	0.75 ^(b)
n-octyl	3.05, 5.61, 5.80, 5.94	
n-decyl		1.0 ^(b)
tetradecyl	3.05, 5.61, 5.75, 5.79, 5.95, 6.07	0.95 ^(b)
phenyl	3.05, 5.63, 5.70 (Br), 5.95, 6.27	0.8
phenyl* (NEP salt)	2.95, 3.35, 4.45 (Br), 5.59, 5.67, 5.90, 6.17	0.95
n-butyl		1.0 ^(c)
sec-butyl	3.0 (Br, W), 5.63, 5.75, 5.83, 5.97, 6.25	0.8 ^(b)
n-propyl	3.0 (Br, W), 5.63, 5.81 (Br), 5.97, 6.25	0.8 ^(b)
isobutyl	3.0 (Br, W), 5.63, 5.81 (Br), 5.97, 6.08, 6.25	0.75 ^(b)
o-isopropylphenyl		0.95 ^(d)
2-piperidinoethyl	3.38, 5.63, 5.78, 5.97, 6.25, 6.62	0.95 ^(c)
2-morpholinoethyl	3.38, 5.63, 5.78, 5.97, 6.25, 6.62	0.95 ^(c)

 R_1

p-chlorophenyl	2.95, 4.25 (Br), 5.62, 5.8, 5.85, 5.93, 6.2
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 R_2

2-naphthyl

 R_7 (wherein X' is $-SR_7$)

phenyl	2.95, 3.35, 4.05, 5.05, 5.25, 5.5, 5.85, 6.2, 6.7, 6.8, 6.85, 7.15, 7.25	0.85 ^(b)
p-chlorophenyl	2.95, 3.35, 4.05, 5.25, 5.6, 5.9, 6.25, 6.35, 6.65, 6.75, 6.85, 7.15	0.8 ^(b)

*Infrared curves run in chloroform. All others in KBr pellets.

Chromatographic systems:—

- (a) chloroform: 95% ethanol: formic acid (2:1:2)
- (b) benzene: acetic acid: water (2:2:1)
- (c) butanol: water: acetic acid (5:4:1)
- (d) isoamylacetate: sodium acetate (0.1 M, pH 4.5)
- (e) pyridine: toluene: water (5:20:10; McIlvaine's buffer pH 3.0)

EXAMPLE I

General Methods for Acylation of 6-Aminopenicillanic Acid

To a solution of the appropriate aryl halocarbonyl 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 R_2OH (0.1 mole). The reaction mixture is maintained under an atmosphere of nitrogen and stirred for a period of from 20 minutes to 3 hours, care being taken to exclude moisture. The temperature may range from about -70° to about $-20^\circ C$. The infrared spectrum of the mixture is then taken to determine and confirm the presence of the ketene ester. A solution of 6-aminopenicillanic acid-triethylamine salt (0.1 mole) in methylene chloride (50 ml.) is added and the mixture stirred at -70° to $-20^\circ C$. for ten minutes. The cooling bath is then removed and the reaction mixture stirred continuously and allowed to warm to room temperature. The product is isolated by one of the methods below.

Method A—The reaction mixture is evaporated to dryness under reduced pressure and the residue taken up in citrate buffer (pH 5.5). The product is extracted from the buffer solution with chloroform. The chloroform extract is washed with citrate buffer (pH 5.5) then dried with anhydrous sodium sulfate and evaporated to dryness to give the sodium salt.

Method B—The procedure of Method A is followed but using a citrate buffer, said buffer comprising citric acid and disodium phosphate or dipotassium phosphate, and using n-butanol as extracting solvent in place of chloroform. The product obtained after

evaporation of the n-butanol solvent is triturated with ether to produce the sodium or potassium salt of the penicillin product, respectively, as an amorphous solid.

Method C—This procedure, a variation of Method A, uses a saturated aqueous solution of sodium (or potassium) bicarbonate in place of citrate buffer to produce the sodium (or potassium) salt of the penicillin product. It is generally used for the recovery of those penicillin products which are poorly soluble in methylene chloride or chloroform.

Method D—The reaction mixture is extracted twice with saturated aqueous sodium or potassium bicarbonate, washed with water, dried and evaporated to dryness to give the sodium (or potassium) salt. The product, if not a solid, is triturated with ether.

Method E—This method, a modification of Method D, is used for those penicillins which are difficultly soluble in methylene chloride. The sodium (or potassium) bicarbonate solution (Method D) is extracted with n-butanol, the butanol extract dried and evaporated to dryness.

Method F—This method is used to isolate the free acid form of the penicillins.

The residue remaining after evaporation of the reaction mixture to dryness is taken up in aqueous acid, e.g. HCl, at pH 2.7 and the product extracted therefrom by means of n-butanol. The butanol extract is washed with aqueous acid (pH 2.7) and then lyophilized.

Method F—1—The butanol extract of Method F is neutralized with an n-butanol solution of potassium 2-ethyl hexanoate to precipitate the potassium salt of the penicillin.

The following compounds are thus prepared.

solvent is trituro-
sodium or potas-
sodium or potas-
product, respec-

is a variation of
aqueous solution
borate in place
the sodium (or
product. It is
of those peni-
rly soluble in 50
m.

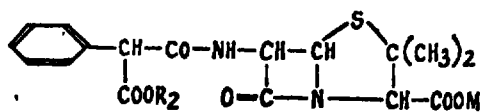
mixture is ex-
aqueous sodium
ed with water,
is to give the 55
the product, if
ter.

modification
use penicillins
in methylene 60
um) bicarbon-
acted with n-
and evapor-

sed to isolate 65
ins.

aporation of
taken up in
2.7 and the 70
near of n-
washed with
yophilized.

extract of
n n-butanol
xanoate to 75
e penicillin.
is prepared.



R ₂	Method	M
methyl	A	Na
ethyl	A	Na
n-propyl	A	Na
i-propyl	A	Na
n-butyl	A	Na
sec-butyl	A	Na
i-butyl	A	Na
t-butyl	A	Na
2-ethyl-1-butyl	D	K
hexyl	B	Na
octyl	D	K
decyl	D	K
dodecyl	B	Na
tetradecyl	B	Na
octadecyl	D	K
2-chloroethyl	A	Na
2-chloropropyl	A	Na
3-chloropropyl	A	Na
1-methyl-2-chloroethyl	A	Na
2-chloro-1-butyl	A	Na
3-chloro-1-butyl	A	Na
4-chloro-1-butyl	A	Na
1-ethyl-2-chloroethyl	A	Na
1-methyl-3-chloropropyl	A	Na
1-methyl-2-chloropropyl	A	Na
2,2-dimethyl-2-chloroethyl	A	Na

R ₂	Method	M
1,1-dimethyl-2-chloroethyl	A	Na
2-bromoethyl	B	K
2-bromopropyl	B	K
3-bromopropyl	B	K
1-methyl-2-bromoethyl	B	K
2-bromo-1-butyl	B	K
4-bromo-1-butyl	B	K
1-ethyl-2-bromoethyl	B	K
1,1-dimethyl-2-bromoethyl	B	K
1,3-dichloropropyl	A	Na
2,3-dibromopropyl	A	Na
1,1-dichloromethylethyl	A	Na
2-bromo-3-chloropropyl	A	Na
2-chloro-3-bromopropyl	A	Na
1,4-dibromo-2-butyl	A	Na
3,4-dichloro-1-butyl	A	Na
3,4-dichloro-2-butyl	A	Na
1-bromoethyl-2-chloroethyl	A	Na
2,3-dibromo-2-methylpropyl	A	Na
1,1-dichloromethylethyl	A	Na
2,2-dichloroethyl	A	Na
1,1-dimethyl-2,2-dichloroethyl	A	Na
1-methyl-1-trichloromethylethyl	A	Na
2,3,3-tribromopropyl	A	Na
2,2,3-tribromopropyl	A	Na
2,2,3-trichlorobutyl	A	Na
2-chloro-2,3-dibromobutyl	A	Na
2,2,3,3-tetrabromopropyl	A	Na
2,2,2-trichloroethyl	A	Na
2,2,2-trifluoroethyl	A	Na

R ₁	Method	M
2-ethoxyethyl	F-1	K
2-isopropoxyethyl	F-1	K
2-n-butoxyethyl	F-1	K
2-isobutoxyethyl	F-1	K
2-methoxypropyl	F-1	K
3-sec-butoxypropyl	F-1	K
3-n-propoxypropyl	F-1	K
4-methoxy-n-butyl	F-1	K
4-ethoxy-n-butyl	F-1	K
4-butoxy-n-butyl	F-1	K
1,1-dimethyl-2-methoxyethyl	F-1	K
1,1-dimethyl-2-ethoxyethyl	F-1	K
1-cyanoethyl	E	K
2-cyanoethyl	E	K
3-cyanopropyl	E	K
4-cyanobutyl	E	K
2-cyano-1-methylpropyl	E	K
2-cyano-1-methylethyl	E	K
1-cyano-1-methylethyl	E	K
1-chloromethyl-2-cyanoethyl	B	K
1-cyano-2-chloropropyl	B	K
1-cyano-2,2-dichloropropyl	B	K
1-cyano-1-chloromethyl-2-chloroethyl	B	K
1-cyano-2,2,2-trichloroethyl	B	K
1-cyano-2,2,2-tribromoethyl	B	K
1-methyl-1-(1'-cyano-1'-methylethoxy)ethyl	B	K
1-methyl-1-(1'-cyano-1'-methylethoxy)propyl	B	K
2-formyloxyethyl	B	Na
2-acetoxyethyl		Na

ad	M	R ₂	Method	M
K		2-propionyloxyethyl	B	Na
K		2-butyryloxyethyl	B	Na
K		2-acetoxypropyl	B	Na
K		3-butyryloxypropyl	B	Na
K		3-acetoxypropyl	B	Na
K		2-acetoxy-n-butyl	B	Na
K		4-acetoxy-n-butyl	B	Na
K		4-propionyloxy-n-butyl	B	Na
K		1-methyl-2-acetoxyethyl	B	Na
K		1-methyl-3-acetoxypropyl	B	Na
K		carbomethoxymethyl	B	Na
K		carbobutoxymethyl	B	Na
K		2-carbethoxyethyl	B	Na
K		2-carboisopropoxyethyl	B	Na
K		3-carbomethoxypropyl	B	Na
K		3-carbobutoxypropyl	B	Na
K		4-carbethoxybutyl	C	Na
K		4-carbopropoxybutyl	C	Na
K		1-methyl-2-carbomethoxyethyl	C	Na
K		2-carbethoxypropyl	C	Na
K		1-carbethoxyethyl	C	Na
K		1-carbethoxypropyl	C	Na
K		1-chloromethyl-2-carbethoxyethyl	B	K
K		1-trichloromethyl-2-carbomethoxyethyl	B	K
K		1-carbethoxy-2-chloropropyl	B	K
K		1-carbopropoxy-2-chloropropyl	B	K
K		1-carbethoxy-2,2-dichloropropyl	B	K
Na		1-carbethoxy-1-chloromethyl-2-chloroethyl	B	K
Na		1-carbomethoxy-2,2,2-trichloroethyl	B	K

R ₂	Method	M
1-carbethoxy-2,2-dichloroethyl	B	K
1-carbomethoxy-2-chloroethyl	B	K
1-carboisobutyloxy-2,2,2-trichloroethyl	B	K
1-carbomethoxymethyl-2,2,2-trichloroethyl	B	K
acetyl	E	Na
acetyl	E	Na
2-oxopentyl	E	Na
1-methyl-3-oxobutyl	E	Na
4-oxopentyl	E	Na
2-methyl-3-oxobutyl	E	Na
1,1-dimethylacetyl	E	Na
1-methyl-4-oxopentyl	E	Na
1-ethyl-2-oxobutyl	E	Na
1-methyl-3-oxobutyl	E	Na
1-acetyl-1-methylpropyl	B	Na
1,2-dimethyl-3-oxobutyl	B	Na
1,1-dimethyl-3-oxobutyl	B	Na
2-methyl-3-oxopentyl	B	Na
2-acetylbutyl	B	Na
1-acetylbutyl	B	Na
1-methyl-3-oxohexyl	B	Na
1-ethyl-2-methyl-3-oxobutyl	B	Na
1-methyl-4-methyl-3-oxopentyl	B	Na
2-acetylpropyl	B	Na
3-oxopentyl	B	Na
1-methyl-2-oxohexyl	B	Na
4-oxohexyl	B	Na
5-oxohexyl	B	Na
1-methoxy-2,2,2-trichloroethyl	A	Na

R ₂	Method	M
2-fluoroethyl	A	Na
3-fluoropropyl	A	Na
1-chloromethyl-2-fluoroethyl	A	Na
2,2,3,3,4,4,4-heptafluorobutyl	A	Na
1-nitro-1-trifluoromethyl-2,2,2-trifluoroethyl	A	Na
1-trichloromethyl-2,3,3,3-tetrachloropropyl	A	Na
2-chloro-3,3-difluoropropyl	A	Na
1-methoxy-2-chloro-2,2-difluoroethyl	A	Na
1-trifluoromethyl-2-nitroethyl	A	Na
4,4,4-trifluorobutyl	A	Na
dicarbethoxyethoxymethyl	B	Na
1,1-dicarbethoxymethyl-2-ethoxyethyl	B	Na
carbethoxyethoxymethyl	B	Na
chlorodicarbomethoxymethyl	B	Na
bromodicarbomethoxymethyl	B	Na
1-isopropoxy-2,2,2-trichloroethyl	A	Na
1-sec-butoxy-2,2,2-trichloroethyl	A	Na
1-isobutyloxy-2,2,2-trichloroethyl	A	Na
1-t-butoxy-2,2,2-trichloroethyl	A	Na
dicarbomethoxyethoxymethyl	B	Na
cyclopropyl	A	Na
cyclobutyl	A	Na
cyclopentyl	A	Na
cyclohexyl	A	Na
cycloheptyl	A	Na
1-methyl-1-cyclopentyl	A	Na
2-methyl-1-cyclopentyl	A	Na
3-methyl-1-cyclopentyl	A	Na
2,2-dimethyl-1-cyclopentyl	B	K

d	M	R ₂	Method	M
Na		1,3-dimethyl-1-cyclopentyl	B	K
Na		2,5-dimethyl-1-cyclopentyl	B	K
Na		2,4-dimethyl-1-cyclopentyl	B	K
Na		1,2,2-trimethyl-1-cyclopentyl	B	K
Na		1,2,5-trimethyl-1-cyclopentyl	B	K
Na		2,3,4-trimethyl-1-cyclopentyl	B	K
Na		1,2,4-trimethyl-1-cyclopentyl	B	K
Na		1-isopropyl-1-cyclopentyl	B	K
Na		3-isopropyl-1-cyclopentyl	B	K
Na		1-methyl-1-cyclohexyl	B	K
Na		2-methyl-1-cyclohexyl	B	K
Na		3-methyl-1-cyclohexyl	B	K
Na		3-methyl-1-indanyl	A	Na
Na		3-ethyl-1-indanyl	A	Na
Na		5-methyl-1-indanyl	B	K
Na		7-methyl-1-indanyl	B	K
Na		2,2-dimethyl-1-indanyl	B	K
Na		2,3-dimethyl-1-indanyl	B	K
Na		2,3-diethyl-1-indanyl	B	K
Na		3,3-dimethyl-1-indanyl	B	K
Na		2-chloro-1-indanyl	A	Na
Na		4-chloro-1-indanyl	A	Na
Na		2-bromo-1-indanyl	A	Na
Na		3-bromo-1-indanyl	A	Na
Na		1-chloro-2-indanyl	A	Na
Na		9-fluorenyl	B	K
Na		2,4-dipropyl-1-cyclopentyl	B	K
Na		3-isobutyl-5-methyl-1-cyclohexyl	B	K
K		2-isobutyl-5-methyl-1-cyclohexyl	B	K

R ₂	Method	M
1,5-dimethyl-2-isopropyl-1-cyclohexyl	B	K
2,2,3,6,6-pentamethyl-1-cyclohexyl	B	K
2,2,4,4,6-pentamethyl-1-cyclohexyl	B	K
2-methyl-4-sec-butyl-1-cyclohexyl	B	K
1-(2-methyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(4-methyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(7-methyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(1,3-dimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(3,4-dimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(5,8-dimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(1,2,7-trimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(4,5,7-trimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(1,5,8-trimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
2-(1-methyl-1,2,3,4-tetrahydronaphthyl)	B	K
2-(6-methyl-1,2,3,4-tetrahydronaphthyl)	B	K
2-(2,6-dimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
2-(4,4-dimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
2-(1,1,4,5-tetramethyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(2-chloro-1,2,3,4-tetrahydronaphthyl)	B	K
1-(3-chloro-1,2,3,4-tetrahydronaphthyl)	B	K
2-(1-bromo-1,2,3,4-tetrahydronaphthyl)	B	K
1-(2-bromo-1,2,3,4-tetrahydronaphthyl)	B	K
2-(3-bromo-1,2,3,4-tetrahydronaphthyl)	B	K
phenyl	B	Na
o-tolyl	B	Na
m-tolyl	B	Na
p-tolyl	B	Na
o-ethylphenyl	B	Na
m-ethylphenyl	B	Na

Mod	M	R ₁	Method	M
K		o-n-propylphenyl	B	Na
K		p-n-propylphenyl	B	Na
K		o-isopropylphenyl	B	Na
K		p-t-butylphenyl	B	Na
K		o-methoxyphenyl	B	Na
K		m-methoxyphenyl	B	Na
K		p-methoxyphenyl	B	Na
K		o-ethoxyphenyl	B	Na
K		m-ethoxyphenyl	B	Na
K		p-ethoxyphenyl	B	Na
K		p-n-butoxyphenyl	B	Na
K		o-chlorophenyl	A	Na
K		m-chlorophenyl	A	Na
K		p-chlorophenyl	A	Na
K		o-bromophenyl	A	Na
K		m-bromophenyl	A	Na
K		m-fluorophenyl	A	Na
K		p-fluorophenyl	A	Na
K		o-formylphenyl	A	Na
K		m-formylphenyl	A	Na
K		o-acetylphenyl	A	Na
K		p-acetylphenyl	A	Na
K		p-butyrylphenyl	A	Na
Na		o-nitrophenyl	C	K
Na		m-nitrophenyl	C	K
Na		p-nitrophenyl	C	K
Na		o-carbomethoxyphenyl	C	Na
Na		m-carbomethoxyphenyl	C	Na
Na		p-carbomethoxyphenyl	C	Na

R ₂	Method	M
o-carbethoxyphenyl	C	Na
p-carbo-n-propoxyphenyl	C	Na
p-carbo-n-octyloxyphenyl	C	Na
o-dimethylaminophenyl	F-1	K
o-diethylaminophenyl	F-1	K
o-di-n-butylaminophenyl	F-1	K
m-dimethylaminophenyl	F-1	K
m-di-n-propylaminophenyl	F-1	K
p-dimethylaminophenyl	F-1	K
p-methylethylaminophenyl	F-1	K
p-methylisopropylaminophenyl	F-1	K
2,3-dimethylphenyl	D	K
2,4-dimethylphenyl	D	K
2,5-dimethylphenyl	D	K
2,6-dimethylphenyl	D	K
3,4-dimethylphenyl	D	K
3,5-dimethylphenyl	D	K
2,3-diethylphenyl	D	K
2,4-diethylphenyl	D	K
2,6-diethylphenyl	D	K
2,4-di-n-propylphenyl	D	K
2,6-di-n-propylphenyl	D	K
5-ethyl-3-methylphenyl	D	K
6-ethyl-2-methylphenyl	D	K
2-ethyl-4-methylphenyl	D	K
2-methyl-6-n-propylphenyl	D	K
4-isopropyl-3-methylphenyl	D	K
2-methyl-4-sec-butylphenyl	B	Na
3-methyl-4-t-butylphenyl	B	Na

od	M	R ₂	Method	M
	Na	2,3,4-trimethylphenyl	B	Na
	Na	2,4,6-trimethylphenyl	B	Na
	Na	3,4,5-trimethylphenyl	B	Na
1	K	2,6-dimethyl-4-ethylphenyl	B	Na
1	K	3,5-dimethyl-4-ethylphenyl	B	Na
1	K	4,6-dimethyl-2-ethylphenyl	B	Na
	K	2,6-diethyl-4-methylphenyl	B	Na
	K	4,5-dimethyl-2-isopropylphenyl	B	Na
	K	2,3,4,6-tetramethylphenyl	B	Na
	K	3,6-diethyl-2,4-dimethylphenyl	B	Na
	K	4-butyl-5-isopropyl-2-methylphenyl	B	Na
	K	pentamethylphenyl	B	Na
	K	2,6-dichlorophenyl	A	Na
	K	2,4-dibromophenyl	A	Na
	K	2,6-dibromophenyl	A	Na
	K	2,3,4-trichlorophenyl	A	Na
	K	2,4,6-trichlorophenyl	A	Na
	K	3,4,5-trichlorophenyl	A	Na
	K	2,4,6-tribromophenyl	A	Na
	K	2,3,5,6-tetrachlorophenyl	A	Na
	K	2,3,4,6-tetrabromophenyl	A	Na
	K	pentachlorophenyl	A	Na
	K	pentabromophenyl	A	Na
	K	2,4-dinitrophenyl	C	Na
	K	2,6-dinitrophenyl	C	Na
	K	3,5-dinitrophenyl	C	Na
	K	2,3,6-trinitrophenyl	C	Na
Na		2,3,4,6-tetranitrophenyl	C	Na
Na		pentanitrophenyl	C	Na

R ₁	Method	M
2,4-difluorophenyl	A	Na
2,6-difluorophenyl	A	Na
2,3,5-trifluorophenyl	A	Na
2,4,6-trifluorophenyl	A	Na
2,3,5,6-tetrafluorophenyl	A	Na
pentafluorophenyl	A	Na
3-chloro-2-fluorophenyl	A	Na
3-chloro-4-fluorophenyl	A	Na
2-bromo-4-fluorophenyl	A	Na
2,6-dichloro-4-fluorophenyl	A	Na
4,5-dichloro-2-fluorophenyl	A	Na
4-bromo-3,5-difluorophenyl	A	Na
4,6-dibromo-2-fluorophenyl	A	Na
2-bromo-3,5-dichloro-4-fluorophenyl	A	Na
3-fluoro-2,4,6-trichlorophenyl	A	Na
4-methoxy-2-methylphenyl	A	Na
5-bromo-2-methoxyphenyl	A	Na
4-bromo-3-methoxyphenyl	A	Na
2-chloro-6-methoxyphenyl	A	Na
3-methoxy-2-methylphenyl	B	K
2-ethoxy-3-methylphenyl	B	K
2-methoxy-6-propylphenyl	B	K
2-carbomethoxy-5-fluorophenyl	B	K
5-fluoro-2-methoxyphenyl	B	K
2-acetyl-4-fluorophenyl	B	K
4-acetyl-2-fluorophenyl	B	K
6-chloro-2-methylphenyl	B	Na
4-chloro-2-methylphenyl	B	Na
2-chloro-4-methylphenyl	B	Na

hod	M	R ₂	Method	M
	Na	2-fluoro-4-methylphenyl	B	Na
	Na	4-fluoro-3-methylphenyl	B	Na
	Na	2-bromo-6-methylphenyl	B	Na
	Na	3-bromo-5-methylphenyl	B	Na
	Na	2-bromo-4-t-butylphenyl	B	Na
	Na	2-chloro-4-isopropylphenyl	B	Na
	Na	2-ethyl-4-fluorophenyl	B	Na
	Na	2-isobutyl-4-fluorophenyl	B	Na
	Na	6-bromo-3,4-dimethylphenyl	B	K
	Na	4-chloro-2,3-dimethylphenyl	B	K
	Na	4-chloro-3,5-dimethylphenyl	B	K
	Na	4-chloro-2,5-dimethylphenyl	B	K
	Na	4-chloro-2,6-dimethylphenyl	B	K
	Na	4-chloro-6-isopropyl-3-phenyl	B	Na
	Na	4-bromo-3-isopropyl-6-methylphenyl	B	K
	Na	4-chloro-2,3-diethylphenyl	B	K
	Na	2-chloro-4,5-dimethylphenyl	B	K
	Na	4,6-dichloro-2-methylphenyl	B	K
	Na	2-chloro-3,4-dimethylphenyl	B	K
	K	4,6-dibromo-2-methylphenyl	B	K
	K	2,4-dichloro-3,5-dimethylphenyl	B	K
	K	4-chloro-2,3,5-trimethylphenyl	B	K
	K	4-chloro-2-nitrophenyl	B	K
	K	4-chloro-2,6-dinitrophenyl	B	K
	K	6-chloro-2,4-dinitrophenyl	B	K
	K	3-fluoro-4-nitrophenyl	B	K
	Na	3-chloro-4-fluoro-6-nitrophenyl	B	K
	Na	2-bromo-6-fluoro-4-nitrophenyl	E	K
	Na	2,4-dibromo-3-fluoro-6-nitrophenyl	E	K

R ₂	Method	M
4-chloro-5-fluoro-2-nitrophenyl	E	K
4-acetyl-2-fluoro-5-nitrophenyl	E	K
2-acetyl-6-bromo-4-fluorophenyl	E	K
2-fluoro-4-propionylphenyl	E	K
2-fluoro-4-butyrylphenyl	E	K
3,4-dicarbomethoxy-2,5,6-tribromophenyl	B	K
2-acetyl-4-chlorophenyl	B	K
4-acetyl-2-chlorophenyl	B	K
4-acetyl-2-bromophenyl	B	K
2-acetyl-3,5-dichlorophenyl	A	Na
2-acetyl-6-chloro-4-methylphenyl	A	Na
4-chloro-2-propionylphenyl	A	Na
2-acetyl-6-dimethylaminophenyl	F-1	K
4-dimethylamino-2-methylphenyl	F-1	K
4-carbomethoxy-2-dimethylaminophenyl	F-1	K
2-carbomethoxy-5-dimethylaminophenyl	F-1	K
4- <i>t</i> -butyl-3-nitrophenyl	B	Na
2-methyl-4-nitro-5-isopropylphenyl	B	Na
2-methyl-6-nitro-5-isopropylphenyl	B	Na
6-nitro-1,2,3,4-tetramethylphenyl	B	Na
2-methoxy-5-nitro-4-propylphenyl	B	Na
2-nitro-3,4,5-trimethylphenyl	B	Na
2-ethyl-6-methyl-4-nitrophenyl	B	Na
4-chloro-5-fluoro-2-nitrophenyl	B	Na
2,3-dimethoxyphenyl	A	Na
2,6-dimethoxyphenyl	A	Na
3,4-dimethoxy-4-methylphenyl	A	Na
3,5-dimethoxy-2-methylphenyl	A	Na
2,5-dimethoxy-4-propylphenyl	A	Na

Method	M	R ₂	Method	M
E	K	3,5-diethoxy-2,6-dimethylphenyl	A	Na
E	K	3,4,5-trimethoxyphenyl	A	Na
E	K	m-acetylphenyl	B	K
E	K	o-propionylphenyl	B	K
E	K	p-propionylphenyl	B	K
E	K	3-carbomethoxy-5-methoxyphenyl	B	K
E	K	2-carbomethoxy-4-methoxyphenyl	B	K
E	K	2-carbomethoxy-6-methoxyphenyl	B	K
E	K	2,5-dicarbomethoxyphenyl	B	K
E	Na	3,4-dicarbomethoxyphenyl	B	K
E	Na	3,4-dicarbomethoxyphenyl	B	K
E	Na	2,3-dicarbomethoxyphenyl	B	K
-1	K	2,6-dicarbomethoxyphenyl	B	K
-1	K	2,4-dicarbomethoxyphenyl	B	K
-1	K	3,5-dicarbomethoxyphenyl	B	K
1	K	2,4-dicarbomethoxy-3,5-dimethylphenyl	B	K
	Na	2-carbomethoxy-3-methoxy-5-methylphenyl	E	K
	Na	4-carbomethoxy-2,6-dichlorophenyl	E	K
	Na	2-carbomethoxy-3,5-dimethoxy-4,6-dimethylphenyl	E	K
	Na	4-carbomethoxy-2,6-dimethoxyphenyl	E	K
	Na	2-bromo-4-carbomethoxy-6-methoxyphenyl	E	K
	Na	4-carbomethoxy-2-methoxy-3-nitrophenyl	E	K
	Na	5-carbomethoxy-2-methoxy-3-nitrophenyl	E	K
	Na	3-carbomethoxy-2,4-dinitro-6-methoxyphenyl	E	K
	Na	4-indanyl	A	Na
	Na	5-indanyl	A	Na
	Na	5-methyl-4-indanyl	A	Na
	Na	1-methyl-4-indanyl	A	Na
	Na	6-methyl-4-indanyl	A	Na

R ₂	Method	M
7-methyl-4-indanyl	A	Na
3-methyl-4-indanyl	A	Na
1-methyl-5-indanyl	A	Na
2-methyl-5-indanyl	A	Na
7-methyl-5-indanyl	A	Na
6-t-butyl-5-indanyl	A	Na
4,6-dimethyl-5-indanyl	C	Na
1,1-dimethyl-4-indanyl	C	Na
1,1,2-trimethyl-4-indanyl	C	Na
1,1,2-triethyl-4-indanyl	B	K
1,1,2,3-tetramethyl-4-indanyl	B	K
1,1,5,6-tetramethyl-4-indanyl	B	K
5,7-dimethyl-4-indanyl	B	K
5-chloro-4-indanyl	A	Na
7-chloro-4-indanyl	A	Na
7-bromo-4-indanyl	A	Na
6-chloro-5-indanyl	A	Na
1,7-dimethyl-4-indanyl	B	K
1,1,7-trimethyl-4-indanyl	B	K
4-(1-indanyl)phenyl	B	K
2,4-(dicyclopent-2-enyl)phenyl	B	K
4-(α -dimethylbenzyl)phenyl	B	K
1-naphthyl	B	Na
2-naphthyl	B	Na
1(5,6,7,8-tetrahydronaphthyl	B	Na
2-(5,6,7,8-tetrahydronaphthyl)	B	Na
3-(2-methyl-4-pyronyl)	B	Na
3-quinolyl	F-1	K
4-quinolyl	F-1	K

Method	M
A	Na
A	Na
A	Na
A	Na
A	Na
A	Na
C	Na
C	Na
C	Na
B	K
B	K
B	K
B	K
A	Na
A	Na
A	Na
A	Na
B	K
B	K
B	K
3	K
3	K
1	Na
	Na
	Na
	Na
	Na
-1	K
-1	K

R ₂	Method	M
5-quinolyl	F-1	K
6-quinolyl	F-1	K
7-quinolyl	F-1	K
8-quinolyl	F-1	K
5-(1,4-naphthoquinonyl)	B	Na
6-(1,4-naphthoquinonyl)	B	Na
4-(coumarinyl)	C	K
5-(coumarinyl)	C	K
6-(coumarinyl)	C	K
3-thianaphthenyl	B	Na
4-thianaphthenyl	B	Na
1-phenazinyl	F-1	K
2-phenazinyl	F-1	K
2-(anthraquinonyl)	B	Na
4-(6-methylquinolyl)	F-1	K
2-(4-methylquinolyl)	F-1	K
1-fluorocetyl	A	Na
2-fluorenyl	A	Na
6-1,2-naphthoquinonyl)	B	Na
7-(1,2-naphthoquinolyl)	B	Na
1-anthraquinonyl	B	Na
7-isoquinolyl	F-1	K
8-isoquinolyl	F-1	K
4-(1,3-benzodioxolyl)	B	K
5-(1,3-benzodioxolyl)	B	K
3-(4-pyranyl)	B	K
1-(3-methyl-5,6,7,8-tetrahydronaphthyl)	C	Na
1-(4-methyl-5,6,7,8-tetrahydronaphthyl)	C	Na
2-(1-methyl-5,6,7,8-tetrahydronaphthyl)	C	Na

R ₂	Method	M
2-(3-methyl-5,6,7,8-tetrahydronaphthyl)	C	Na
2-(4-methyl-5,6,7,8-tetrahydronaphthyl)	C	Na
2-(5-methyl-5,6,7,8-tetrahydronaphthyl)	C	Na
1-(4,4-dimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
1-(4,8-dimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
2-(1,6-dimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
1-(2,4,6-trimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
1-(2,4,7-trimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
1-(3,4,6-trimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
2-(1,5,6-trimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
2-(3,4,6-trimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
2-(3,4,7-trimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
2-(1,4,7-trimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
1-(1,2,4-triethyl-5,6,7,8-tetrahydronaphthyl)	E	K
2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthyl)	E	K
3-bromo-2-propionylphenyl	E	K
4-bromo-2-butyryl-3,5-dimethylphenyl	B	K
2-isopropyl-4-isobutyryl-5-methylphenyl	B	Na
2-chloro-6-isopropyl-3-methyl-4-nitrophenyl	B	Na
2-acetyl-5-dimethylaminophenyl	F-1	Na
2-carbomethoxy-5-methoxy-4-nitrophenyl	B	K
2-furyl	E	Na
3-furyl	B	K
3-carbomethoxy-2,4,6-trinitrophenyl	B	K
2-(1,4-naphthoquinonyl)	B	K
2-dimethylaminoethyl	F-1	K
2-dibutylaminoethyl	F-1	K,
2-diisopropylaminoethyl	F-1	K
2-di(n-propyl)aminoethyl	F-1	K

R ₂	Method	M
3-aziridinopropyl	C	K
3-di-(n-propyl)amino-2-propyl	F-1	K
2-diethylamino-1-propyl	F-1	K
3-pyrrolidino-2-propyl	F-1	K
3-piperidino-2-propyl	F-1	K
3-diethylamino-2-propyl	F-1	K
3-morpholino-2-propyl	F-1	K
3-di-(n-butyl)amino-2-propyl	F-1	K
3-dimethylamino-2-propyl	F-1	K
2-pyrrolidino-1-propyl	F-1	K
2-di(n-butyl)amino-1-propyl	F-1	K
2-thiomorpholino-1-propyl	F-1	K
2-(2-imidazolino)-1-propyl	F-1	K
3-(1,4,5,6-tetrahydropyrimidino)-2-propyl	F-1	K
2-acetamidoethyl	B	K
2-butyramidoethyl	B	K
3-propionamidopropyl	B	K
3-acetamido-2-propyl	B	K
2-acetamido-1-propyl	B	K
2-(methylethylamino)ethyl	B	K
2-(methylbutylamino)ethyl	B	K
2-(ethylisopropylamino)ethyl	B	K
2-ethylbutylamino)ethyl	B	K
3-methylpropylamino)propyl	B	K
3-ethylisopropylamino)propyl	B	K
3-(methylethylamino)-2-propyl	B	K
3-(ethylbutylamino)-2-propyl	B	K
2-methyl(ethylamino)-1-propyl	B	K
2-(methylbutylamino)-1-propyl	B	K

R ₁	Method	M
azetidinomethyl	F—1	K
2-pyridylmethyl	B	Na
4-pyridylmethyl	B	Na
4-imidazolylmethyl	B	Na
2-(N-phenylimidazolyl)methyl	B	Na
phthalimidomethyl	B	Na
3-(N-methyl)pyridyl	F—1	K
4-(N-methyl)pyridyl	F—1	K
allyl	A	Na
crotyl	A	Na
3-buten-1-yl	A	Na
3-penten-1-yl	A	Na
4-penten-1-yl	A	Na
3-penten-2-yl	B	K
1-penten-5-yl	B	K
2-methyl-3-buten-1-yl	B	K
3-methyl-1-buten-3-yl	B	K
5-hexen-2-yl	B	K
1-hexen-3-yl	B	K
4-hexen-1-yl	B	K
1-hexen-4-yl	B	K
2-hexen-1-yl	B	K
2-hexen-4-yl	B	K
3-hexen-2-yl	C	Na
3-hexen-1-yl	C	Na
2-methyl-3-penten-2-yl	C	Na
4-methyl-3-penten-2-yl	C	Na
2-methyl-4-penten-2-yl	D	K
4-methyl-4-penten-2-yl	D	K

10d M
 -1 K
 Na
 Na
 Na
 Na
 Na
 1 K
 1 K
 Na
 Na
 Na
 Na
 Na
 K
 K
 K
 K
 K
 K
 K
 K
 Na
 Na
 Na
 Na
 K
 K

R ₂	Method	M
2,2-dimethyl-3-buten-1-yl	D	K
2-hepten-1-yl	D	K
4-hepten-1-yl	B	Na
6-hepten-1-yl	B	Na
1-hepten-4-yl	B	Na
2-hepten-4-yl	B	Na
2-methyl-3-hexen-2-yl	B	Na
2-methyl-4-hexen-2-yl	B	Na
2-methyl-4-hexen-6-yl	B	Na
2-methyl-5-hexen-2-yl	E	K
2-methyl-5-hexen-3-yl	F	Na
2-methyl-5-hexen-4-yl	F	Na
3-methyl-2-hexen-4-yl	F	Na
3-methyl-3-hexen-2-yl	F	Na
3-methyl-4-hexen-3-yl	F	Na
3-methyl-5-hexen-3-yl	F-1	Na
2,2-dimethyl-3-penten-1-yl	F-1	Na
2,3-dimethyl-2-penten-4-yl	F-1	Na
2,4-dimethyl-1-penten-3-yl	F-1	Na
2,4-dimethyl-1-penten-4-yl	F-1	Na
2,4-dimethyl-2-penten-4-yl	B	Na
2,2,3-trimethyl-3-buten-1-yl	B	Na
2-octen-1-yl	B	Na
4-octen-1-yl	B	Na
1-octen-3-yl	B	Na
propargyl	A	Na
1-butyne-3-yl	A	Na
1-butyne-4-yl	A	Na
2-butyne-1-yl	A	Na

R ₁	Method	M
1-pentyn-3-yl	A	Na
2-methyl-3-butyn-1-yl	A	Na
3-methyl-1-pentyn-3-yl	B	Na
2-hexyn-1-yl	B	Na
1-hexyn-3-yl	B	Na
2,3-dimethyl-4-pentyn-3-yl	B	Na
5-methyl-3-hexyn-2-yl	B	Na
3-methyl-3-hexyn-3-yl	B	Na
3-ethyl-1-pentyn-3-yl	B	Na
2-methyl-3-hexyn-2-yl	C	Na
3-methyl-1-heptyn-3-yl	C	Na
2,4-dimethyl-5-hexyn-3-yl	C	Na
2,2,3-trimethyl-4-pentyn-3-yl	C	Na
3-octyn-1-yl	C	Na
2-octyn-1-yl	C	Na
3-octyn-2-yl	C	Na
benzyl	A	Na
o-chlorobenzyl	A	Na
m-chlorobenzyl	A	Na
p-bromobenzyl	A	Na
m-methylbenzyl	B	Na
p-ethylbenzyl	B	Na
o-nitrobenzyl	C	K
m-nitrobenzyl	C	K
o-methoxybenzyl	C	K
p-ethoxybenzyl	C	K
m-acetylbenzyl	B	K
p-butyrylbenzyl	B	K
o-carbomethoxybenzyl	B	Na

R ₁	Method	M
o-n-propylphenyl	B	K
o-isopropylphenyl	B	K
p-isopropylphenyl	B	K
p-butylphenyl	B	K
p-t-butylphenyl	B	K
p-sec-butylphenyl	B	K
2,5-dimethylphenyl	B	K
3,5-dimethylphenyl	B	K
2,5-diethylphenyl	B	K
3-methyl-5-ethylphenyl	B	K
2-methyl-5-isopropylphenyl	B	K
4-t-butyl-2-isopropylphenyl	B	K
o-chlorophenyl	B	Na
m-chlorophenyl	B	Na
p-chlorophenyl	B	Na
o-bromophenyl	B	Na
m-bromophenyl	B	Na
p-bromophenyl	B	Na
m-fluorophenyl	B	Na
p-fluorophenyl	B	Na
2,4-dichlorophenyl	A	Na
2,5-dichlorophenyl	A	Na
3,4-dichlorophenyl	A	Na
4-bromo-3-chlorophenyl	A	Na
2,3,5-trichlorophenyl	A	Na
2,4,5-trichlorophenyl	A	Na
2,4-dibromophenyl	A	Na
2,5-dibromophenyl	A	Na
2,4,5-tribromophenyl	A	Na

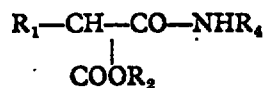
d	M	R ₇	Method	M
	K	4-chloro-2-methylphenyl	B	Na
	K	5-chloro-2-methylphenyl	B	Na
	K	6-chloro-3-methylphenyl	B	Na
	K	4-chloro-3-methylphenyl	B	Na
		3-chloro-4-methylphenyl	B	Na
	K	6-chloro-3-isopropylphenyl	B	Na
	K	4-bromo-3-methylphenyl	B	Na
	K	2-bromo-4-methylphenyl	B	Na
	K	5-bromo-2-methylphenyl	B	Na
	K	2-chloro-3,5-dimethylphenyl	B	K
	K	4-chloro-2,5-dimethylphenyl	B	K
	K	5-chloro-2,4-dimethylphenyl	B	K
	Na	4,6-dichloro-3-dimethylphenyl	A	Na
	Na	2,4-dichloro-3-dimethylphenyl	A	Na
		2,4-difluorophenyl	A	Na
	Na	o-trifluoromethylphenyl	A	Na
	Na	m-trifluoromethylphenyl	A	Na
	Na	p-trifluoromethylphenyl	A	Na
	Na	m-methoxyphenyl	C	Na
	Na	p-methoxyphenyl	C	Na
	Na	o-ethoxyphenyl	C	Na
	Na	m-ethoxyphenyl	C	Na
	Na	p-ethoxyphenyl	C	Na
	Na	p-propoxyphenyl	C	Na
	Na	p-butoxyphenyl	C	Na
	Na	p-isobutoxyphenyl	C	Na
	Na	2-methoxy-4-methylphenyl	C	Na
	Na	2-methoxy-3-methylphenyl	C	Na
	Na	3-methoxy-2-methylphenyl	C	Na

R ₇	Method	M
3-methoxy-4-methylphenyl	C	Na
4-methoxy-2-methylphenyl	C	Na
4-methoxy-3-methylphenyl	C	Na
5-methoxy-2-methylphenyl	C	Na
5-methoxy-3-methylphenyl	C	Na
6-methoxy-3-methylphenyl	C	Na
3-t-butyl-4-methoxyphenyl	B	K
5-ethyl-2-methoxyphenyl	B	K
4-methoxy-3,5-dimethylphenyl	B	K
2,5-dimethoxyphenyl	F	H
3,4-dimethoxyphenyl	F	H
3,4-di-isopropoxyphenyl	F	H
4-methoxy-2,5-dipropylphenyl	F-1	K
4-methoxy-3,5-dipropylphenyl	F-1	K
4-methoxy-3,5-di-isopropoxyphenyl	F-1	K
2-chloro-4-methoxyphenyl	A	Na
4-chloro-3-methoxyphenyl	A	Na
2-bromo-5-methoxyphenyl	A	Na
3-bromo-4-methoxyphenyl	A	Na
4-bromo-3-methoxyphenyl	A	Na
5-bromo-2-methoxyphenyl	A	Na
4-butoxy-2-chlorophenyl	E	Na
5,2-dichloro-4-methoxyphenyl	B	K
3-ethyl-4-methoxyphenyl	B	K

R₄ = penicillanic acid residue.

EXAMPLE II

The following penicillins are prepared by the procedures of Example I from the appropriate aryl halo carbonyl ketenes.



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	Method	M
methyl	A	Na
ethyl	A	Na
n-butyl	A	Na
t-butyl	A	Na
hexyl	B	Na
decyl	D	K
tetradecyl	B	Na
octadecyl	D	K
2-chloroethyl	A	Na
3-chloropropyl	A	Na
1-methyl-2-chloroethyl	A	Na
2-chloro-1-butyl	A	Na
4-chloro-1-butyl	A	Na
1-ethyl-2-chloroethyl	A	Na
1-methyl-3-chloropropyl	A	Na
1,1-dimethyl-2-chloroethyl	A	Na
2-bromoethyl	B	K
3-bromopropyl	B	K
1-methyl-2-bromoethyl	B	K
1-ethyl-2-bromoethyl	B	K
1,3-dichloropropyl	A	Na
1,1-dichloromethylethyl	A	Na
2-bromo-3-chloropropyl	A	Na
1,4-dibromo-2-butyl	A	Na

R ₂	Method	M
3,4-dichloro-2-butyl	A	A
1-bromomethyl-2-chloroethyl	A	Na
1,1-dimethyl-2,2-dichloroethyl	A	Na
2,2,3-tribromopropyl	A	Na
2,2,3-trichlorobutyl	A	Na
2,2,3,3-tetrabromopropyl	A	Na
2,2,2-trichloroethyl	A	Na
2,2,2-trifluoroethyl	A	Na
3,3,3-trifluoropropyl	A	Na
2-nitroethyl	B	K
3-nitropropyl	B	K
2-nitrobutyl	B	K
4-nitrobutyl	B	K
2,2-dinitroethyl	C	Na
1-ethyl-2,2-dinitroethyl	C	Na
2-chloro-2-nitropropyl	B	Na
3-methyl-3-nitropropyl	B	Na
2-chloro-2-nitrobutyl	B	Na
1-trichloromethyl-2-nitroethyl	B	Na
1-trifluoromethylethyl	A	Na
1,1-dimethyl-2,2,2-trifluoroethyl	A	Na
1,1-dimethyl-2,2,2-trichloroethyl	A	Na
2-methoxyethyl	F-1	K
2-n-butoxyethyl	F-1	K
3-methoxypropyl	F-1	K
3-sec-butoxypropyl	F-1	K
4-methoxy-n-butyl	F-1	K
1,1-dimethyl-2-methoxyethyl	F-1	K
2-cyanoethyl	E	K

Method	M	R ₂	Method	M
A	A	4-cyanobutyl	E	K
A	Na	1-cyano-2-chloropropyl	B	K
A	Na	1-cyano-2,2-dichloropropyl	B	K
A	Na	1-cyano-2,2,2-trichloroethyl	B	K
	Na	1-methyl-1-(1'-cyano-1'-methlethoxy)ethyl	B	K
A	Na	2-acetoxyethyl	B	Na
A	Na	2-butyryloxyethyl	B	Na
A	Na	3-acetoxypropyl	B	Na
B	K	2-acetoxy-n-butyl	B	Na
B	K	1-methyl-2-acetoxyethyl	B	Na
B	K	carbomethoxymethyl	B	Na
B	K	carbobutoxymethyl	B	Na
C	Na	3-carbobutoxypropyl	B	Na
C	Na	4-carbethoxybutyl	C	Na
B	Na	2-carbethoxypropyl	C	Na
B	Na	1-carbethoxypropyl	C	Na
B	Na	1-trichloromethyl-2-carbomethoxyethyl	B	K
B	Na	1-carbethoxy-2-chloropropyl	B	K
A	Na	1-carbethoxy-2,2-dichloropropyl	B	K
A	Na	1-carbomethoxy-2,2,2-trichloroethyl	B	K
A	Na	1-carbomethoxy-2-chloroethyl	B	K
5-1	K	1-carbomethoxymethyl-2,2,2-trichloroethyl	B	K
1-1	K	acetonyl	E	Na
1-1	K	1-methyl-3-oxobutyl	E	Na
1-1	K	4-oxopentyl	E	Na
1-1	K	1,1-dimethylacetonyl	E	Na
1-1	K	1-ethyl-2-oxobutyl	E	Na
1-1	K	1-acetyl-1-methylpropyl	B	Na
K		1,2-dimethyl-3-oxobutyl	B	Na

R ₂	Method	M
2-methyl-3-oxopentyl	B	Na
1-acetylbutyl	B	Na
1-methyl-3-oxohexyl	B	Na
2-acetylpropyl	B	Na
3-oxopentyl	B	Na
4-oxohexyl	B	Na
5-oxohexyl	B	Na
1-methoxy-2,2,2-trichloroethyl	A	Na
1-ethoxy-2,2,2-trichloroethyl	A	Na
1-butoxy-2,2,2-trichloroethyl	A	Na
1-methoxy-2,2,2-trifluoroethyl	A	Na
1-ethoxy-2,2,2-trifluoroethyl	A	Na
2,3-diacetoxypropyl	B	K
2,3-dicapryloxypropyl	B	K
2,3-distearoyloxypropyl	B	K
(1,2,3-tricarbomethoxy)-2-propyl	B	K
(1,2,3-tricarbobutoxy)-2-propyl	B	K
2-chloro-3,3-dimethoxypropyl	B	K
3,3-diethoxypropyl	B	K
2-oxo-3-chloropropyl	B	Na
1-trichloromethyl-3-oxobutyl	B	K
2-fluoroethyl	A	Na
3-fluoropropyl	A	Na
1-trichloromethyl-2,3,3,3-tetrachloropropyl	A	Na
4,4,4-trifluorobutyl	A	Na
1-methoxy-2-chloro-2,2-difluoroethyl	A	Na
phenyl	B	Na
o-tolyl	B	Na
m-tolyl	B	Na

d	M	R ₂	Method	M
	Na	p-tolyl	B	Na
	Na	o-ethylphenyl	B	Na
	Na	p-n-propylphenyl	B	Na
	Na	o-isopropylphenyl	B	Na
	Na	p-t-butylphenyl	B	Na
	Na	o-methoxyphenyl	B	Na
	Na	p-methoxyphenyl	B	Na
	Na	m-ethoxyphenyl	B	Na
	Na	p-n-butoxyphenyl	B	Na
	Na	o-chlorophenyl	A	Na
	Na	m-chlorophenyl	A	Na
	Na	p-chlorophenyl	A	Na
K		m-bromophenyl	A	Na
K		m-fluorophenyl	A	Na
		p-fluorophenyl	A	Na
K		o-formylphenyl	A	Na
K		m-formylphenyl	A	Na
K		p-acetylphenyl	A	Na
K		p-butyrylphenyl	A	Na
Na		o-nitrophenyl	C	K
K		m-nitrophenyl	C	K
Na		m-carbomethoxyphenyl	C	Na
Na		p-carbomethoxyphenyl	C	Na
Na		o-carbomethoxyphenyl	C	Na
Na		p-carbo-n-propoxyphenyl	C	Na
Na		o-dimethylaminophenyl	F-1	K
Na		o-di-n-butylaminophenyl	F-1	K
Na		m-di-n-propylaminophenyl	F-1	K
Na		p-methylethylaminophenyl	F-1	K

R ₂	Method	M
p-methylisopropylaminophenyl	F-1	K
2,3-dimethylphenyl	D	K
2,6-dimethylphenyl	D	K
2,5-diethylphenyl	D	K
2,4-di-n-propylphenyl	D	K
5-ethyl-3-methylphenyl	D	K
4-isopropyl-3-methylphenyl	D	K
3-methyl-4-t-butylphenyl	B	Na
2,4,6-trimethylphenyl	B	Na
4,5-dimethyl-2-isopropylphenyl	B	Na
2,4-dimethyl-3-ethylphenyl	B	Na
2,3,4,6-tetramethylphenyl	B	Na
4-butyl-5-isopropyl-3-methylphenyl	B	Na
pentamethylphenyl	B	Na
2,6-dichlorophenyl	A	Na
2,4-dibromophenyl	A	Na
2,3,4-trichlorophenyl	A	Na
2,4,6-tribromophenyl	A	Na
2,3,5,6-tetrachlorophenyl	A	Na
pentachlorophenyl	A	Na
pentabromophenyl	A	Na
3,5-dinitrophenyl	C	Na
2,3,6-trinitrophenyl	C	Na
2,3,4,6-tetranitrophenyl	C	Na
pentanitrophenyl	C	Na
2,3,5-trifluorophenyl	A	Na
2,3,5,6-tetrafluorophenyl	A	Na
pentafluorophenyl	A	Na
2-chloro-5-fluorophenyl	A	Na

M	R ₂	Method	M
K	2-bromo-3-fluorophenyl	A	Na
K	2,4-dichloro-3-fluorophenyl	A	Na
	4-bromo-3,5-difluorophenyl	A	Na
	2-bromo-3,5-dichloro-4-fluorophenyl	A	Na
K	3-fluoro-2,4,6-trichlorophenyl	A	Na
K	2-methoxy-4-methylphenyl	A	Na
K	5-bromo-2-methoxyphenyl	A	Na
Na	2-chloro-6-methoxyphenyl	A	Na
Na	2-ethoxy-3-methylphenyl	B	K
Na	2-methoxy-6-propylphenyl	B	K
Na	2-carbomethoxy-5-fluorophenyl	B	K
Na	5-fluoro-2-methoxyphenyl	B	K
Na	2-acetyl-4-fluorophenyl	B	K
	6-chloro-2-methylphenyl	B	Na
Na	2-chloro-5-methylphenyl	B	Na
Na	2-fluoro-4-methylphenyl	B	Na
Na	2-bromo-4- <i>t</i> -butylphenyl	B	Na
Na	2-chloro-4-isopropylphenyl	B	Na
Na	2-ethyl-4-fluorophenyl	B	Na
Na	2-isobutyl-4-fluorophenyl	B	Na
Na	5-bromo-2,3-dimethylphenyl	B	K
Na	4-chloro-2,3-dimethylphenyl	B	K
Na	5-chloro-2,4-dimethylphenyl	B	K
Na	4-chloro-6-isopropyl-3-methylphenyl	B	Na
Na	4-bromo-3-isopropyl-6-methylphenyl	B	K
Na	4-chloro-2,3-diethylphenyl	B	K
Na	4,6-dibromo-2-methylphenyl	B	K
Na	2,4-dichloro-3,5-dimethylphenyl	B	K
Na	4-chloro-2,3,5-trimethylphenyl	B	K

R ₂	Method	M
4-chloro-2-nitrophenyl	B	K
4-chloro-2,3-dinitro-6-methylphenyl	E	K
3-fluoro-4-nitrophenyl	B	K
3-chloro-4-fluoro-6-nitrophenyl	B	K
6-bromo-4-fluoro-2-nitrophenyl	E	K
2,6-dibromo-3-fluoro-6-nitrophenyl	E	K
4-chloro-5-fluoro-2-nitrophenyl	E	K
4-acetyl-2-fluoro-5-nitrophenyl	E	K
2-acetyl-6-bromo-4-fluorophenyl	E	K
2-fluoro-4-butyrylphenyl	E	K
5-(1,3-benzodioxolyl)	B	K
3,4-dicarbomethoxy-2,5,6-tribromophenyl	B	K
2-acetyl-4-chlorophenyl	B	K
4-acetyl-2-bromophenyl	B	K
2-acetyl-3,5-dichlorophenyl	A	Na
2-acetyl-6-chloro-4-methylphenyl	A	Na
4-chloro-2-propionylphenyl	A	Na
2-acetyl-6-dimethylaminophenyl	F-1	K
4-dimethylamino-2-methylphenyl	F-1	K
4-carbomethoxy-2-dimethylaminophenyl	F-1	K
2-carbomethoxy-5-dimethylaminophenyl	F-1	K
4-t-butyl-3-nitrophenyl	B	Na
2-methyl-4-nitro-5-isopropylphenyl	B	Na
6-nitro-1,2,3,4-tetramethylphenyl	B	Na
2-methoxy-5-nitro-4-propylphenyl	B	Na
2,6-dimethoxyphenyl	A	Na
3,4-dimethoxy-4-methylphenyl	A	Na
3,5-dimethoxy-2,6-dimethylphenyl	A	Na
3,4,5-trimethoxyphenyl	A	Na

Method	M	R ₂	Method	M
B	K	m-acetylphenyl	B	K
E	K	o-propionylphenyl	B	K
B	K	3-carbomethoxy-5-methoxyphenyl	B ₁	K
B	K	2-carbomethoxy-6-methoxyphenyl	B	K
	K	2,5-dicarbomethoxyphenyl	B	K
E	K	3,4-dicarbomethoxyphenyl	B	K
E	K	2,6-dicarbomethoxyphenyl	B	K
E	K	2,4-dicarbomethoxy-3,5-dimethylphenyl	B	K
E	K	4-carbomethoxy-2,5-dimethyl-4-methoxyphenyl	E	K
E	K	2-carbomethoxy-6-methoxy-4-methylphenyl	E	K
B	K	4-carbomethoxy-2,6-dichlorophenyl	E	K
B	K	2-carbomethoxy-3,5-dimethoxy-4,6-dimethylphenyl	E	K
B	K	5-carbomethoxy-2,3-dimethoxyphenyl	E	K
B	K	2-bromo-4-carbomethoxy-6-methoxyphenyl	E	K
A	Na	4-carbomethoxy-2-methoxy-3-nitrophenyl	E	K
A	Na	3-carbomethoxy-2,4-dinitro-6-methoxyphenyl	E	K
A	Na	4-indanyl	A	Na
F-1	K	5-indanyl	A	Na
F-1	K	5-methyl-4-indanyl	A	Na
F-1	K	1-methyl-4-indanyl	A	Na
F-1	K	7-methyl-4-indanyl	A	Na
3	Na	3-methyl-4-indanyl	A	Na
3	Na	1-methyl-5-indanyl	A	Na
1	Na	6-methyl-5-indanyl	A	Na
1	Na	6-t-butyl-5-indanyl	A	Na
	Na	4,6-dimethyl-5-indanyl	C	Na
	Na	1,1-dimethyl-4-indanyl	C	Na
	Na	1,1,2-trimethyl-4-indanyl	C	Na
	Na	1,1,2-triethyl-4-indanyl	B	K

R ₂	Method	M
1,1,2,3-tetramethyl-4-indanyl	B	K
1,1,5,6-tetramethyl-4-indanyl	B	K
5-chloro-4-indanyl	A	Na
7-bromo-4-indanyl	A	Na
6-chloro-5-indanyl	A	Na
1,1,7-trimethyl-4-indanyl	B	Na
(4-(1-indanyl)phenyl	B	Na
1-naphthyl	B	Na
2-naphthyl	B	Na
1-(5,6,7,8-tetrahydronaphthyl)	B	Na
2-(5,6,7,8-tetrahydronaphthyl)	B	Na
3-(2-methyl-4-pyronyl	B	Na
4-quinolyl	F-1	K
6-quinolyl	F-1	K
8-quinolyl	F-1	K
5-(1,4-naphthoquinonyl)	B	Na
6-(1,4-naphthoquinonyl)	B	Na
4-(coumarinyl)	C	K
6-(coumarinyl)	C	K
3-thianaphthenyl	B	Na
1-phenazinyl	F-1	K
2-phenazinyl	F-1	K
2-(anthraquinonyl)	B	Na
4-(6-methylquinolyl)	F-1	K
1-fluorenyl	A	Na
2-fluorenyl	A	Na
6-(1,2-naphthoquinonyl)	B	Na
1-anthraquinonyl	B	Na
7-isoquinolyl	F-1	K

Method	M	R ₂	Method	M
B	K	8-naphthyl	F-1	K
3	K	5-(1,3-benzodioxolyl)	B	K
1	Na	3-(4-pyronyl)	B	K
1	Na	1-(3-methyl-5,6,7,8-tetrahydronaphthyl)	C	Na
1	Na	2-(1-methyl-5,6,7,8-tetrahydronaphthyl)	C	Na
	Na	2-(4-methyl-5,6,7,8-tetrahydronaphthyl)	C	Na
	Na	1-(4,8-dimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
	Na	2-(1,6-dimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
	Na	1-(2,4,6-trimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
	Na	1-(3,4,6-trimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
	Na	2-(1,5,6-trimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
	Na	2-(3,4,7-trimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
-1	K	1-(1,2,4-triethyl-5,6,7,8-tetrahydronaphthyl)	E	K
-1	K	2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthyl)	E	K
-1	K	4-bromo-2-carbomethoxy-5-methylphenyl	C	Na
	Na	2-chloro-4,5-dimethyl-6-nitrophenyl	B	Na
	Na	2-isobutyryl-4,6-dimethylphenyl	C	Na
	K	2-acetyl-5-dimethylaminophenyl	F-1	K
	K	2-furyl	E	Na
	Na	3-furyl	E	K
1	K	2-(1,4-naphthoquinonyl)	B	K
1	K	cyclopropyl	A	Na
	Na	cyclobutyl	A	Na
	K	cyclopentyl	A	Na
	Na	cyclohexyl	A	Na
	Na	cycloheptyl	A	Na
	Na	1-methyl-1-cyclopentyl	A	Na
	Na	2-methyl-1-cyclopentyl	A	Na
	K			

R_2	Method	M
3-methyl-1-cyclopentyl	A	Na
2,2-dimethyl-1-cyclopentyl	B	K
1,3-dimethyl-1-cyclopentyl	B	K
2,4-dimethyl-1-cyclopentyl	B	K
1,2,2-trimethyl-1-cyclopentyl	B	K
1,2,5-trimethyl-1-cyclopentyl	B	K
1,2,4-trimethyl-1-cyclopentyl	B	K
1-isopropyl-1-cyclopentyl	B	K
3-isopropyl-1-cyclopentyl	B	K
1-methyl-1-cyclohexyl	B	K
2-methyl-1-cyclohexyl	B	K
4-methyl-1-cyclohexyl	B	K
1-ethyl-1-cyclohexyl	B	K
1-isopropyl-1-cyclohexyl	B	K
3-isopropyl-1-cyclohexy.	B	K
4-t-butyl-1-cyclohexyl	B	K
2,2-dimethyl-1-cyclohexyl	B	K
1,2-dimethyl-1-cyclohexyl	B	K
1,3-dimethyl-1-cyclohexyl	C	Na
2,6-dimethyl-1-cyclohexyl	C	Na
3,5-dimethyl-1-cyclohexyl	C	Na
1,2,2-trimethyl-1-cyclohexyl	D	Na
2,2,6-trimethyl-1-cyclohexyl	D	Na
1,3,3-trimethyl-1-cyclohexyl	D	Na
2,2,5-trimethyl-1-cyclohexyl	E	Na
1,2,6-trimethyl-1-cyclohexyl	E	Na
1,3,5-trimethyl-1-cyclohexyl	E	Na
2-methyl-6-propyl-1-cyclohexyl	E	Na
1-propyl-3-methyl-1-cyclohexyl	E	Na

thod	M	R ₂	Method	M
1	Na	1,4-dimethyl-1-cyclohexyl	F	K
3	K	1-ethyl-2-methyl-1-cyclohexyl	F	K
1	K	2,2,6,6-tetramethyl-1-cyclohexyl	F-1	K
1	K	1,2,4,5-tetramethyl-1-cyclohexyl	F-1	K
1	K	1-methyl-1-cycloheptyl	F-1	K
1	K	1-(1,2,3,4-tetrahydronaphthyl)	F-1	K
1	K	3-methyl-1-indanyl	B	K
1	K	3-ethyl-1-indanyl	B	K
1	K	5-methyl-1-indanyl	B	K
1	K	7-methyl-1-indanyl	B	K
1	K	2,2-dimethyl-1-indanyl	B	K
1	K	2,3-diethyl-1-indanyl	B	K
1	K	3,3-dimethyl-1-indanyl	B	K
1	K	2-chloro-1-indanyl	A	Na
1	K	2-bromo-1-indanyl	A	Na
1	K	3-bromo-1-indanyl	A	Na
1	K	4-chloro-1-indanyl	A	Na
1	K	1-chloro-2-indanyl	A	Na
1	Na	9-fluorenyl	B	K
1	Na	2,3,4-trimethyl-1-cyclopentyl	B	K
1	Na	4,4-dimethyl-1-cyclohexyl	B	K
1	Na	1,4,5-trimethyl-1-cyclohexyl	B	K
1	Na	2-propyl-4-methyl-1-cyclohexyl	B	K
1	Na	2,6-diethyl-1-cyclohexyl	B	K
1	Na	2,4-dipropyl-1-cyclopentyl	B	K
1	Na	3-isobutyl-5-methyl-1-cyclohexyl	B	K
1	Na	2,2,3,6,6-pentamethyl-1-cyclohexyl	B	K
1	Na	1,5-dimethyl-2-isopropyl-1-cyclohexyl	B	K
1	Na	2-methyl-4-sec-butyl-1-cyclohexyl	B	K

R ₂	Method	M
1-(2-methyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(3-methyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(4-methyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(7-methyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(1,3-dimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(2,4-dimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(3,4-dimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(5,8-dimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(1,2,7-trimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(1,4,7-trimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(4,5,7-trimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(1,5,8-trimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
2-(1-methyl-1,2,3,4-tetrahydronaphthyl)	B	K
2-(6-methyl-1,2,3-tetrahydronaphthyl)	B	K
2-(2,6-dimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
2-(4,4-dimethyl-1,2,3,4-tetrahydronaphthyl)	B	K
2-(1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthyl)	B	K
2-(1,2,3,4-tetrahydronaphthyl)	F-1	K
1-indanyl	B	K
2-indanyl	B	K
2-methyl-1-indanyl	B	K
1-methyl-1-indanyl	B	K
2-methyl-2-indanyl	B	K
1-ethyl-1-indanyl	B	K
2-bicyclo-[4.4.0]-decyl	A	Na
3-bicyclo-[4.4.0]-decyl	A	Na
7-adamantanyl	A	Na
thujyl	B	K

Method	M	R ₂	Method	M
B	K	fenchyl	B	K
B	K	1-(methyl-1,2,3,4-tetrahydronaphthyl)	B	K
B	K	2-pyridylmethyl	B	Na
B	K	4-pyridylmethyl	B	Na
B	K	4-imidazolylmethyl	B	Na
B	K	2-(N-phenylimidazolyl)methyl	B	Na
B	K	phthalimidomethyl	B	Na
3	K	2-(N-methylanilino)ethyl	B	Na
3	K	2-dimethylaminoethyl	F-1	Na
1	K	2-dibutylaminoethyl	F-1	Na
	K	2-diisopropylaminoethyl	F-1	K
	K	3-diethylaminopropyl	F-1	Na
	K	2-(2-imidazolino)ethyl	F	H
	K	2-piperidinoethyl	F	H
	K	3-morpholinopropyl	F	H
	K	3-thiomorpholinopropyl	F-1	K
	K	2-pyrrolidinoethyl	F-1	K
-1	K	2-(2-imidazolino)ethyl	F-1	K
	K	2-pyrroloethyl	F-1	K
	K	2-(n-methyl)piperazinoethyl	F	H
	K	3-(N-butyl)piperazinopropyl	F	H
	K	2-(1,4,5,6-tetrahydropyrimidino)ethyl	F-1	K
	K	3-pyrrolopropyl	F-1	K
	K	3-imidazolopropyl	F-1	K
	Na	3-di-(n-propylamino)-2-propyl	F-1	K
	Na	2-diethylamino-1-propyl	F-1	K
	Na	3-pyrrolidino-2-propyl	F-1	K
	K	3-piperidino-2-propyl	F-1	K
		3-diethylamino-2-propyl	F-1	K

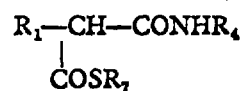
R ₂	Method	M
3-morpholino-2-propyl	F-1	K
3-di-(n-butyl)amino-2-propyl	F-1	K
3-dimethylamino-2-propyl	F-1	K
2-acetamidoethyl	B	K
3-butyramidopropyl	B	K
3-acetamido-2-propyl	B	K
2-acetamido-1-propyl	B	K
2-diethylaminoethyl	A	K
2-(methylethylamino)ethyl	A	K
2-(ethylbutylamino)ethyl	A	K
2-(methylisopropylamino)ethyl	B	K
3-(methylpropylamino)propyl	B	K
3-(ethylisopropylamino)propyl	B	K
2-aziridinoethyl	B	K
2-thiomorpholinoethyl	B	K
2-(4-methylpiperidino)ethyl	B	K
3-diisopropylaminopropyl	C	Na
3-piperidinopropyl	C	Na
3-pyrrolidinopropyl	C	Na
3-(1,4,5,6-tetrahydropyrimidino)propyl	C	Na
3-azetidinopropyl	B	K
3-(2,6-dimethylpiperidino)propyl	B	K
2-(N-ethylanilino)ethyl	F-1	K
3-(N-methylanilino)propyl	F-1	K
3-(methylethylamino)-2-propyl	C	Na
3-(ethylbutylamino)-2-propyl	C	Na
3-pyrrolo-2-propyl	D	K
3-(2-imidazolino)-2-propyl	D	K
3-imidazolo-2-propyl	D	K

Method	M	R ₂	Method	M
F-1	K	1-(1-methylamino-1-propyl)	D	K
F-1	K	1-(1-n-butylamino-1-propyl)	E	K
F-1	K	2-N-methylpiperazino-1-propyl	E	K
B	K	2-pyrrolo-1-propyl	E	K
	K	2-(2-imidazolino)-1-propyl	E	K
B	K	2-(2,5-dimethylpyrrolidino)-1-propyl	E	K
B	K	aziridinomethyl	E	K
A	K	piperidinomethyl	E	K
A	K	(2-imidazolino)methyl	E	K
A	K	N-ethylpiperazinomethyl	E	K
B	K	(4-methylpiperidino)methyl	E	K
B	K	pyrrolomethyl	E	K
B	K	3-(N-isopropylanilino)propyl	F-1	K
B	K	3-(N-methylanilino)-2-propyl	F-1	K
B	K	2-(N-methylanilino)-1-propyl	F-1	K
B	K	3-(N-methyl)pyridyl	F-1	K
C	Na	allyl	A	Na
C	Na	crotyl	A	Na
C	Na	3-buten-1-yl	A	Na
C	Na	3-penten-1-yl	A	Na
	K	1-penten-5-yl	B	K
	K	2-methyl-3-buten-1-yl	B	K
-1	K	5-hexen-2-yl	B	K
-1	K	4-hexen-1-yl	B	K
	Na	1-hexen-4-yl	B	K
	Na	3-hexen-2-yl	C	Na
	K	2-methyl-3-penten-2-yl	C	Na
	K	4-methyl-3-penten-2-yl	C	Na
	K	2,2-dimethyl-3-buten-1	D	K

R ₂	Method	M
2-hepten-1-yl	D	K
6-hepten-1-yl	B	Na
2-hepten-4-yl	B	Na
2-methyl-3-hexen-2-yl	B	Na
2-methyl-4-hexen-3-yl	B	Na
2-methyl-5-hexen-2-yl	E	K
2-methyl-5-hexen-4-yl	F	Na
3-methyl-2-hexen-4-yl	F	Na
3-methyl-5-hexen-3-yl	F-1	Na
2,2-dimethyl-3-penten-1-yl	F-1	Na
2,3-dimethyl-2-penten-4-yl	F-1	Na
2,4-dimethyl-2-penten-4-yl	B	Na
2,2,3-trimethyl-3-buten-1-yl	B	Na
2-octen-1-yl	B	Na
1-octen-3-yl	B	Na
propargyl	A	Na
1-butyne-3-yl	A	Na
2-butyne-1-yl	A	Na
1-pentyne-3-yl	A	Na
2-methyl-3-butyne-1-yl	A	Na
2-hexyn-1-yl	B	Na
1-hexyn-3-yl	B	Na
2-heptyne-1-yl	B	Na
2,3-dimethyl-4-pentyn-3-yl	B	Na
5-methyl-3-hexyn-2-yl	B	Na
3-ethyl-1-pentyne-3-yl	B	Na
3-methyl-1-heptyne-3-yl	C	Na
2,4-dimethyl-5-hexyn-3-yl	C	Na
2,2,3-trimethyl-4-pentyn-3-yl	C	Na

R ₂	Method	M
3-octyn-1-yl	C	Na
3-octyn-2-yl	C	Na
benzyl	A	Na
o-chlorobenzyl	A	Na
p-bromobenzyl	A	Na
m-Methylbenzyl	B	Na
p-ethylbenzyl	B	Na
o-nitrobenzyl	C	K
m-nitrobenzyl	C	K
o-methoxybenzyl	C	K
p-methoxybenzyl	C	K
p-butyrylbenzyl	B	K
o-carbomethoxybenzyl	B	Na
o-fluorobenzyl	A	Na
o-dimethylaminobenzyl	F-1	K
benzylhydryl	B	Na
trityl	B	Na
cholesteryl	B	Na
2-furylmethyl	D	Na
3-pyridylmethyl	F	H
[2,2-diethyl-1,3-dioxolon-4-yl]-methyl	B	Na
(2-pyrrolidono)methyl	B	Na
(4-imidazolyl)methyl	F-1	K
1-indanylmethyl	B	Na
phthalimidomethyl	F-1	K
(4-N-methyl)pyridyl	F-1	K

Substitution of R_2OH by R_7SH in this procedure produces the following penicillins:



R_7	Method	M
phenyl	A	Na
o-tolyl	A	Na
p-tolyl	A	Na
m-tolyl	B	K
p-tolyl	B	K
p-isopropylphenyl	B	K
p-t-butylphenyl	B	K
2,5-dimethylphenyl	B	K
2,5-diethylphenyl	B	K
2-methyl-5-isopropylphenyl	B	K
4-t-butyl-2-isopropylphenyl	B	K
o-chlorophenyl	B	Na
p-chlorophenyl	B	Na
m-bromophenyl	B	Na
p-fluorophenyl	B	Na
2,4-dichlorophenyl	A	Na
3,4-dichlorophenyl	A	Na
2,3,5-trichlorophenyl	A	Na
2,4-dibromophenyl	A	Na
2,4,5-tribromophenyl	A	Na
4-chloro-2-methylphenyl	B	Na
6-chloro-3-methylphenyl	B	Na
3-chloro-4-methylphenyl	B	Na
6-chloro-3-isopropylphenyl	B	Na
2-bromo-4-isopropylphenyl	B	Na
2-chloro-3,5-dimethylphenyl	B	Na
5-chloro-2,4-dimethylphenyl	B	Na

[illegible]

R ₇	Method ¹	M
4,6-dichloro-3-methylphenyl	A	Na
2,4-difluorophenyl	A	Na
m-trifluoromethylphenyl	A	Na
p-trifluoromethylphenyl	A	Na
m-methoxyphenyl	C	Na
p-methoxyphenyl	C	Na
o-ethoxyphenyl	C	Na
p-butoxyphenyl	C	Na
2-methoxy-4-methylphenyl	C	Na
3-methoxy-2-methylphenyl	C	Na
3-methoxy-4-methylphenyl	C	Na
5-methoxy-3-methylphenyl	C	Na
3-t-butyl-4-methoxyphenyl	B	K
4-methoxy-2,5-dimethylphenyl	B	K
2,5-dimethoxyphenyl	F	H
3,1-di-isopropoxyphenyl	F	H
4-methoxy-2,5-dirpropylphenyl	F-1	K
2-chloro-4-methoxyphenyl	A	Na
4-bromo-3-methoxyphenyl	A	Na
5-bromo-2-methoxyphenyl	A	Na
4-butoxy-2-chlorophenyl	E	Na
2,5-dichloro-4-ethoxyphenyl	B	K
3-ethyl-4-methoxyphenyl	B	K

EXAMPLE III

Other arylhalocarbonyl ketenes 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, are converted to penicillins by the methods of Example I. For convenience only the R_2 values are listed.

R_2	Method	M
methyl	A	Na
n-butyl	A	Na
decyl	D	K
tetradecyl	B	Na
2-chloroethyl	A	Na
3-chloropropyl	A	Na
3-chloro-1-butyl	A	Na
1-methyl-3-chloropropyl	A	Na
2,2-dimethyl-2-chloroethyl	A	Na
2-bromoethyl	B	K
3-bromopropyl	B	K
4-bromo-1-butyl	B	K
1,3-dichloropropyl	A	Na
2,3-dibromopropyl	A	Na
2-bromo-3-chloropropyl	A	Na
3,4-dichloro-1-butyl	A	Na
2,2-dichloroethyl	A	Na
2,3,3-tribromopropyl	A	Na
2,2,3-trichlorobutyl	A	Na
2,2,3,3-tetrabromopropyl	A	Na
2,2,2-trichloroethyl	A	Na
2,2,2-trifluoroethyl	A	Na
3,3,3-trifluoropropyl	A	Na
2-nitroethyl	B	K
3-nitropropyl	B	K
3-nitrobutyl	B	K
1-methyl-2-nitropropyl	B	K
2,2-dinitroethyl	C	Na

R ₂	Method	M
1-methyl-2,2-dinitroethyl	C	Na
2-bromo-2-nitroethyl	B	Na
2-chloro-2-nitropropyl	B	Na
1-methyl-2-bromo-2-nitroethyl	B	Na
2-chloro-2-nitrobutyl	B	Na
1-trichloromethyl-2-nitroethyl	B	Na
1-trifluoromethylethyl	A	Na
1,1-dimethyl-2,2,2-trifluoroethyl	A	Na
2-methoxyethyl	F-1	K
2-n-butoxyethyl	F-1	K
3-methoxypropyl	F-1	K
3-sec-butoxypropyl	F-1	K
4-ethoxy-n-butyl	F-1	K
1,1-dimethyl-2-methoxyethyl	F-1	K
2-cyanoethyl	E	K
3-cyanopropyl	E	K
1-cyano-2-chloropropyl	B	K
1-cyano-2,2-dichloropropyl	B	K
1-cyano-2,2,2-trichloroethyl	B	K
1-cyano-2,2,2-tribromoethyl	B	K
1-methyl-1-(1'-cyano-1'-methylethoxy)propyl	B	K
2-acetoxyethyl	B	Na
2-acetoxypentyl	B	Na
3-butyryloxypropyl	B	Na
4-propionyloxy-n-butyl	B	Na
carbobutoxymethyl	B	Na
2-carbethoxyethyl	B	Na
3-carbobutoxypropyl	B	Na
4-carbethoxybutyl	C	Na

R ₂	Method	M
2-carbethoxypropyl	C	Na
1-trichloromethyl-2-carbomethoxyethyl	B	K
1-carbethoxy-2-chloropropyl	B	K
1-carbethoxy-2,2-dichloropropyl	B	K
1-carbomethoxy-2,2,2-trichloroethyl	B	K
1-carbethoxy-2,2-dichloroethyl	B	K
1-carbomethoxymethyl-2,2,2-trichloroethyl	B	K
acetonyl	E	Na
2-oxopentyl	E	Na
2-methyl-3-oxobutyl	E	Na
1,1-dimethylacetonyl	E	Na
1-acetyl-1-methylpropyl	B	Na
2-methyl-3-oxopentyl	B	Na
1-acetonylbutyl	B	Na
1-ethyl-2-methyl-3-oxobutyl	B	Na
4-oxohexyl	B	Na
1-methoxy-2,2,2-trichloroethyl	A	Na
1-ethoxy-2,2,2-trichloroethyl	A	Na
1-methoxy-2,2,2-trifluoroethyl	A	Na
1-butoxy-2,2,2-trifluoroethyl	A	Na
2,3-diacetoxypropyl	B	K
2,3-dicapryloxypropyl	B	K
2,3-distearoyloxypropyl	B	K
(1,2,3-tricarboxmethoxy)-2-propyl	B	K
(1,2,3-tricarbobutoxy)-2-propyl	B	K
2-chloro-3,3-dimethoxypropyl	B	K
1-methyl-2,2-diethoxyethyl	B	K
2-oxo-3-chloropropyl	B	Na
1-trichloromethyl-3-oxobutyl	B	K

R ₂	Method	M
2-fluoroethyl	A	Na
1-nitro-1-trifluoromethyl-2,2,2-trifluoroethyl	A	Na
4,4,4-trifluorobutyl	A	Na
dicarbethoxyethoxymethyl	B	Na
1,1-dicarbethoxymethyl-2-ethoxyethyl	B	Na
carbethoxyethoxymethyl	B	Na
chlorodicarbomethoxymethyl	B	Na
bromodicarbomethoxymethyl	B	Na
1-isopropoxy-2,2,2-trichloroethyl	A	Na
1-t-butoxy-2,2,2-trichloroethyl	A	Na
dicarbomethoxyethoxymethyl	B	Na
phenyl	B	Na
o-tolyl	B	Na
p-tolyl	B	Na
m-ethylphenyl	B	Na
o-n-propylphenyl	B	Na
o-isopropylphenyl	B	Na
p-t-butylphenyl	B	Na
o-methoxyphenyl	B	Na
p-methoxyphenyl	B	Na
m-ethoxyphenyl	B	Na
p-n-butoxyphenyl	B	Na
o-chlorophenyl	A	Na
p-chlorophenyl	A	Na
m-bromophenyl	A	Na
p-fluorophenyl	A	Na
o-formylphenyl	A	Na
m-formylphenyl	A	Na

R_2	Method	M
o-acetylphenyl	A	Na
p-butyrylphenyl	A	Na
o-nitrophenyl	C	K
m-nitrophenyl	C	K
o-carbomethoxyphenyl	C	Na
m-carbomethoxyphenyl	C	Na
p-carbo-n-propoxyphenyl	C	Na
o-dimethylaminophenyl	F-1	K
o-diethylaminophenyl	F-1	K
o-di-n-butylaminophenyl	F-1	K
m-di-n-propylaminophenyl	F-1	K
p-methylethylaminophenyl	F-1	K
p-methylisopropylaminophenyl	F-1	K
2,3-dimethylphenyl	D	K
2,5-dimethylphenyl	D	K
2,3-diethylphenyl	D	K
2,4-di-n-propylphenyl	D	K
6-ethyl-2-methylphenyl	D	K
2-methyl-4-sec-butylphenyl	B	Na
3-methyl-4-t-butylphenyl	B	Na
2,3,4-trimethylphenyl	B	Na
2,6-dimethyl-4-ethylphenyl	B	Na
4,6-dimethyl-2-methylphenyl	B	Na
4,5-dimethyl-2-isopropylphenyl	B	Na
2,3,4,6-tetramethylphenyl	B	Na
4-butyl-5-isopropyl-2-methylphenyl	B	Na
pentamethylphenyl	B	Na
2,6-dichlorophenyl	A	Na
2,6-dibromophenyl	A	Na

R ₂	Method	M
2,4,6-trichlorophenyl	A	Na
2,4,6-tribromophenyl	A	Na
2,3,5,6-tetrachlorophenyl	A	Na
pentachlorophenyl	A	Na
2,4-dinitrophenyl	C	Na
2,3,4,6-tetranitrophenyl	C	Na
pentanitrophenyl	C	Na
2,4-difluorophenyl	A	Na
2,4,6-trifluorophenyl	A	Na
pentafluorophenyl	A	Na
3-chloro-4-fluorophenyl	A	Na
2-bromo-4-fluorophenyl	A	Na
2,6-dichloro-4-fluorophenyl	A	Na
4,6-dibromo-2-fluorophenyl	A	Na
2-bromo-3,5-dichloro-4-fluorophenyl	A	Na
3-fluoro-2,4,6-trichlorophenyl	A	Na
4-bromo-3-methoxyphenyl	A	Na
2-chloro-6-methoxyphenyl	A	Na
3-methoxy-2-methylphenyl	B	K
2-methoxy-6-propylphenyl	B	K
2-carbomethoxy-5-fluorophenyl	B	K
5-fluoro-2-methoxyphenyl	B	K
4-acetyl-2-fluorophenyl	B	K
4-chloro-2-methylphenyl	B	Na
2-bromo-6-methylphenyl	B	Na
2-bromo-4-t-butylphenyl	B	Na
2-chloro-4-isopropylphenyl	B	Na
2-isobutyl-4-fluorophenyl	B	Na
6-bromo-3,4-dimethylphenyl	B	K

R ₂	Method	M
4-chloro-2,3-dimethylphenyl	B	K
4-bromo-3-isopropyl-3-methylphenyl	B	K
4-chloro-2,3-diethylphenyl	B	K
2-chloro-3,4-dimethylphenyl	B	K
4,6-dibromo-2-methylphenyl	B	K
2,4-dichloro-3,5-dimethylphenyl	B	K
4-chloro-2,3,5-trimethylphenyl	B	K
4-chloro-2-nitrophenyl	B	K
6-chloro-2,4-dinitrophenyl	B	K
3-chloro-4-fluoro-6-nitrophenyl	B	K
2,4-dibromo-3-fluoro-6-nitrophenyl	E	K
4-chloro-5-fluoro-2-nitrophenyl	E	K
4-acetyl-2-fluoro-5-nitrophenyl	E	K
2-acetyl-6-bromo-4-fluorophenyl	E	K
2-fluoro-4-propionylphenyl	E	K
3,4-dicarbomethoxy-2,5,6-tribromophenyl	B	K
2-acetyl-4-chlorophenyl	B	K
2-acetyl-3,5-dichlorophenyl	A	Na
2-acetyl-6-chloro-4-methylphenyl	A	Na
4-chloro-2-propionylphenyl	A	Na
2-acetyl-6-dimethylaminophenyl	F-1	K
4-dimethylamino-2-methylphenyl	F-1	K
4-carbomethoxy-2-dimethylaminophenyl	F-1	K
4-t-butyl-3-nitrophenyl	B	Na
2-methyl-4-nitro-5-isopropylphenyl	B	Na
6-nitro-1,2,3,4-tetramethylphenyl	B	Na
2-methoxy-5-nitro-4-propylphenyl	B	Na
2-ethyl-6-methyl-4-nitrophenyl	B	Na
2,3-dimethoxyphenyl	A	Na

R ₂	Method	M
3,5-dimethoxy-2-methylphenyl	A	Na
2,5-dimethoxy-4-propylphenyl	A	Na
3,4,5-trimethoxyphenyl	A	Na
m-acetylphenyl	B	K
o-propionylphenyl	B	K
p-propionylphenyl	B	K
2-carbomethoxy-4-methoxyphenyl	B	K
2-carbomethoxy-6-methoxyphenyl	B	K
3,4-dicarbomethoxyphenyl	B	K
2,3-dicarbomethoxyphenyl	B	K
2,4-dicarbomethoxyphenyl	B	K
2,4-dicarbomethoxy-3,5-dimethylphenyl	B	K
4-carbomethoxy-2,5-dimethyl-4-methoxyphenyl	E	K
4-carbomethoxy-2,6-dichlorophenyl	E	K
2-carbomethoxy-3,5-dimethoxy-4,6-dimethylphenyl	E	K
2-bromo-4-carbomethoxy-6-methoxyphenyl	E	K
5-carbomethoxy-2-methoxy-3-nitrophenyl	E	K
3-carbomethoxy-2,4-dinitro-6-methoxyphenyl	E	K
4-indanyl	A	Na
5-indanyl	A	Na
5-methyl-4-indanyl	A	Na
6-methyl-4-indanyl	A	Na
3-methyl-4-indanyl	A	Na
1-methyl-5-indanyl	A	Na
7-methyl-5-indanyl	A	Na
6-t-butyl-5-indanyl	A	Na
4,6-dimethyl-5-indanyl	C	Na
1,1,-dimethyl-4-indanyl	C	Na
1,1,2-triethyl-4-indanyl	B	K

R ₂	Method	M
1,1,2,3-tetramethyl-4-indanyl	B	K
5,7-dimethyl-4-indanyl	B	K
7-chloro-4-indanyl	A	Na
7-bromo-4-indanyl	A	Na
6-bromo-5-indanyl	A	Na
1,1,7-trimethyl-4-indanyl	B	K
4-(1-indanyl)phenyl	B	K
2,4-(dicyclopent-2-enyl)phenyl	B	K
4-(α,α -dimethylbenzyl)phenyl	B	K
1-naphthyl	B	Na
2-naphthyl	B	Na
1-(5,6,7,8-tetrahydronaphthyl	B	Na
2-(5,6,7,8-tetrahydronaphthyl)	B	Na
3-(2-methyl-4-pyronyl)	B	Na
3-quinolyl	F-1	K
5-quinolyl	F-1	K
8-quinolyl	F-1	K
5-(1,4-naphthoquinonyl)	B	Na
6-(1,4-naphthoquinonyl)	B	Na
4-(coumarinyl)	C	K
5-(coumarinyl)	C	K
3-thianaphthenyl	B	Na
1-phenaziny	F-1	K
2-phenaziny	F-1	K
2-(anthraquinonyl)	B	Na
2-(4-methylquinolyl)	F-1	K
1-fluoroenyl	A	Na
2-fluoroenyl	A	Na
7-(1,2-naphthoquinonyl)	B	Na

R ₂	Method	M
1-anthraquinonyl	B	Na
8-isoquinolyl	F-1	K
4-(1,3-benzodioxolyl)	B	K
5-(1,3-benzodioxolyl)	B	K
3-(4-pyronyl)	B	K
1-(4-methyl-5,6,7,8-tetrahydronaphthyl)	C	Na
2-(3-methyl-5,6,7,8-tetrahydronaphthyl)	C	Na
2-(5-methyl-5,6,7,8-tetrahydronaphthyl)	C	Na
1-(4,4-dimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
2-(1,6-dimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
1-(2,4,7-trimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
2-(1,5,6-trimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
2-(3,4,6-trimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
1-(1,2,4-triethyl-5,6,7,8-tetrahydronaphthyl)	E	K
2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthyl)	E	K
4-bromo-2-carbomethoxy-5-methylphenyl	F	H
2-acetyl-6-chloro-5-methylphenyl	B	K
2-acetyl-4,5-dimethyl-6-ethylphenyl	D	Na
2-acetyl-5-dimethylaminophenyl	F-1	K
2-furyl	C	K
3-furyl	C	K
2-(1,4-naphthoquinonyl)	B	K
cyclopropyl	A	Na
cyclobutyl	A	Na
cyclopentyl	A	Na
cyclohexyl	A	Na
cycloheptyl	A	Na
1-methyl-1-cyclopentyl	A	Na
3-methyl-1-cyclopentyl	A	Na

R_2	Method	M
1,3-methyl-1-cyclopentyl	B	K
2,5-methyl-1-cyclopentyl	B	K
1,2,2-trimethyl-1-cyclopentyl	B	K
1,2,5-trimethyl-1-cyclopentyl	B	K
1-isopropyl-1-cyclopentyl	B	K
3-isopropyl-1-cyclopentyl	B	K
1-methyl-1-cyclohexyl	B	K
3-methyl-1-cyclohexyl	B	K
1-ethyl-1-cyclohexyl	B	K
1-isopropyl-1-cyclohexyl	B	K
4-t-butyl-1-cyclohexyl	B	K
4,4-isopropyl-1-cyclohexyl	B	K
1,2-isopropyl-1-cyclohexyl	B	K
3,4-dimethyl-1-cyclohexyl	C	Na
1,3-dimethyl-1-cyclohexyl	C	Na
2,4-dimethyl-1-cyclohexyl	C	Na
2,2,3-trimethyl-1-cyclohexyl	D	Na
1,3,3-trimethyl-1-cyclohexyl	D	Na
2,4,4-trimethyl-1-cyclohexyl	D	Na
3,3,5-trimethyl-1-cyclohexyl	E	Na
1,4,4-trimethyl-1-cyclohexyl	E	Na
1,3,4-trimethyl-1-cyclohexyl	E	Na
2-chloro-1-indanyl	E	Na
3-bromo-1-indanyl	E	Na
2-methyl-6-propyl-1-cyclohexyl	E	Na
2-propyl-4-methyl-1-cyclohexyl	E	Na
1,4-dimethyl-1-cyclohexyl	F	K
1-ethyl-3-methyl-1-cyclohexyl	F	K
2,6-diethyl-1-cyclohexyl	F	K

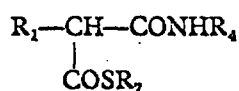
R ₂	Method	M
2,2,5,5-diethyl-1-cyclohexyl	F-1	K
1,2,4,5-diethyl-1-cyclohexyl	F-1	K
1-methyl-1-cycloheptyl	F-1	K
1-(1,2,3,4-tetrahydronaphthyl)	F-1	K
2-(1,2,3,4-tetrahydronaphthyl)	F-1	K
1-indanyl	B	K
2-indanyl	B	K
1-methyl-1-indanyl	B	K
1-ethyl-1-indanyl	B	K
2-bicyclo-[4.4.0]-decyl	A	Na
3-bicyclo-[4.4.0]-decyl	A	Na
7-adamantanyl	A	Na
thujyl	B	K
1-(1-methyl-1,2,3,4-tetrahydronaphthyl)	B	K
1-(2-chloro-1,2,3,4-tetrahydronaphthyl)	B	K
2-dimethylaminoethyl	F-1	K
3-diethylaminopropyl	F-1	K
2-piperidinoethyl	F-1	K
3-morpholinopropyl	F-1	K
3-thiomorpholinopropyl	F-1	K
2-pyrrolidinoethyl	F-1	K
2-(2-imidazolino)ethyl	F-1	K
2-pyrroloethyl	F-1	K
3-(N-methyl)piperazinopropyl	F-1	K
2-di-(n-propyl)aminoethyl	B	Na
2-di-(n-butyl)aminoethyl	B	Na
3-diisopropylaminopropyl	B	Na
3-imidazolopropyl	B	Na
3-(2-imidazolinopropyl	B	Na

R ₂	Method	M
3-(2,5-dimethylpyrrolidino)propyl	B	Na
3-aziridinopropyl	B	Na
3-pyrrolopropyl	B	Na
aziridinomethyl	C	K
pyrrolidinomethyl	C	K
morpholinomethyl	C	K
(1,4,5,6-tetrahydropyrimidino)methyl	C	K
pyrrolomethyl	C	K
3-diisopropylamino-2-propyl	C	K
2-dimethylamino-1-propyl	C	K
3-aziridino-2-propyl	C	K
2-(N-methylanilino)ethyl	B	Na
2-(N-ethylanilino)ethyl	F-1	K
3-(N-methylanilino)propyl	F-1	K
3-(N-isopropylanilino)propyl	F-1	K
3-(N-methylanilino)-2-propyl	F-1	K
2-(N-methylanilino)-1-propyl	F-1	K
3-N-ethylpiperazino-2-propyl	B	Na
3-(2-imidazolino)-2-propyl	A	Na
3-(4-methylpiperidino)-2-propyl	A	Na
2-aziridino-1-propyl	B	K
2-morpholino-1-propyl	B	K
2-thiomorpholino-1-propyl	B	K
2-imidazolo-1-propyl	B	K
2-(1,4,5,6-tetrahydropyrimidino)-1-propyl	B	K
2-dipropylamino-1-propyl	B	K
2-butyramidoethyl	B	K
3-acetamidopropyl	B	K
2-acetamido-1-propyl	B	K

R ₂	Method	M
2-piperidinoethyl	B	K
3-piperidinopropyl	B	K
2-pyrrolidinoethyl	B	K
2-(1,4,5,6-tetrahydropyrimidino)ethyl	F-1	K
3-di-(n-propylamino)-2-propyl	F-1	K
2-diethylamino-1-propyl	F-I	K
3-pyrrolidino-2-propyl	F-1	K
3-piperidino-2-propyl	F-1	K
3-diethylamino-2-propyl	F-1	K
3-morpholino-2-propyl	F-1	K
3-di-(n-butyl)amino-2-propyl	F-1	K
3-dimethylamino-2-propyl	F-1	K
2-azetidinoethyl	F-1	K
3-azetidino-2-propyl	F-I	K
2-pyridylmethyl	B	Na
4-pyridylmethyl	B	Na
4-imidazolylmethyl	B	Na
2-(N-phenylimidazolyl)methyl	B	Na
phthalimidomethyl	B	Na
benzyl	A	Na
o-chlorobenzyl	A	Na
m-chlorobenzyl	A	Na
p-bromobenzyl	A	Na
m-methylbenzyl	B	Na
o-nitrobenzyl	C	K
p-ethoxybenzyl	C	K
m-acetylbenzyl	B	K
o-carbomethoxybenzyl	B	Na
o-fluorobenzyl	A	Na

R ₂	Method	M
p-dimethylaminobenzyl	F-1	K
benzohydryl	B	Na
trityl	B	Na
cholesteryl	B	Na
2-furylmethyl	D	Na
2-pyridylmethyl	F	H
2,2-dimethyl-1,3-dioxolon-4-yl-1-methyl	B	Na
2-pyrrolidinomethyl	B	Na
(4-imidazolyl)methyl	F-1	K
2-indanylmethyl	B	Na
phthalimidomethyl	F-1	K

The above procedure is repeated but using the appropriate thiophenol R₇SH in place of R₂OH to produce penicillins of the formula:



R ₇	Method	M
phenyl	A	Na
o-tolyl	A	Na
m-tolyl	A	Na
p-ethylphenyl	B	K
p-isopropylphenyl	B	K
p-butylphenyl	B	K
p-sec-butylphenyl	B	K
3,5-dimethylphenyl	B	K
2,5-diethylphenyl	B	K
4-t-butyl-2-isopropylphenyl	B	K
o-chlorophenyl	B	Na
m-chlorophenyl	B	Na

R ₁	Method	M
p-bromophenyl	B	Na
p-fluorophenyl	B	Na
3,4-dichlorophenyl	A	Na
2,4,5-trichlorophenyl	A	Na
2,4-dibromophenyl	A	Na
2,4,5-tribromophenyl	A	Na
4-chloro-2-methylphenyl	B	Na
3-chloro-4-methylphenyl	B	Na
5-bromo-2-methylphenyl	B	Na
4-chloro-3,5-dimethylphenyl	B	K
5-chloro-2,4-dimethylphenyl	B	K
2,4-dichloro-3-methylphenyl	A	Na
2,4-difluorophenyl	A	Na
m-difluorophenyl	A	Na
p-methoxyphenyl	C	Na
o-methoxyphenyl	C	Na
m-methoxyphenyl	C	Na
p-isobutoxyphenyl	C	Na
3-methoxy-4-methylphenyl	C	Na
6-methoxy-3-methylphenyl	C	Na
3-t-butyl-4-methoxyphenyl	B	K
4-methoxy-3,5-dimethylphenyl	B	K
3,4-dimethoxyphenyl	F	H
3,4-di-isopropoxyphenyl	F	H
4-methoxy-3,5-dipropylphenyl	F-1	K
4-methoxy-3,5-di-isopropoxyphenyl	F-1	K
4-chloro-3-methoxyphenyl	A	Na
2-bromo-5-methoxyphenyl	A	Na
4-butoxy-2-chlorophenyl	E	Na

R_1	Method	M
2,5-dichloro-4-ethoxyphenyl	B	K

EXAMPLE IV

Again following the procedures of Example I, the aryl halo carbonyl ketenes wherein the aryl group, R_1 , for each of the R_2 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 converted to penicillins of Formula III.

R_2	Method	M
methyl	A	Na
ethyl	A	Na
i-propyl	A	Na
n-butyl	A	Na
t-butyl	A	Na
octyl	D	K
dodecyl	B	Na
octadecyl	D	K
2-chloroethyl	A	Na
3-chloropropyl	A	Na
2-chloro-1-butyl	A	Na
4-chloro-1-butyl	A	Na
1-methyl-3-chloropropyl	A	Na
2,2-dimethyl-2-chloroethyl	A	Na
2-bromoethyl	B	K
1-methyl-2-bromoethyl	B	K
4-bromo-1-buty.	B	K
1,3-dichloropropyl	A	Na

R ₂	Method	M
1,1-dichloromethylethyl	A	Na
2-chloro-3-bromopropyl	A	Na
1,4-dibromo-2-butyl	A	Na
3,4-dichloro-1-butyl	A	Na
1 bromomethyl-2-chloroethyl	A	Na
2,3-dibromo-2-methylpropyl	A	Na
2,2-dichloroethyl	A	Na
2,3,3-tribromopropyl	A	Na
2,2,3-trichlorobutyl	A	Na
2-chloro-2,3-dibromobutyl	A	Na
2,2,3,3-tetrabromopropyl	A	Na
2,2,2-trichloroethyl	A	Na
2,2,2-trifluoroethyl	A	Na
2-(2-trifluoromethyl)propyl	A	Na
2-nitroethyl	B	K
3-nitropropyl	B	K
3-nitrobutyl	B	K
1-methyl-2-nitropropyl	B	K
2,2-dinitroethyl	C	Na
1-methyl-2,2-dinitroethyl	C	Na
2-chloro-2-nitropropyl	B	Na
2-bromo-2-nitropropyl	B	Na
1-methyl-2-chloro-2-nitroethyl	B	Na
1-methyl-2-bromo-2-nitroethyl	B	Na
1-trichloromethyl-2-nitroethyl	B	Na
1-trifluoromethylethyl	A	Na
1,1-dimethyl-2,2,2-trichloroethyl	A	Na
2-methoxyethyl	F-1	K
2-isopropoxyethyl	F-1	K

R ₂	Method	M
3-sec-butoxypropyl	F-1	K
4-methoxy-n-butyl	F-1	K
4-butoxy-n-butyl	F-1	K
1,1-dimethyl-2-ethoxyethyl	F-1	K
2-cyanoethyl	E	K
3-cyanopropyl	E	K
2-cyano-1-methylethyl	E	K
1-cyano-2-chloropropyl	B	K
1-cyano-2,2-dichloropropyl	B	K
1-cyano-2,2,2-trichloroethyl	B	K
1-cyano-2,2,2-tribromoethyl	B	K
2-acetoxyethyl	B	Na
2-butyryloxyethyl	B	Na
3-acetoxypropyl	B	Na
1-methyl-3-acetoxypropyl	B	Na
carbomethoxymethyl	B	Na
2-carbethoxyethyl	B	Na
3-carbobutoxypropyl	B	Na
4-carbethoxybutyl	C	Na
1-carbethoxypropyl	C	Na
1-chloromethyl-2-carbethoxyethyl	B	K
1-trichloromethyl-2-carbomethoxyethyl	B	K
1-carbethoxy-2,2-dichloropropyl	B	K
1-carbomethoxy-2,2,2-trichloroethyl	B	K
1-carbomethoxy-2-chloroethyl	B	K
1-carbomethoxymethyl-2,2,2-trichloroethyl	B	K
acetyl	E	Na
4-oxopentyl	E	Na
2-methyl-3-oxobutyl	E	Na

R ₂	Method	M
1-methyl-4-oxopentyl	E	Na
1-methyl-3-oxobutyl	E	Na
2-acetylbutyl	B	Na
2-acetylpropyl	B	Na
3-oxopentyl	B	Na
5-oxohexyl	B	Na
1-methoxy-2,2,2-trichloroethyl	A	Na
1-propoxy-2,2,2-trichloroethyl	A	Na
1-methoxy-2,2,2-trifluoroethyl	A	Na
1-ethoxy-2,2,2-trifluoroethyl	A	Na
2,3-diacetoxypropyl	B	K
2,3-dicaproyloxypropyl	B	K
2,3-distearoyloxypropyl	B	K
(1,2,3-tricarbomethoxy)-2-propyl	B	K
(1,2,3-tricarbobutoxy)-2-propyl	B	K
3,3-diethoxypropyl	B	K
2-chloro-3,3-dimethoxypropyl	B	Na
2-oxo-3-chloropropyl	B	K
1-trichloromethyl-3-oxobutyl	B	K
3-fluoropropyl	A	Na
2,2,3,3,4,4,4-heptafluorobutyl	A	Na
1-methoxy-2-chloro-2,2-difluoroethyl	A	Na
dicarbethoxyethoxymethyl	B	Na
1,1-dicarbethoxymethyl-2-ethoxyethyl	B	Na
carbethoxyethoxymethyl	B	Na
chlorodicarbomethoxymethyl	B	Na
bromodicarbomethoxymethyl	B	Na
1-isopropoxy-2,2,2-trichloroethyl	A	Na
1-t-butoxy-2,2,2-trichloroethyl	A	Na

R ₂	Method	M
dicarbomethoxyethoxymethyl	B	Na
phenyl	B	Na
o-tolyl	B	Na
m-n-propylphenyl	B	Na
o-isopropylphenyl	B	Na
p-t-butylphenyl	B	Na
o-methoxyphenyl	B	Na
m-methoxyphenyl	B	Na
o-ethoxyphenyl	B	Na
p-n-butoxyphenyl	B	Na
o-chlorophenyl	A	Na
m-chlorophenyl	A	Na
m-bromophenyl	A	Na
p-fluorophenyl	A	Na
m-formylphenyl	A	Na
o-acetylphenyl	A	Na
p-butyrylphenyl	A	Na
m-nitrophenyl	C	K
p-nitrophenyl	C	K
m-carbomethoxyphenyl	C	Na
o-carbomethoxyphenyl	C	Na
p-carbo-n-propoxyphenyl	C	Na
o-dimethylaminophenyl	F-1	K
o-di-n-butylaminophenyl	F-1	K
m-di-n-propylaminophenyl	F-1	K
p-methylisopropylaminophenyl	F-1	K
3,4-dimethylphenyl	D	K
2,4-diethylphenyl	D	K
2,6-di-n-propylphenyl	D	K

R ₂	Method	M
6-ethyl-2-methylphenyl	D	K
2-methyl-6-n-propylphenyl	D	K
2-methyl-4-sec-butylphenyl	B	Na
2,3,4-trimethylphenyl	B	Na
3,4,5-trimethylphenyl	B	Na
2,6-dimethyl-4-ethylphenyl	B	Na
4,6-dimethyl-2-methylphenyl	B	Na
4,5-dimethyl-2-isopropylphenyl	B	Na
2,3,4,6-tetramethylphenyl	B	Na
4-butyl-5-isopropyl-2-methylphenyl	B	Na
pentamethylphenyl	B	Na
2,6-dichlorophenyl	A	Na
2,4-dibromophenyl	A	Na
2,4,6-trichlorophenyl	A	Na
2,4,6-tribromophenyl	A	Na
pentachlorophenyl	A	Na
3,5-dinitrophenyl	C	Na
pentanitrophenyl	C	Na
2,3,5-trifluorophenyl	A	Na
pentafluorophenyl	A	Na
3-chloro-4-fluorophenyl	A	Na
2,6-dichloro-4-fluorophenyl	A	Na
4-bromo-3,5-difluorophenyl	A	Na
3-fluoro-2,4,6-trichlorophenyl	A	Na
2-methoxy-4-methylphenyl	A	Na
5-bromo-2-methoxyphenyl	A	Na
2-chloro-6-methoxyphenyl	A	Na
2-ethoxy-3-methylphenyl	B	K
2-carbomethoxy-5-fluorophenyl	B	K

R ₂	Method	M
5-fluoro-2-methoxyphenyl	B	K
2-acetyl-4-fluorophenyl	B	K
4-chloro-2-methylphenyl	B	Na
4-fluoro-3-methylphenyl	B	Na
2-bromo-4-t-butylphenyl	B	Na
6-bromo-3,4-dimethylphenyl	B	K
4-chloro-2,3-dimethylphenyl	B	K
4-chloro-6-isopropyl-3-methylphenyl	B	Na
4-chloro-2,3-diethylphenyl	B	K
2-chloro-3,4-dimethylphenyl	B	K
2,4-dichloro-3,5-dimethylphenyl	B	K
4-chloro-2,3,5-trimethylphenyl	B	K
4-chloro-2,6-dinitrophenyl	B	K
3-fluoro-4-nitrophenyl	B	K
4-chloro-5-fluoro-2-nitrophenyl	E	K
4-acetyl-2-fluoro-5-nitrophenyl	E	K
2-fluoro-4-propionylphenyl	E	K
3,4-dicarbomethoxy-2,5,6-tribromophenyl	B	K
2-acetyl-4-chlorophenyl	B	K
2-acetyl-6-chloro-4-methylphenyl	A	Na
4-chloro-2-propionylphenyl	A	Na
2-acetyl-6-dimethylaminophenyl	F-1	K
4-dimethylamino-2-methylphenyl	F-1	K
4-carbomethoxy-2-dimethylaminophenyl	F-1	K
2-methoxy-5-nitro-4-propylphenyl	B	Na
2-nitro-3,4,5-trimethylphenyl	B	Na
2,6-dimethoxyphenyl	A	Na
3,5-dimethoxy-4-methylphenyl	A	Na
3,5-diethoxy-2,6-dimethylphenyl	A	Na

R ₂	Method	M
3,4,5-trimethoxyphenyl	A	Na
m-acetylphenyl	B	K
o-propionylphenyl	B	K
3-carbomethoxy-5-methoxyphenyl	B	K
3,4-dicarbomethoxyphenyl	B	K
2,6-dicarbomethoxyphenyl	B	K
4-carbomethoxy-2,5-dimethyl-4-methoxyphenyl	E	K
4-carbomethoxy-2,6-dichlorophenyl	E	K
2-carbomethoxy-3,5-dimethoxy-4,6-dimethylphenyl	E	K
2-bromo-4-carbomethoxy-6-methoxyphenyl	E	K
4-carbomethoxy-2-methoxy-3-nitrophenyl	E	K
3-carbomethoxy-2,4-dinitro-6-methoxyphenyl	E	K
4-indanyl	A	Na
5-indanyl	A	Na
5-methyl-4-indanyl	A	Na
3-methyl-4-indanyl	A	Na
1-methyl-5-indanyl	A	Na
6-t-butyl-5-indanyl	A	Na
4,6-dimethyl-5-indanyl	C	Na
1,1,2,3-tetramethyl-4-indanyl	B	K
5,7-dimethyl-4-indanyl	B	K
5-chloro-4-indanyl	A	Na
6-chloro-5-indanyl	A	Na
1,7-dimethyl-4-indanyl	B	K
4-(1-indanyl)phenyl	B	K
2,4-(dicyclopent-2-enyl)phenyl	B	K
4-(α,α -dimethylbenzyl)phenyl	B	K
1-naphthyl	Bq	Na
2-naphthyl	B	Na
1-(5,6,7,8-tetrahydronaphthyl)	B	Na

R ₂	Method	M
2-(5,6,7,8-tetrahydronaphthyl)	B	Na
3-(2-methyl-4-pyronyl)	B	Na
4-quinolyl	F-1	K
7-quinolyl	F-1	K
5-(1,4-naphthoquinonyl)	B	Na
6-(1,4-naphthoquinonyl)	B	Na
6-(coumarinyl)	C	K
4-thianaphthenyl	B	Na
1-phenazinyl	F-1	K
2-phenazinyl	F-1	K
2-(anthraquinonyl)	B	Na
4-(6-methylquinolyl)	F-1	K
1-fluorenyl	A	Na
2-fluorenyl	A	Na
6-(1,2-naphthoquinonyl)	B	Na
7-(1,2-naphthoquinonyl)	B	Na
1-anthraquinonyl	B	Na
7-isoquinolyl	F-1	K
5-(1,3-benzodioxolyl)	B	K
3-(4-pyronyl)	B	K
1-(3-methyl-5,6,7,8-tetrahydronaphthyl)	C	Na
2-(4-methyl-5,6,7,8-tetrahydronaphthyl)	C	Na
1-(4,8-dimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
1-(3,4,6-trimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
2-(3,4,6-trimethyl-5,6,7,8-tetrahydronaphthyl)	E	K
2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthyl)	E	K
2-acetyl-5-dimethylaminophenyl	F-1	K
2-acetyl-5-ethoxyphenyl	B	Na
2-butyryl-3,5-dimethylphenyl	B	Na

R ₂	Method	M
2-furyl	B	K
3-furyl	B	K
cyclopropyl	A	Na
cyclobutyl	A	Na
cyclopentyl	A	Na
cyclohexyl	A	Na
cycloheptyl	A	Na
1-methyl-1-cyclopentyl	A	Na
2-methyl-1-cyclopentyl	A	Na
2,2-dimethyl-1-cyclopentyl	B	K
1,3-dimethyl-1-cyclopentyl	B	K
2,4-dimethyl-1-cyclopentyl	B	K
1,2,5-trimethyl-1-cyclopentyl	B	K
1,2,4-trimethyl-1-cyclopentyl	B	K
1-isopropyl-1-cyclopentyl	B	K
1-methyl-1-cyclohexyl	B	K
1-ethyl-1-cyclohexyl	B	K
1-isopropyl-1-cyclohexyl	B	K
4-t-butyl-1-cyclohexyl	B	K
2,2-dimethyl-1-cyclohexyl	B	K
1,2-dimethyl-1-cyclohexyl	B	K
1,3-dimethyl-1-cyclohexyl	C	Na
3,5-dimethyl-1-cyclohexyl	C	Na
1,2,2-trimethyl-1-cyclohexyl	D	Na
1,3,3-trimethyl-1-cyclohexyl	D	Na
3,5,3-trimethyl-1-cyclohexyl	E	Na
1-chloro-2-indanyl	B	K
2-bromo-1-indanyl	B	K
1,2,6-trimethyl-1-cyclohexyl	E	Na

R ₂	Method	M
2-methyl-6-propyl-1-cyclohexyl	E	Na
1-propyl-3-methyl-1-cyclohexyl	E	Na
1,4-dimethyl-1-cyclohexyl	F	K
1-ethyl-2-methyl-1-cyclohexyl	F	K
1-methyl-1-cycloheptyl	F-1	K
1-(1,2,3,4-tetrahydronaphthyl	F-1	K
1-indanyl	B	K
2-indanyl	B	K
2-methyl-1-indanyl	B	K
1-methyl-1-indanyl	B	K
1-ethyl-1-indanyl	B	K
2-bicyclo-[4.4.0]-decyl	A	Na
7-adamantanyl	A	Na
fenchyl	B	K
1-(1-methyl-1,2,3,4-tetrahydronaphthyl)	B	K
2-(3-chloro-1,2,3,4-tetrahydronaphthyl)	B	K
2-piperidinoethyl	F-1	K
2-morpholinoethyl	F-1	K
3-thiomorpholinopropyl	F-1	K
2-pyrrolidinoethyl	F-1	K
3-pyrrolopropyl	F-1	K
2-(1,4,5,6-tetrahydropropyrimidino)ethyl	F-1	K
3-di-(n-propylamino)-2-propyl	F-1	K
3-pyrrolidinopropyl	B	K
2-dimethylaminoethyl	F	H
2-dibutylaminoethyl	F	H
2-pyrroloethyl	F	H
2-imidazoloethyl	F	H
2-(2,5-dimethylpyrrolidino)ethyl	F	H

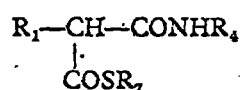
R ₂	Method	M
2-azetidinoethyl	F-1	K
2-azetidino-1-propyl	F-1	K
3-dimethylaminopropyl	F-1	K
3-diisopropylaminopropyl	F-1	K
3-aziridinopropyl	F-1	K
3-(N-methylpiperazino)propyl	F-1	K
3-(2-imidazolino)propyl	F-1	K
3-(1,4,5,6-tetrahydropyrimidino)propyl	F-1	K
pyrrolidinomethyl	C	Na
thiomorpholinomethyl	C	Na
pyrrolomethyl	C	Na
(2-imidazolino)methyl	C	Na
piperidinomethyl	C	Na
2-pyrrolidino-1-propyl	C	Na
2-morpholino-1-propyl	C	Na
2-pyrrolo-1-propyl	C	Na
2-imidazo-1-propyl	C	Na
3-imidazo-2-propyl	C	Na
3-(2-imidazolino)-2-propyl	C	Na
2-(methylethylamino)ethyl	C	Na
2-(methylbutylamino)ethyl	C	Na
3-(methylpropylamino)propyl	C	Na
3-(methylethylamino)-2-propyl	C	Na
2-(methylbutylamino)-1-propyl	C	Na
2-acetamidoethyl	C	Na
3-propionamidopropyl	C	Na
3-acetamido-2-propyl	C	Na
2-diethylamino-1-propyl	F-1	K
3-pyrrolidino-2-propyl	F-1	K

R ₂	Method	M
3-piperidino-2-propyl	F-1	K
3-diethylamino-2-propyl	F-1	K
3-morpholino-2-propyl	F-1	K
3-di-(n-butyl)amino-2-propyl	F-1	K
3-dimethylamino-2-propyl	F-1	K
2-(2,6-dimethylpiperidino)ethyl	F-1	K
3-(methylethylamino)propyl	F-1	K
3-piperidinopropyl	F-1	K
2-(N-methylanilino)ethyl	B	Na
2-(N-ethylanilino)ethyl	F-1	K
3-(N-methylanilino)propyl	F-1	K
3-(N-isopropylanilino)propyl	F-1	K
3-(N-methylanilino)-2-propyl	F-1	K
2-(N-methylanilino)-1-propyl	F-1	K
2-pyridylmethyl	B	Na
4-pyridylmethyl	B	Na
4-imidazolylmethyl	B	Na
2-(N-phenylimidazolyl)methyl	B	Na
phthalimidomethyl	B	Na
3-(N-methyl)pyridyl	F-1	K
allyl	A	Na
crotyl	A	Na
3-penten-1-yl	A	Na
1-penten-5-yl	B	K
2-methyl-3-buten-1-yl	B	K
5-hexen-2-yl	B	K
1-hexen-4-yl	B	K
2-hexen-4-yl	B	K
3-hexen-1-yl	C	Na

R ₂	Method	M
2-methyl-3-penten-2-yl	C	Na
4-methyl-4-penten-2-yl	D	K
2,2-dimethyl-3-buten-1-yl	D	K
2-hepten-1-yl	D	K
1-hepten-4-yl	B	Na
2-methyl-3-hexen-2-yl	B	Na
2-methyl-4-hexen-6-yl	B	Na
2-methyl-5-hexen-2-yl	E	K
2-methyl-5-hexen-4-yl	F	Na
3-methyl-3-hexen-2-yl	F	Na
2,2-dimethyl-3-penten-1-yl	F-1	Na
2,4-dimethyl-1-penten-3-yl	F-1	Na
2,2,3-trimethyl-3-buten-1-yl	B	Na
2-octen-1-yl	B	Na
4-octen-1-yl	B	Na
propargyl	A	Na
1-butyne-3-yl	A	Na
1-pentyne-3-yl	A	Na
3-methyl-1-pentyne-3-yl	B	Na
2-hexyne-1-yl	B	Na
2-heptyne-1-yl	B	Na
5-methyl-3-hexyne-2-yl	B	Na
3-ethyl-1-pentyne-3-yl	B	Na
3-methyl-1-heptyne-3-yl	C	Na
3-octyne-1-yl	C	Na
benzyl	A	Na
p-chlorobenzyl	A	Na
o-bromobenzyl	A	Na
p-methylbenzyl	B	Na

R_2	Method	M
o-ethylbenzyl	B	Na
m-nitrobenzyl	C	K
m-methoxybenzyl	C	K
p-acetylbenzyl	B	K
p-carbomethoxybenzyl	B	Na
p-fluorobenzyl	A	Na
o-dimethylaminobenzyl	F-1	K
benzohydryl	B	Na
trityl	B	Na
cholesteryl	B	Na
2-furylmethyl	D	Na
[2,2-dimethyl-1,3-dioxolon-4-yl]-methyl	B	Na
(2-pyrrolidono)methyl	B	Na
1-indanylmethyl	B	Na
phthalimidomethyl	F-1	K

Repetition of the above procedure but using the appropriate thiophenol R_7SH in place of R_2OH produces the following penicillins:



R_7	Method	M
phenyl	A	Na
o-tolyl	A	Na
m-tolyl	A	Na
o-isopropylphenyl	B	K
p-butylphenyl	B	K
2,5-dimethylphenyl	B	K
3-methyl-5-ethylphenyl	B	K
2-methyl-5-isopropylphenyl	B	K

R ₇	Method	M
o-chlorophenyl	B	Na
p-chlorophenyl	B	Na
m-bromophenyl	B	Na
p-fluorophenyl	B	Na
3,4-dichlorophenyl	A	Na
2,3,5-trichlorophenyl	A	Na
2,4-dibromophenyl	A	Na
2,4,5-tribromophenyl	A	Na
6-chloro-3-methylphenyl	B	Na
4-chloro-3-methylphenyl	B	Na
6-chloro-3-isopropylphenyl	B	Na
4-bromo-3-methylphenyl	B	Na
2-chloro-3,5-dimethylphenyl	B	K
4,6-dichloro-3-methylphenyl	A	Na
2,4-difluorophenyl	A	Na
o-trifluoromethylphenyl	A	Na
p-methoxyphenyl	C	Na
o-ethoxyphenyl	C	Na
m-ethoxyphenyl	C	Na
p-butoxyphenyl	C	Na
2-methoxy-3-methylphenyl	C	Na
4-methoxy-2-methylphenyl	C	Na
5-methoxy-2-methylphenyl	C	Na
5-ethyl-2-methoxyphenyl	B	K
4-methoxy-2,5-dimethylphenyl	B	K
2,5-dimethoxyphenyl	F	H
3,4-di-isopropoxyphenyl	F	H
4-methoxy-2,5-dipropylphenyl	F-1	K
4-methoxy-3,5-di-isopropoxyphenyl	F-1	K

R ₁	Method	M
2-chloro-4-methoxyphenyl	A	Na
4-bromo-3-methoxyphenyl	A	Na
4-butoxy-2-chlorophenyl	E	Na
2,5-dichloro-4-ethoxyphenyl	B	K

EXAMPLE V

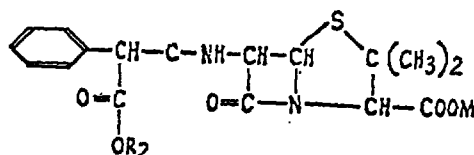
The sodium and potassium salts of Examples I—IV are converted to the corresponding acids by careful neutralization of aqueous solutions of their salts with aqueous phosphoric acid followed by extraction of the acid form into methylisobutylketone. The methylisobutylketone solutions are washed with water, dried with anhydrous sodium sulfate, filtered and evaporated to give the free acids.

EXAMPLE VI

The free acids of Examples I—V are converted to their calcium, magnesium, ammonium, procaine, N,N'-dibenzylethylenediamine, N-ethylpiperidine, dibenzylamine, 1-phenylamine, triethylamine, N-benzyl-β-phenethylamine, N,N'-bis-(dehydroabietyl)-ethylenediamine and benzhydrylamine salts by reaction of aqueous solutions thereof with one equivalent of the appropriate base. The salts are recovered by freeze drying.

TABLE III

Melting Points of Salts



R ₂	M	M.P. (°C.)
2-imidazoloethyl	H	110 (dec.)
5-indanyl	morpholine	116—117

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R ₂	M	M.P. (°C.)
5-indanyl	N-ethylpiperidine	139—141
5-indanyl	triethylamine	141—143
o-isopropylphenyl	potassium	193 (dec.)
4-indanyl	N-ethylpiperidine	136—139
o-ethylphenyl	N-ethylpiperidine	140 (dec.)
o-tolyl	N-ethylpiperidine	140—145 (dec.)
3,4-dimethylphenyl	N-ethylpiperidine	145—147
2,3-dimethylphenyl	N-ethylpiperidine	151—153
6-chloro-2-methylphenyl	N-ethylpiperidine	150—151
4-chloro-2-methylphenyl	N-ethylpiperidine	149—151
2-chloro-5-methylphenyl	N-ethylpiperidine	144—145 (dec.)
4-chloro-3,5-dimethylphenyl	N-ethylpiperidine	140—142
4-chloro-2,3-dimethylphenyl	N-ethylpiperidine	144—147
2,5-dimethylphenyl	N-ethylpiperidine	144—150 (dec.)
3,5-dimethylphenyl	N-ethylpiperidine	147—149
2,4-dimethylphenyl	N-ethylpiperidine	142—149 (dec.)
2,6-dimethylphenyl	N-ethylpiperidine	150—151
m-ethylphenyl	N-ethylpiperidine	132—137
2-methoxy-4-methylphenyl	N-ethylpiperidine	150—152
2-methyl-3-methoxyphenyl	N-ethylpiperidine	150—152
2-(N-methylanilino)ethyl	N-ethylpiperidine	69—77
3-(N-methylanilino)-2-propyl	N-ethylpiperidine	86—92
3-(N-ethylanilino)-2-propyl	N-ethylpiperidine	86—97
2-(N-ethylanilino)ethyl	N-ethylpiperidine	69—77
o-ethoxyphenyl	N-ethylpiperidine	138—142

EXAMPLE VII

5 The benzyl and substituted benzyl esters of Examples I—IV are converted to their corresponding free acids by catalytic hydrogenation at room temperature. The general procedure comprises hydrogenating the benzyl ester in water in the presence of a suspension of pre-hydrogenated 10% palladium on charcoal until hydrogenation is complete. For every 0.05

mole of benzyl ester used, 5.7 g. of catalyst and 1000 ml. of water are used.

When hydrogenation is complete as determined by the hydrogen uptake, the reaction mixture is filtered, the filtrate adjusted to pH 7.5 with sodium or potassium bicarbonate then evaporated to dryness under reduced pressure and below 40°C.

The products are purified by column

chromatography on cellulose and eluted with butanol-ethanol-water mixture and recovered from the eluate by evaporation of the solvent.

EXAMPLE VIII

5 A solution of the triethylamine salt of α -[carbo - (5 - indanyloxy)]benzyl penicillin (0.5 g.) in a small volume of saturated aqueous sodium bicarbonate (5 ml.) is stirred at room temperature. Samples are withdrawn at 10 minutes, 30 minutes and then at half-hour intervals and examined by paper chromatography in the system isoamyl acetate: citrate-phosphate buffer (pH 4.5) and by bioautographs (*Bacillus subtilis*). The samples are also

15 extracted with chloroform (3 $\times$ 3 ml.), the combined extracts concentrated and the concentrate and the spent aqueous sample examined by paper chromatography and bioautographs.

20 The ester, which initially produces a single spot (R_f 0.91) on a papergram, appears to rapidly equilibrate to two epimers as evidenced by the appearance of two spots in the papergram, R_f 0.81 and 0.91.

25 Hydrolysis of the ester is essentially complete within two hours as evidenced by the absence of the ester on the papergram and the presence of α -carboxy benzyl penicillin along with a small amount of benzyl penicillin.

30 In like manner, α - [carbo(5 - indanyloxy)]-benzylpenicillin sodium salt, α - [carb(1-ethoxy - 2,2,2 - trichloroethoxy)]benzylpenicillin sodium salt, α - (carballyloxy)benzylpenicillin sodium salt, α - (carbocyclohexyloxy)benzyl - penicillin sodium salt, and α - (carbophenylthio) - benzylpenicillin are converted to the corresponding acids.

EXAMPLE IX

40 A solution of the sodium salt of α - [carbo(2 - di - (n - propyl)amino - ethoxy)]benzylpenicillin water (0.5 g. in 5 ml.) is held at room temperature for 24 hours. The pH is automatically regulated at 7.0—7.2 by the

45 addition of sodium bicarbonate. The solution is then freeze dried and the by-product phenol removed by trituration of the residue with ethanol to give the disodium salt.

50 Repetition of this procedure but at 35° C. for two hours also produces the disodium salt.

By means of this procedure the following penicillin ester sodium salts are converted to their corresponding disodium salts:

α - [carbo - (5 - indanyloxy)]benzylpenicillin

55 α - [carbo - (dicarbethoxyethoxy methoxy)]-benzylpenicillin

α - (carbopropargyloxy)benzylpenicillin

α - [carbo(2 - bicyclo - [4.4.0] - decyloxy)]-benzylpenicillin

60 α - (carbophenylthio)benzylpenicillin

EXAMPLE X

To α - carbo[(2 - N - methylanilino)-ethoxy]benzylpenicillin sodium salt (0.1 g.) in chloroform (5 ml.) there is added a solution of citrate buffer (pH 5.5, 5 ml.) and the resulting mixture thoroughly shaken for 75 minutes. The aqueous layer is checked every 15 minutes by paper chromatography using the system isoamyl acetate: citrate-phosphate buffer (pH 4.5) and bioautographs (*Bacillus subtilis*).

70 Within 15 minutes α -carboxybenzyl penicillin is present in the aqueous phase together with a high proportion of the starting ester. After 60 minutes no ester is present in the aqueous phase. The major product observed is α -carboxybenzylpenicillin. A small amount of benzylpenicillin, its degradation product, is also present.

75 The α -carboxybenzyl penicillin is isolated by lyophilization and the crude product is further purified by chromatography on Sephadex LH 20 (a cross-linked dextrose available from HB Pharmacia, Uppsala, Sweden).

EXAMPLE XI

85 A tablet base is prepared by blending the following ingredients in the proportion by weight indicated.

Sucrose, U.S.P.	80.3
Tapioca starch	13.2
Magnesium stearate	6.5
	90

Sufficient α - [carbo(2 - di - (n - propyl)-amino)ethoxy]benzylpenicillin sodium salt is blended into the base to provide tablets containing 25, 100 and 250 mg. of active ingredient.

EXAMPLE XII

100 Capsules containing 25, 100 and 250 mg. of active ingredient are prepared by blending sufficient α - [carbo(5 - indanyloxy)]benzylpenicillin sodium salt in the following mixture (proportions given in parts by weight).

Calcium carbonate, U.S.P.	17.6
Dicalcium phosphate	18.8
Magnesium trisilicate	5.2
Lactose, U.S.P.	5.2
Potato starch	5.2
Magnesium stearate A	0.8
Magnesium stearate B	0.35
	105

EXAMPLE XIII

110 A suspension of α - [carbo(1 - ethoxy-2,2,2-trichloroethoxy)]benzylpenicillin sodium salt is prepared with the following composition:

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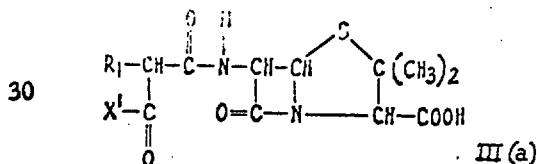
- Penicillin compound g 31.42
 70% Aqueous sorbitol 9 714.29
 Glycerine, U.S.P. g 185.35
 Gum acacia (10% solution) ml 100
 Polyvinyl pyrrolidone g 0.5
 Butyl parahydroxybenzoate g 0.172
 Propyl parahydroxybenzoate g 0.094
 Distilled water to make one liter
 Various sweetening and flavoring agents may be added to this suspension, as well as acceptable colors. The suspension contains approximately 25 mg. of penicillin compound per milliliter.

EXAMPLE XIV

- The sodium salt of α - [carbo - (3 - di-(n - propyl)amino)propoxy]benzylpenicillin (10 g.) is intimately mixed and ground with sodium citrate (4% by weight). The ground, dry mixture is filled into vials, sterilized with ethylene oxide and the vials sterilely stoppered. For parenteral administration, sufficient water is added to the vials to form solutions containing 25 mg. of active ingredients per ml.

WHAT WE CLAIM IS:—

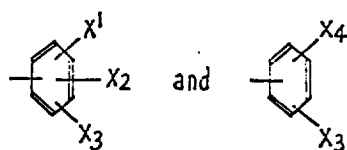
1. Compounds of the formula:



and the pharmaceutically acceptable salts thereof,

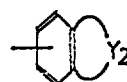
wherein R_1 is

- 35 thienyl,
 furyl,
 pyridyl,
 phenyl,
 or substituted phenyl wherein the substituent is (lower)alkyl, chloro, bromo, (lower)-alkoxy, di(lower)alkylamino or trifluoromethyl;
 40 X^1 is $-\text{OR}_2$ or $-\text{SR}_2$ wherein R_2 is isopropylphenyl,

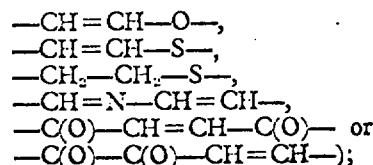


- 45 (wherein X_1 is chloro, bromo, fluoro, lower alkyl, or lower alkoxy;
 X_2 is lower alkyl or chloro;
 X_3 is hydrogen or methyl; and

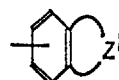
X_1 is nitro, di(lower alkyl)amino);
 furyl,
 quinolyl,
 methyl substituted quinolyl,
 phenazinyl,
 9,10-anthraquinonyl,
 phenanthrenequinonyl,
 anthracenyl,
 phenanthryl,
 (1,3-benzodioxolyl),
 2-(2-methyl-4-pyronyl),
 3-(4-pyronyl) or
 (N-methyl)pyridyl:



(wherein Y_2 is:



or



(wherein Z' is lower alkylene and is $-(\text{CH}_2)_3-$ and $-(\text{CH}_2)_4-$, or substituted derivatives thereof wherein the substituent is methyl, chloro or bromo)

substituted benzyl, with the proviso that R_1 cannot be thienyl or furyl when X_1 is substituted benzyl

(wherein the substituent is:

chloro,
 bromo,
 fluoro,
 lower alkyl,
 lower alkoxy,
 lower alkanoyl,
 carbo(lower)alkoxy, when R_1 is other than phenyl nitro, and
 di(lower)alkylamino),
 phthalimidomethyl,
 benzohydryl,
 trityl,
 cholesteryl,
 alkenyl having up to 8 carbon atoms,
 alkynyl having up to 8 carbon atoms,
 cycloalkyl or
 (lower alkyl) substituted cycloalkyl having from 3 to 7 carbon atoms in the cycloalkyl moiety,
 bicyclo [4-4-0] decyl,
 thujyl,
 fenchyl,
 isofenchyl,
 7-adamantanyl,
 (2-pyrrolidono)methyl,



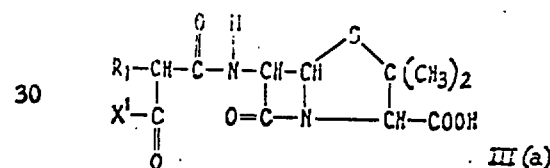
- Penicillin compound g 31.42
 70% Aqueous sorbitol 9 714.29
 Glycerine, U.S.P. g 185.35
 Gum acacia (10% solution) ml 100
 Polyvinyl pyrrolidone g 0.5
 Butyl parahydroxybenzoate g 0.172
 Propyl parahydroxybenzoate g 0.094
 Distilled water to make one liter
- Various sweetening and flavoring agents may be added to this suspension, as well as acceptable colors. The suspension contains approximately 25 mg. of penicillin compound per milliliter.

EXAMPLE XIV

- The sodium salt of α - [carbo - (3 - di-(n - propyl)amino)propoxy]benzylpenicillin (10 g.) is intimately mixed and ground with sodium citrate (4% by weight). The ground, dry mixture is filled into vials, sterilized with ethylene oxide and the vials sterilely stoppered. For parenteral administration, sufficient water is added to the vials to form solutions containing 25 mg. of active ingredients per ml.

WHAT WE CLAIM IS:—

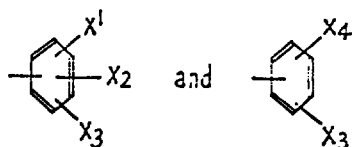
1. Compounds of the formula:



and the pharmaceutically acceptable salts thereof,

wherein R_1 is

- thienyl,
 35 furyl,
 pyridyl,
 phenyl,
 or substituted phenyl wherein the substituent is (lower)alkyl, chloro, bromo, (lower)-alkoxy, di(lower)alkylamino or trifluoromethyl;
 40 X' is $-\text{OR}_2$ or $-\text{SR}$, wherein R_2 is isopropylphenyl,



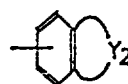
- (wherein X_1 is chloro, bromo, fluoro, lower alkyl, or lower alkoxy;
 45 X_2 is lower alkyl or chloro;
 X_3 is hydrogen or methyl; and

X_1 is nitro, di(lower alkyl)amino);
 furyl,
 quinolyl,
 methyl substituted quinolyl,
 phenazinyl,
 9,10-anthraquinonyl,
 phenanthrenequinonyl,
 anthracenyl,
 phenanthryl,
 (1,3-benzodioxolyl),
 2-(2-methyl-4-pyronyl),
 3-(4-pyronyl) or
 (N-methyl)pyridyl:

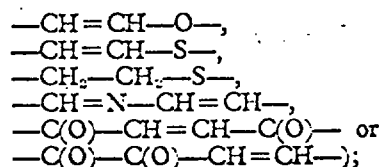
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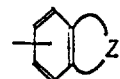


(wherein Y_2 is:



65

or



(wherein Z' is lower alkylene and is $-(\text{CH}_2)_3-$ 70
 and $-(\text{CH}_2)_4-$, or substituted derivatives thereof wherein the substituent is methyl, chloro or bromo)

substituted benzyl, with the proviso that R_1 cannot be thienyl or furyl when X_1 is substituted benzyl 75

(wherein the substituent is:

chloro,
 bromo,
 fluoro,
 80 lower alkyl,
 lower alkoxy,
 lower alkanoyl,
 carbo(lower)alkoxy, when R_1 is other than phenyl nitro, and
 85 di(lower)alkylamino),
 phthalimidomethyl,
 benzohydryl,
 trityl,
 90 cholesteryl,
 alkenyl having up to 8 carbon atoms,
 alkynyl having up to 8 carbon atoms,
 cycloalkyl or
 (lower alkyl) substituted cycloalkyl having
 95 from 3 to 7 carbon atoms in the cycloalkyl moiety,
 bicyclo [4.4.0] decyl,
 thujyl,
 fenchyl,
 isofenchyl,
 100 7-adamantanyl,
 (2-pyrrolidono)methyl,

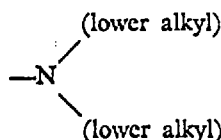
- 5 (4-imidazolyl)methyl,
1-indanylmethyl,
2-indanylmethyl,
[2,2 - di - (lower alkyl) - 1,3 - dioxolon-
4 - yl]methyl,
furylmethyl,
pyridylmethyl,

10 *ac* indanyl or substituted derivatives thereof
wherein the substituent is methyl, chloro or
bromo;

ac tetrahydronaphthyl and substituted deri-
vatives thereof wherein the substituent is
methyl, chloro or bromo;

- 15 1 - (lower)alkoxy - 2,2,2 - trichloroethyl
when R₁ is pyridyl,
1 - (lower)alkoxy - 2,2,2 - trifluoroethyl
when R₁ is other than phenyl,
[carbo(lower)alkoxy] lower alkoxy-methyl,
20 [di - carbo(lower)alkoxy] lower alkoxy-
methyl,
—CH₂—CH₂—NR₃R₆,
—CH₂—CH₂—CH₂—NR₃R₆,
—CH₂—CH(CH₃)—NR₃R₆ or
25 —CH(CH₃)—CH₂—NR₃R₆, or
—(lower alkylene)—Y₁

wherein —NR₃R₆ is —NH(lower alkanoyl),

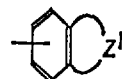


30 wherein the (lower alkyl) groups may be alike
or different; and —N(lower alkyl)anilino; and
Y₁ is:

- 35 azetidino,
aziridino,
pyrrolidino,
piperidino,
morpholino,
thiomorpholino,
(N-lower alkyl)piperazino,
pyrrolo,
imidazolo,
40 2-imidazolino,
2,5-dimethylpyrrolidino,
1,4,5,6-tetrahydropyrimidino,
4-methylpiperidino or
2,6-dimethylpiperidino;

- 45 wherein each of lower alkoxy, lower alkyl or
lower alkanoyl have from 1 to 4 carbon atoms,
and (lower alkylene) contains from 1 to 3
carbon atoms; and R₇ is hydrogen, phenyl,
mono-, di-, or tri-substituted phenyl wherein
50 the substituent is at least one of chloro,
bromo, fluoro, lower alkyl, lower alkoxy or
trifluoromethyl, with the proviso that only one

of the positions, ortho to the thio group of
the phenyl moiety be substituted; wherein each
of lower alkyl and lower alkoxy contain from
1 to 4 carbon atoms, with the proviso that
when R₁ is thienyl, furyl, phenyl, or substi-
tuted phenyl, R₂ cannot be substituted phenyl.
2. The compounds of claim 1, wherein R₁
is phenyl and R₂ is



wherein Z' is lower alkylene and the pharma-
ceutically acceptable salts thereof.

3. A compound of the formula III, wherein
R₁ is 2-, 3-, or 4-pyridyl and X', X₁, X₂,
X₃, X₄, R₂—R₇, Y₁, Y₂ and Z' are as pre-
viously defined and the pharmaceutically
acceptable salts thereof.

4. α - [carbo(5 - indanyloxy)]benzylpeni-
cillin and the pharmaceutically acceptable salts
thereof.

5. α - [carbo(4 - indanyloxy)]benzylpeni-
cillin and the pharmaceutically acceptable salts
thereof.

6. α - [carbo{2 - (5,6,7,8 - tetrahydro-
naphthylloxy)}]benzylpenicillin and the phar-
maceutically acceptable salts thereof.

7. α - [carbo(4 - chloro - 2 - methylpheno-
oxy)]benzylpenicillin and the pharmaceutically
acceptable salts thereof.

8. α - [carbo(o - isopropylphenoxy)]benzyl-
penicillin and the pharmaceutically acceptable
salts thereof.

9. α - [carbo(3,4 - dimethylphenoxy)]-
benzylpenicillin and the pharmaceutically
acceptable salts thereof.

10. α - [carbo(4 - chloro - 2,3 - dimethyl-
phenoxy)]benzylpenicillin and the pharma-
ceutically acceptable salts thereof.

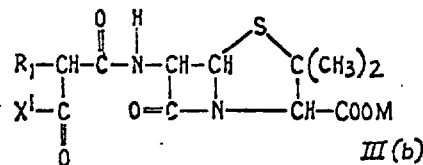
11. α - [carbo(2 - chloro - 4 - methyl-
phenoxy)]benzylpenicillin and the pharma-
ceutically acceptable salts thereof.

12. α - [carbo(2,3 - dimethylphenoxy)]-
benzylpenicillin and the pharmaceutically
acceptable salts thereof.

13. α - [carbo(2,4 - dimethylphenoxy)]-
benzylpenicillin and the pharmaceutically
acceptable salts thereof.

14. α - [carbo(4 - methoxy - 2 - methyl-
phenoxy)]benzylpenicillin and the pharma-
ceutically acceptable salts thereof.

15. A process for preparing acyl penicillins
of the formula:



wherein M is hydrogen, sodium, potassium or
tri-(lower alkyl)amine,

when

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alk
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X' is

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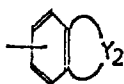


wherein R_1 is

- 5 thienyl,
furyl,
pyridyl,
phenyl,
or substituted phenyl wherein the substituent is (lower)alkyl, chloro, bromo, (lower)-alkoxy, di(lower)alkylamino or trifluoromethyl;

X' is $-OR_2$ or $-SR_2$ wherein R_2 is

- hydrogen or sodium
phenyl or
substituted phenyl wherein the substituent is at least one of chloro, bromo, fluoro, lower alkyl, lower alkoxy, lower alkanoyl, carbo(lower)alkoxy, nitro, or di(lower)alkylamino;
furyl,
quinolyl,
methyl substituted quinolyl,
phenazinyl,
9,10-anthraquinonyl,
phenanthrenequinonyl,
anthracenyl,
phenanthryl,
(1,3-benzodioxolyl),
3-(2-methyl-4-pyronyl),
3-(4-pyronyl) or
(N-methyl)pyridyl;



(wherein Y_2 is:

- 35 $-CH=CH-O-$,
90 $-CH=CH-S-$,
 $-CH_2-CH_2-S-$,
40 $-CH=N-CH=CH-$,
95 $-CH=CH-CH=CH-$,
 $-C(O)=CH=CH-C(O)-$ or
 $-C(O)-C(O)-CH=CH-$;



- 45 (wherein Z' is lower alkylene and is $-(CH_2)_2-$ and $-(CH_2)_1-$, or substituted derivatives thereof wherein the substituent is methyl, chloro or bromo);

- 50 benzyl,
substituted benzyl,

(wherein the substituent is:

- 105 chloro,
bromo,
fluoro,

- lower alkyl, 55
lower alkoxy,
lower alkanoyl,
carbo(lower)alkoxy,
nitro, and
di(lower)alkylamino); 60
phthalimidomethyl,
benzohydryl,
trityl,
cholesteryl,
alkenyl having up to 8 carbon atoms, 65
alkynyl having up to 8 carbon atoms,
cycloalkyl or
(lower alkyl) substituted cycloalkyl having
from 3 to 7 carbon atoms in the cycloalkyl
moiety, 70
bicyclo [4.4.0]decyl,
thujyl,
fenchyl,
isofenchyl,
7-adamantanyl, 75
(2-pyrrolidono)methyl,
(4-imidazolyl)methyl,
1-indanylmethyl,
2-indanylmethyl,
[2,2 - di - (lower alkyl) - 1,3 - dioxolon - 4-yl]methyl, 80
furylmethyl,
pyridylmethyl,

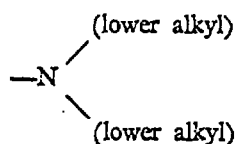
ac indanyl or substituted derivatives thereof wherein the substituent is methyl, chloro, or bromo; 85

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

alkyl or substituted (lower)alkyl (wherein the substituent is at least one of: 90

- chloro,
bromo,
fluoro,
nitro, 95
carbo(lower alkoxy),
lower alkanoyl,
lower alkoxy or
cyano,
(lower)alkylmercapto, 100
(lower)alkylsulfinyl,
(lower)alkylsulfonyl;
 $-CH_2-CH_2-NR_3R_4$,
 $-CH_2-CH_2-CH_2-NR_3R_4$,
 $-CH_2-CH(CH_3)-NR_3R_4$ or 105
 $-CH(CH_3)-CH_2-NR_3R_4$ or
 $-(lower alkylene)-Y_1$

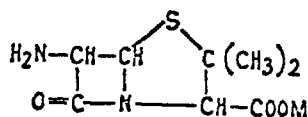
wherein $-NR_3R_4$ is $-NH(lower alkanoyl)$,



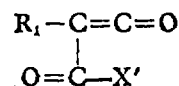
wherein the (lower alkyl) groups may be alike or different; and $\text{---N(lower alkyl)anilino}$; and Y_1 is:

- 5 azetidino,
aziridino,
pyrrolidino,
piperidino,
morpholino,
thiomorpholino,
10 N-(lower alkyl)piperazino,
pyrrolo,
imidazolo,
2-imidazolino,
2,5-dimethylpyrrolidino,
15 1,4,5,6-tetrahydropyrimidino,
4-methylpiperidino or
2,6-dimethylpiperidino;

- wherein each of lower alkoxy, lower alkyl or lower alkanoyl have from 1 to 4 carbon atoms, and (lower alkylene) contains from 1 to 3 carbon atoms; and R_1 is hydrogen or sodium, phenyl, mono-, di-, or tri-substituted phenyl wherein the substituent is at least one of chloro, bromo, fluoro, lower alkyl, lower alkoxy or trifluoromethyl, with the proviso that only one of the positions, ortho to the thio group of the phenyl moiety be substituted; wherein each of lower alkyl and lower alkoxy contain from 1 to 4 carbon atoms, which comprises reacting



wherein M is as defined above with a compound of the formula



wherein R_1 is as defined above, and X' is ---OR_2 or SR , as defined above except that R_2 and R_1 are other than hydrogen, in a reaction-inert solvent at a temperature of from about -70°C . to about 30°C .; and, if desired, forming compounds of the formula III (b) wherein R_2 or R_1 is hydrogen or sodium, by treatment of the ester compounds of formula III (b), by hydrolysis with aqueous sodium carbonate or by mild acid hydrolysis or enzymatically with an esterase or forming compounds of formula III (b) wherein R_2 or R_1 is hydrogen by catalytic hydrogenation at room temperature of compounds of formula III (a) wherein R_2 is benzyl or substituted benzyl.

16. The compounds of formulas III (a) and III (b) prepared by the process substantially as described herein.

17. The process for preparing the compounds of formulas III (a) and III (b) substantially as described herein.

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

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

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