

[54] **PHENYL BUTYRIC ACIDS AND
DERIVATIVES THEREOF**

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R, 260/476 R, 260/479 R, 260/247.7 A,
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260/507 R, 260/251 Q, 260/515 R, 260/516,
260/268 R, 260/517, 260/518 R, 260/293.8,
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M, 260/558 D, 260/295, 260/559 D, 260/559
T, 260/302 R, 260/559 A, 260/562 R,
260/306.7, 260/592, 260/599, 260/307 H,
260/618 D, 424/248, 260/309, 424/274,
424/275, 260/309.6, 424/283, 424/285,
260/310 R, 424/308, 424/309, 260/326.3,

424/317, 424/319, 260/332.2 A, 424/324,
260/332.2, 260/332.5, 260/345.7, 260/346.1
M, 260/347.3, 260/448 R, 260/454, 260/455
R, 260/455 B, 260/456 P, 260/465 D,
260/465 F, 260/469

[51] **Int. Cl.**..... **C07c 63/00**, C07c 69/64

[58] **Field of Search**..... 260/515 A, 469, 448 R,
260/501.15

[56] **References Cited**

UNITED STATES PATENTS

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FOREIGN PATENTS OR APPLICATIONS

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Primary Examiner—James A. Patten

Attorney, Agent, or Firm—Erich M. H. Radde

[57] **ABSTRACT**

Novel substituted phenyl butyric acids and their deriv-
atives are described. Therapeutic compositions and
method of treatment of inflammation is also disclosed.

11 Claims, No Drawings

PHENYL BUTYRIC ACIDS AND DERIVATIVES THEREOF

SUMMARY OF THE INVENTION

This invention describes novel halo and thio butyric acids and their derivatives and their use in therapeutic compositions. In addition, this invention describes the preparation of these halo and thio butyric acids and their derivatives. When the compounds of this invention are administered to mammals, they afford significant treatment for the relief of inflammation and associated pain and fever.

They further provide analgesic and antipyretic methods for the relief and treatment of pain and fever.

BACKGROUND OF THE INVENTION

Continued studies have been carried out in research to develop drugs which would significantly inhibit the development of inflammation and relieve the pain and fever associated with it. While much of this effort has been carried out in the steroid field these have been compounds developed which are non-steroidal and have included such as the alkanolic acids derived from biphenyl, stilbene, indole, naphthylene and various heteryl rings. While many of these compounds have been found to be effective, they have had the drawback of causing various side effects or being effective only on a specific disorder.

I have unexpectedly found that when a halo or thio group or derivative thereof is present in the α , β or γ position of the side chain of a substituted phenylbutyric acid molecule, pharmacological properties exist in the molecule which are useful for the relief and inhibition of inflammation conditions.

I have also found that the compounds of this invention are effective in the treatment of inflammation and the control of arthritic conditions associated with inflammation.

I have further found that α , β or γ halo and thio phenylbutyric acids and their derivatives are novel.

I have also found that the compounds of this invention possess useful analgesic and antipyretic properties and are useful in the treatment of pain and fever.

I have still further found an entirely new class of anti-inflammatory, analgesic and antipyretic pharmaceutical compositions which contain an α , β or γ -halo or thiophenylbutyric acid or derivative thereof as active ingredient.

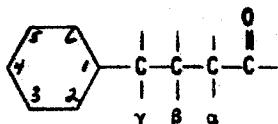
I have also found a convenient method for synthesizing these compounds.

DESCRIPTION AND PREFERRED EMBODIMENTS

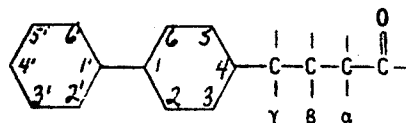
This invention comprises a class of novel chemical compounds which have a phenylbutyric acid group or derivative to which is attached a halo, mercapto, or thio derivative at the α -, β - or γ -position. Also the phenyl ring may further be substituted.

This invention also describes a new method for treating inflammation as well as pain and fever and also novel therapeutic compositions.

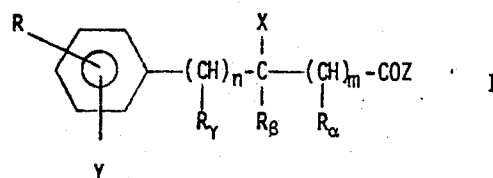
The following numbering system is used in this invention:



except with respect to the biphenyl compounds which is



The compounds of this invention can be represented by the generic structure which is described by the general formula I;



where:

R is alkyl, cycloalkyl, cycloalkenyl, aryloxy, arylthio, aryl or substituted aryl where the substituent is Y; Y is hydrogen, alkyl, halo, nitro, amino, acylamino, mono and diloweralkylamino, mercapto, acylthio, loweralkylthio, loweralkylsulfinyl, loweralkylsulfonyl, hydroxy, loweralkoxy, acyloxy, haloloweralkyl, cyano or acetyl;

$n + m = 2$;

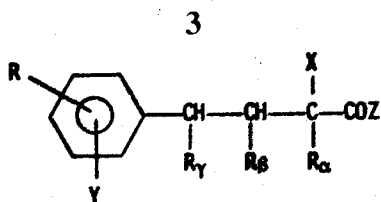
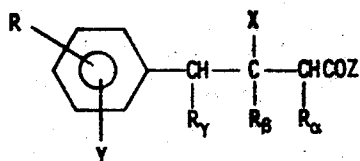
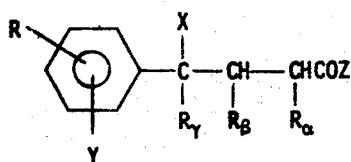
R_α , R_β and R_γ are hydrogen or loweralkyl;

X is in the α -, β - or γ -position and is halo, mercapto, loweralkylthio, acylthio, aroylthio, sulfo, sulfino, loweralkylsulfinyl, loweralkylsulfonyl, thioacylthio, thiosulfo, thiocyanato, amidinothio, carbamylthio, loweralkylcarbamylthio, diloweralkylcarbamylthio, loweralkoxythiocarbonylthio, loweralkoxycarbonylthio, diloweralkylthiocarbamylthio, arloweralkoxycarbonylthio, carboxyarylthio, carboxyacylthio, cyano, amino or substituted amino; Z is hydrogen, $-\text{OH}$, loweralkoxy, arloweralkoxy, $-\text{NH}_2$, loweralkylamino, diloweralkylamino, cycloloweralkylamino,

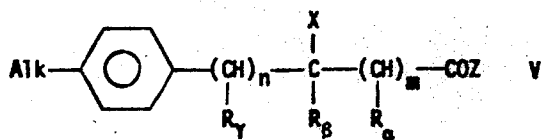
(where A is loweralkylidenyl or heteroloweralkylidenyl), $-\text{NHOH}$, $-\text{NHNH}_2$ or $-\text{OM}$ (where M is an alkali, alkaline earth or aluminum metal or an ammonium salt).

The compounds of this invention contain at least one asymmetric carbon atom in the butyric acid side chain. As a result, the above compounds of formula I may be obtained as racemic mixtures of their dextro (+) and levorotatory (-) isomers. It is to be understood that said *d* and *l* isomers as well as the *dl* mixtures thereof are embraced within the scope of this invention.

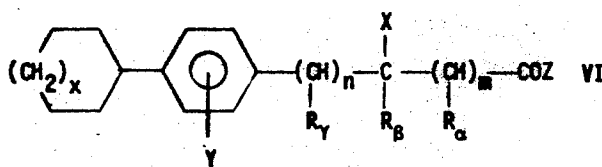
More specifically, the chemical compounds of this invention which have particular usefulness as anti-inflammatory, analgesic and antipyretic agents are described by formulae II-IV:



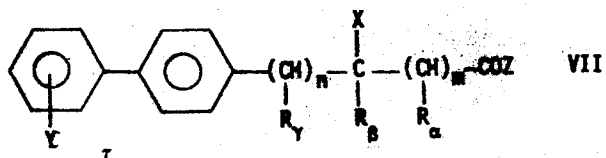
Those compounds whose properties are preferred are described by formulae V-VII:



where Alk is alkyl having 3-7 carbon atoms



where x is 0-2



Those compounds whose properties are even more preferred are described by formulae V-VII where Y is hydrogen or halo, x = 1 and

R_a , R_B and R_Y are hydrogen.

Compounds which are most preferred are those where X is in the α - or β -position.

A special embodiment of this invention describes a method for inhibiting inflammation and the treatment of pain and fever associated with inflammation as well

as having analgesic and antipyretic effectiveness for the relief and treatment of pain and fever not symptomatically related to an inflammation indication. This method affords relief by the administration of a compound of Formula I where

X is loweralkoxy, loweracyloxy, aroyloxy, carbloweralkoxyoxy, carbamyloxy, loweralkylcarbamyloxy, diloweralkylcarbamyloxy, loweralkanesulfonyloxy, benzenesulfonyloxy, toluenesulfonyloxy, carboxyacyloxy, carboxyaroxyloxy, halo, mercapto, loweralkylthio, acylthio, aroylthio, sulfo, sulfino, loweralkylsulfinyl, loweralkylsulfonyl, thioacylthio, thiosulfo, thiocyanato, amidinothio, carbamylthio, loweralkylcarbamylthio, diloweralkylcarbamylthio, loweralkoxythiocarbonylthio, loweralkoxycarbonylthio, diloweralkylthiocarbamylthio, arloweralkoxycarbonylthio, carboxyaroxythio, carboxyacylthio, cyano, amino or substituted amino.

In the descriptive portions of this invention the following definitions apply:

"alkyl" refers to a loweralkyl hydrocarbon group containing from 1 to about 7 carbon atoms which may be straight chained or branched.

"alkenyl" refers to an unsaturated or partially unsaturated hydrocarbon group containing from 2 to about 7 carbon atoms which may be straight chained or branched.

"cycloalkyl" refers to a hydrocarbon ring having up to about seven carbon atoms.

"cycloalkenyl" refers to a partially unsaturated hydrocarbon ring having up to about seven carbon atoms.

"aryl" refers to any benzenoid or non-benzenoid aromatic group but preferably phenyl.

"acyl" refers to any organic radical derived from an organic acid by the removal of its hydroxyl group such as formyl, acetyl, propionyl, 3-carboxy-2-propenyl, camphoryl, benzoyl, toluoyl or heteroyl such as pyridinoyl, piperidinoyl, thenoyl, etc.

The preferred "aroyl" is benzoyl, loweralkylbenzoyl such as toluoyl or halobenzoyl such as p-chlorobenzoyl, etc.

"alkoxy" refers to a loweralkoxy group containing from 1 to about 6 carbon atoms which may be straight chained or branched.

"loweralkylidenyl" refers to a loweralkylidenyl hydrocarbon group containing from 2 to about 6 carbon atoms.

"heteroloweralkylidenyl" refers to a loweralkylidenyl hydrocarbon group containing from about 2 to 5 carbon atoms and having one or more hetero atoms in the chain selected from O, N or S, such as piperidinyl, morpholinyl, etc.

The preferred "alkali" or "alkaline earth" metals are sodium, potassium, calcium and magnesium.

The term "ammonium salt" refers to the cation formed when ammonia or an organic amine react with the carboxyl group to form ammonium salt of the structure given in the formula. The ammonium salts are formed with a (1) loweralkylamines such as methylamine, diethylamine, triethylamine; (2) hydroxyloweralkylamines such as β -hydroxyethylamine; (3) heterocyclic amines such as 2-aminopyridine, piperazine, piperidine; (4) aralkylamines such as α -methylbenzylamine, phenethylamine; (5) cycloalkylamines

such as cyclohexylamine; (6) alkaloids such as quinine, cinchonidine, cinchonine, ephedrine.

Representative compounds of this invention which are particularly useful are as follows:

α -chloro- γ -(o-tolyl)butyric acid
 α -chloro- γ -(m-tolyl)butyric acid
 α -chloro- γ -(p-tolyl)butyric acid
 α -chloro- γ -(p-ethylphenyl)butyric acid
 α -chloro- γ -(p-propylphenyl)butyric acid
 α -chloro- γ -(p-i-propylphenyl)butyric acid
 α -chloro- γ -(p-butylphenyl)butyric acid
 α -chloro- γ -(p-i-butylphenyl)butyric acid
 α -chloro- γ -(p-sec-butylphenyl)butyric acid
 α -chloro- γ -(p-t-butylphenyl)butyric acid
 α -chloro- γ -(p-pentylphenyl)butyric acid
 α -chloro- γ -(p-vinylphenyl)butyric acid
 α -chloro- γ -(p-allylphenyl)butyric acid
 α -chloro- γ -(p-cyclopentylphenyl)butyric acid
 α -chloro- γ -(p-cyclohexylphenyl)butyric acid
 α -chloro- γ -(p-cycloheptylphenyl)butyric acid
 α -chloro- γ -(p-cyclopent-1-enylphenyl)butyric acid
 α -chloro- γ -(p-cyclohex-1-enylphenyl)butyric acid
 α -chloro- γ -(p-cyclohept-1-enylphenyl)butyric acid
 α -chloro- γ -(p-cyclohex-3-enylphenyl)butyric acid
 α -chloro- γ -(p-cyclohex-1,3-dienylphenyl)butyric acid
 α -chloro- γ -(m-phenoxyphenyl)butyric acid
 α -chloro- γ -(p-phenylthiophenyl)butyric acid
 α -chloro- γ -(p-biphenyl)butyric acid
 α -chloro- γ -[p-(2'-chlorobiphenyl)]butyric acid
 α -chloro- γ -[p-(3'-chlorobiphenyl)]butyric acid
 α -chloro- γ -[p-(4'-chlorobiphenyl)]butyric acid
 α -chloro- γ -[p-(2'-nitrobiphenyl)]butyric acid
 α -chloro- γ -(2-chloro-4-biphenyl)butyric acid
 α -chloro- γ -(3-chloro-4-biphenyl)butyric acid
 α -chloro- γ -(2,6-dichloro-4-biphenyl)butyric acid
 α -chloro- γ -(2-methyl-4-biphenyl)butyric acid
 α -chloro- γ -(2-bromo-4-biphenyl)butyric acid
 α -chloro- γ -(2-fluoro-4-biphenyl)butyric acid
 α -chloro- γ -(2-iodo-4-biphenyl)butyric acid
 α -chloro- γ -(2-nitro-4-biphenyl)butyric acid
 α -chloro- γ -(2-amino-4-biphenyl)butyric acid
 α -chloro- γ -(2-acetyl-amino-4-biphenyl)butyric acid
 α -chloro- γ -(2-ethylamino-4-biphenyl)butyric acid
 α -chloro- γ -(2-dimethylamino-4-biphenyl)butyric acid
 α -chloro- γ -(2-mercapto-4-biphenyl)butyric acid
 α -chloro- γ -(2-acetylthio-4-biphenyl)butyric acid
 α -chloro- γ -(2-methylthio-4-biphenyl)butyric acid
 α -chloro- γ -(2-methylsulfinyl-4-biphenyl)butyric acid
 α -chloro- γ -(2-methylsulfonyl-4-biphenyl)butyric acid
 α -chloro- γ -(2-hydroxy-4-biphenyl)butyric acid
 α -chloro- γ -(2-methoxy-4-biphenyl)butyric acid
 α -chloro- γ -(2-acetoxy-4-biphenyl)butyric acid
 α -chloro- γ -(2-trifluoromethyl-4-biphenyl)butyric acid
 α -chloro- γ -(2-cyano-4-biphenyl)butyric acid
 α -chloro- γ -(2-acetyl-4-biphenyl)butyric acid
 α -chloro- γ -(p-i-butylphenyl)butyric acid
 α -chloro- γ -(p-cyclohexylphenyl)butyric acid
 α -chloro- γ -(3-chloro-4-cyclohexylphenyl)butyric acid
 α -chloro- γ -(3-chloro-4-i-butylphenyl)butyric acid
 α -chloro- α -methyl- γ -(p-biphenyl)butyric acid
 α -chloro- β -methyl- γ -(p-biphenyl)butyric acid

α -chloro- γ -methyl- γ -(p-biphenyl)butyric acid
 α -chloro- α,β -dimethyl- γ -(p-biphenyl)butyric acid
 α -chloro- α,γ -dimethyl- γ -(p-biphenyl)butyric acid
 α -chloro- β,γ -dimethyl- γ -(p-biphenyl)butyric acid
 α -chloro- α,β,γ -trimethyl- γ -(p-biphenyl)butyric acid
 α -chloro- α -methyl- γ -(m-phenoxyphenyl)butyric acid
 α -bromo- γ -(p-biphenyl)butyric acid
 α -fluoro- γ -(p-biphenyl)butyric acid
 α -iodo- γ -(p-biphenyl)butyric acid
 α -mercapto- γ -(p-biphenyl)butyric acid
 α -methylthio- γ -(p-biphenyl)butyric acid
 α -acetylthio- γ -(p-biphenyl)butyric acid
 α -benzoylthio- γ -(p-biphenyl)butyric acid
 α -sulfo- γ -(p-biphenyl)butyric acid
 α -sulfinyl- γ -(p-biphenyl)butyric acid
 α -methylsulfinyl- γ -(p-biphenyl)butyric acid
 α -methylsulfonyl- γ -(p-biphenyl)butyric acid
 α -thioacetylthio- γ -(p-biphenyl)butyric acid
 α -thiosulfo- γ -(p-biphenyl)butyric acid
 α -thiocyanato- γ -(p-biphenyl)butyric acid
 α -amidinothio- γ -(p-biphenyl)butyric acid
 α -carbamylthio- γ -(p-biphenyl)butyric acid
 α -ethylcarbamylthio- γ -(p-biphenyl)butyric acid
 α -diethylcarbamylthio- γ -(p-biphenyl)butyric acid
 α -methoxythiocarbonylthio- γ -(p-biphenyl)butyric acid
 α -dimethylthiocarbamylthio- γ -(p-biphenyl)butyric acid
 α -benzyloxycarbonylthio- γ -(p-biphenyl)butyric acid
 α -(o-carboxybenzoylthio)- γ -(p-biphenyl)butyric acid
 α -cyano- γ -(p-biphenyl)butyric acid
 α -dimethylamino- γ -(p-biphenyl)butyric acid
 α -(4-carboxybutyroyloxy)- γ -(p-biphenyl)butyric acid
 α -(4-carboxybut-2-enyloxy)- γ -(p-biphenyl)butyric acid
 α -acetylthio- γ -(p-i-butylphenyl)butyric acid
 α -acetylthio- γ -(3-chloro-4-i-butylphenyl)butyric acid
 α -acetylthio- γ -(p-cyclohexylphenyl)butyric acid
 α -acetylthio- γ -(3-chloro-4-cyclohexylphenyl)butyric acid
 α -acetylthio- γ -[p-(2'-chlorobiphenyl)]butyric acid
 α -acetylthio- γ -(2-chloro-4-biphenyl)butyric acid
 α -acetylthio- α -methyl- γ -(p-biphenyl)butyric acid
 α -acetylthio- α -methyl- γ -(2-chloro-4-biphenyl)butyric acid
 α -acetylthio- α -methyl- γ -(3-chloro-4-cyclohexylphenyl)butyric acid
 α -acetylthio- β -methyl- γ -(p-biphenyl)butyric acid
 α -acetylthio- γ -methyl- γ -(p-biphenyl)butyric acid
 α -acetylthio- α -methyl- γ -(3-chloro-4-i-butylphenyl)butyric acid
methyl α -chloro- γ -(p-biphenyl)butyrate
ethyl α -chloro- γ -(p-biphenyl)butyrate
benzyl α -chloro- γ -(p-biphenyl)butyrate
N-methyl α -chloro- γ -(p-biphenyl)butyramide
N,N-dimethyl α -chloro- γ -(p-biphenyl)butyramide
N-cyclopropyl α -chloro- γ -(p-biphenyl)butyramide
N,N-pentamethylene α -chloro- γ -(p-biphenyl)butyramide
N,N-oxydiethylene α -chloro- γ -(p-biphenyl)butyramide

N,N-thiotrimethylene
 biphenyl)butyramide
 α-chloro-γ-(p-biphenyl)butyric acid, sodium salt
 α-chloro-γ-(p-biphenyl)butyric acid, potassium salt
 α-chloro-γ-(p-biphenyl)butyric acid, calcium salt 5
 α-chloro-γ-(p-biphenyl)butyric acid, aluminum salt
 α-chloro-γ-(p-biphenyl)butyric acid, diethylammonium salt
 α-chloro-γ-(p-biphenyl)butyric acid, cyclohexylammonium salt
 α-chloro-γ-(p-biphenyl)butyric acid, β-hydroxyethylammonium salt
 α-chloro-γ-(p-biphenyl)butyric acid, piperazinium salt
 α-chloro-γ-(p-biphenyl)butyric acid, methylbenzylammonium salt 15
 methyl α-acetylthio-γ-(p-biphenyl)butyrate
 ethyl α-acetylthio-γ-(p-biphenyl)butyrate
 benzyl α-acetylthio-γ-(p-biphenyl)butyrate
 N-methyl α-acetylthio-γ-(p-biphenyl)butyramide 20
 N,N-dimethyl α-acetylthio-γ-(p-biphenyl)butyramide
 N-cyclopropyl α-acetylthio-γ-(p-biphenyl)butyramide
 N,N-pentamethylene α-acetylthio-γ-(p-biphenyl)butyramide 25
 N,N-oxydiethylene α-acetylthio-γ-(p-biphenyl)butyramide
 N,N-thiotrimethylene α-acetylthio-γ-(p-biphenyl)butyramide 30
 α-acetylthio-γ-(p-biphenyl)butyric acid, sodium salt
 α-acetylthio-γ-(p-biphenyl)butyric acid, potassium salt
 α-acetylthio-γ-(p-biphenyl)butyric acid, calcium salt 35
 α-acetylthio-γ-(p-biphenyl)butyric acid, aluminum salt
 α-acetylthio-γ-(p-biphenyl)butyric acid, diethylammonium salt
 α-acetylthio-γ-(p-biphenyl)butyric acid, cyclohexylammonium salt
 α-acetylthio-γ-(p-biphenyl)butyric acid, β-hydroxyethylammonium salt
 α-acetylthio-γ-(p-biphenyl)butyric acid, piperazinium salt 45
 α-acetylthio-γ-(p-biphenyl)butyric acid, methylbenzylammonium salt
 β-chloro-γ-(o-tolyl)butyric acid
 β-chloro-γ-(m-tolyl)butyric acid 50
 β-chloro-γ-(p-tolyl)butyric acid
 β-chloro-γ-(p-ethylphenyl)butyric acid
 β-chloro-γ-(p-propylphenyl)butyric acid
 β-chloro-γ-(p-i-propylphenyl)butyric acid
 β-chloro-γ-(p-butylphenyl)butyric acid
 β-chloro-γ-(p-i-butylphenyl)butyric acid
 β-chloro-γ-(p-sec-butylphenyl)butyric acid
 β-chloro-γ-(p-t-butylphenyl)butyric acid
 β-chloro-γ-(p-pentylphenyl)butyric acid
 β-chloro-γ-(p-vinylphenyl)butyric acid
 β-chloro-γ-(p-allylphenyl)butyric acid
 β-chloro-γ-(p-cycloheptylphenyl)butyric acid
 β-chloro-γ-(p-cyclohexylphenyl)butyric acid
 β-chloro-γ-(p-cycloheptylphenyl)butyric acid
 β-chloro-γ-(p-cyclopent-1-enylphenyl)butyric acid
 β-chloro-γ-(p-cyclohex-1-enylphenyl)butyric acid
 β-chloro-γ-(p-cyclohept-1-enylphenyl)butyric acid

β-chloro-γ-(p-cyclohex-3-enylphenyl)butyric acid
 β-chloro-γ-(p-cyclohex-1,3-dienylphenyl)butyric acid
 β-chloro-γ-(p-phenoxyphenyl)butyric acid
 β-chloro-γ-(p-phenylthiophenyl)butyric acid
 β-chloro-γ-(p-biphenyl)butyric acid 5
 β-chloro-γ-[p-(2'-chlorobiphenyl)]butyric acid
 β-chloro-γ-[p-(3'-chlorobiphenyl)]butyric acid
 β-chloro-γ-[p-(4'-chlorobiphenyl)]butyric acid
 β-chloro-γ-[p-(2'-nitrobiphenyl)]butyric acid
 β-chloro-γ-(2-chloro-4-biphenyl)butyric acid
 β-chloro-γ-(3-chloro-4-biphenyl)butyric acid
 β-chloro-γ-(2,6-dichloro-4-biphenyl)butyric acid
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 β-chloro-γ-(2-ethylamino-4-biphenyl)butyric acid
 β-chloro-γ-(2-dimethylamino-4-biphenyl)butyric acid
 β-chloro-γ-(2-mercapto-4-biphenyl)butyric acid
 β-chloro-γ-(2-acetylthio-4-biphenyl)butyric acid 25
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 β-chloro-γ-(2-methoxy-4-biphenyl)butyric acid
 β-chloro-γ-(2-acetoxy-4-biphenyl)butyric acid
 β-chloro-γ-(2-trifluoromethyl-4-biphenyl)butyric acid 35
 β-chloro-γ-(2-cyano-4-biphenyl)butyric acid
 β-chloro-γ-(2-acetyl-4-biphenyl)butyric acid
 β-chloro-γ-(p-i-butylphenyl)butyric acid
 β-chloro-γ-(p-cyclohexylphenyl)butyric acid
 β-chloro-γ-(3-chloro-4-cyclohexylphenyl)butyric acid
 β-chloro-γ-(3-chloro-4-i-butylphenyl)butyric acid
 α-methyl-β-chloro-γ-(p-biphenyl)butyric acid
 β-chloro-β-methyl-γ-(p-biphenyl)butyric acid
 β-chloro-γ-methyl-γ-(p-biphenyl)butyric acid
 β-chloro-α,β-dimethyl-γ-(p-biphenyl)butyric acid
 β-chloro-α,β,γ-trimethyl-γ-(p-biphenyl)butyric acid
 β-chloro-β-methyl-γ-(m-phenoxyphenyl)butyric acid 50
 β-bromo-γ-(p-biphenyl)butyric acid
 β-fluoro-γ-(p-biphenyl)butyric acid
 β-iodo-γ-(p-biphenyl)butyric acid
 β-chloro-Γ-(p-biphenyl)butyric acid 55
 β-mercapto-γ-(p-biphenyl)butyric acid
 β-methylthio-γ-(p-biphenyl)butyric acid
 β-acetylthio-γ-(p-biphenyl)butyric acid
 β-benzoylthio-γ-(p-biphenyl)butyric acid
 β-sulfo-γ-(p-biphenyl)butyric acid 60
 β-sulfinio-γ-(p-biphenyl)butyric acid
 β-methylsulfinyl-γ-(p-biphenyl)butyric acid
 β-methylsulfonyl-γ-(p-biphenyl)butyric acid
 β-thioacetylthio-γ-(p-biphenyl)butyric acid
 β-thiosulfo-γ-(p-biphenyl)butyric acid 65
 β-thiocyanato-γ-(p-biphenyl)butyric acid
 β-amidinethio-γ-(p-biphenyl)butyric acid
 β-carbamylthio-γ-(p-biphenyl)butyric acid

β -ethylcarbamylothio- γ -(p-biphenyl)butyric acid
 β -diethylcarbamylothio- γ -(p-biphenyl)butyric acid
 β -methoxythiocarbonylthio- γ -(p-biphenyl)butyric acid
 β -methoxythiocarbonylthio- γ -(p-biphenyl)butyric acid
 β -dimethylthiocarbamylothio- γ -(p-biphenyl)butyric acid
 β -benzyloxycarbonylthio- γ -(p-biphenyl)butyric acid
 β -(o-carboxybenzoylthio)- γ -(p-biphenyl)butyric acid
 β -cyano- γ -(p-biphenyl)butyric acid
 β -dimethylamino- γ -(p-biphenyl)butyric acid
 β -(4-carboxybutyroyloxy)- γ -(p-biphenyl)butyric acid
 β -(4-carboxybut-2-enyloxy)- γ -(p-biphenyl)butyric acid
 β -acetylthio- γ -(p-i-butylphenyl)butyric acid
 β -acetylthio- γ -(3-chloro-4-i-butylphenyl)butyric acid
 β -acetylthio- γ -(p-cyclohexylphenyl)butyric acid
 β -acetylthio- γ -(3-chloro-4-cyclohexylphenyl)butyric acid
 β -acetylthio- γ -[p-(2'-chlorobiphenyl)]butyric acid
 β -acetylthio- γ -(2-chloro-4-biphenyl)butyric acid
 β -acetylthio- α -methyl- γ -(p-biphenyl)butyric acid
 β -acetylthio- α -methyl- γ -(2-chloro-4-biphenyl)butyric acid
 β -acetylthio- α -methyl- γ -(3-chloro-4-cyclohexylphenyl)butyric acid
 β -acetylthio- γ -methyl- γ -(p-biphenyl)butyric acid
 β -acetylthio- α -methyl- γ -(3-chloro-4-i-butylphenyl)butyric acid
methyl β -chloro- γ -(p-biphenyl)butyrate
ethyl β -chloro- γ -(p-biphenyl)butyrate
benzyl β -chloro- γ -(p-biphenyl)butyrate
N-methyl β -chloro- γ -(p-biphenyl)butyramide
N,N-dimethyl β -chloro- γ -(p-biphenyl)butyramide
N-cyclopropyl β -chloro- γ -(p-biphenyl)butyramide
N,N-pentamethylene β -chloro- γ -(p-biphenyl)butyramide
N,N-oxydiethylene β -chloro- γ -(p-biphenyl)butyramide
N,N-thiotrimethylene β -chloro- γ -(p-biphenyl)butyramide
 β -chloro- γ -(p-biphenyl)butyric acid, sodium salt
 β -chloro- γ -(p-biphenyl)butyric acid, potassium salt
 β -chloro- γ -(p-biphenyl)butyric acid, calcium salt
 β -chloro- γ -(p-biphenyl)butyric acid, aluminum salt
 β -chloro- γ -(p-biphenyl)butyric acid, diethylammonium salt
 β -chloro- γ -(p-biphenyl)butyric acid, cyclohexylammonium salt
 β -chloro- γ -(p-biphenyl)butyric acid, β -hydroxyethylammonium salt
 β -chloro- γ -(p-biphenyl)butyric acid, piperazinium salt
 β -chloro- γ -(p-biphenyl)butyric acid, methylbenzylammonium salt
methyl β -acetylthio- γ -(p-biphenyl)butyrate
ethyl β -acetylthio- γ -(p-biphenyl)butyrate
benzyl β -acetylthio- γ -(p-biphenyl)butyrate
N-methyl β -acetylthio- γ -(p-biphenyl)butyramide
N,N-dimethyl β -acetylthio- γ -(p-biphenyl)butyramide
N-cyclopropyl β -acetylthio- γ -(p-biphenyl)butyramide

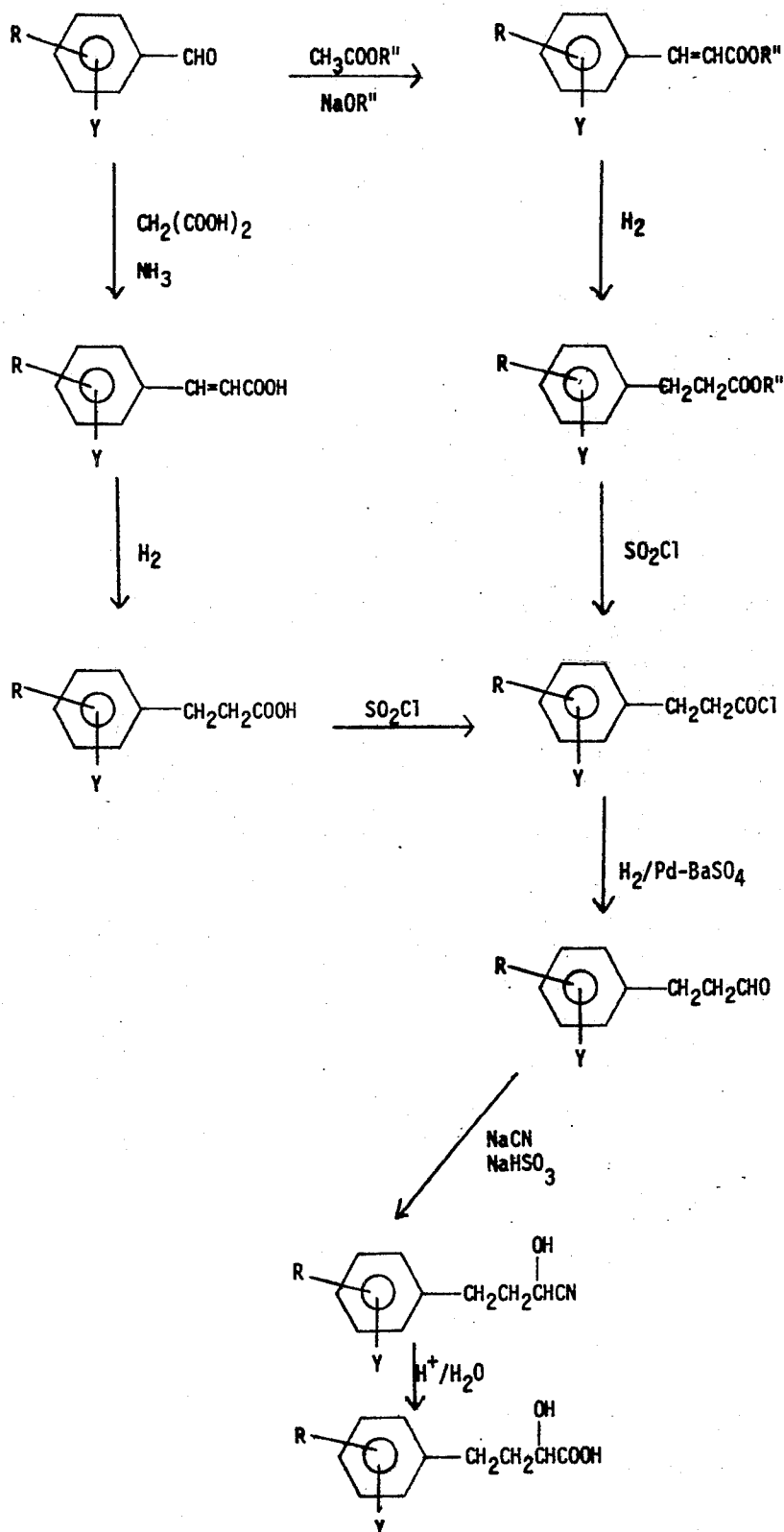
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 β -acetylthio- γ -(p-biphenyl)butyric acid, sodium salt
 β -acetylthio- γ -(p-biphenyl)butyric acid, potassium salt
 β -acetylthio- γ -(p-biphenyl)butyric acid, calcium salt
 β -acetylthio- γ -(p-biphenyl)butyric acid, aluminum salt
 β -acetylthio- γ -(p-biphenyl)butyric acid, diethylammonium salt
 β -acetylthio- γ -(p-biphenyl)butyric acid, cyclohexylammonium salt
 β -acetylthio- γ -(p-biphenyl)butyric acid, β -hydroxyethylammonium salt
 β -acetylthio- γ -(p-biphenyl)butyric acid, piperazinium salt
 β -acetylthio- γ -(p-biphenyl)butyric acid, methylbenzylammonium salt
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 γ -chloro- γ -(m-tolyl)butyric acid
 γ -chloro- γ -(p-tolyl)butyric acid
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 γ -chloro- γ -(p-propylphenyl)butyric acid
 γ -chloro- γ -(p-i-propylphenyl)butyric acid
 γ -chloro- γ -(p-butylphenyl)butyric acid
 γ -chloro- γ -(p-i-butylphenyl)butyric acid
 γ -chloro- γ -(p-sec-butylphenyl)butyric acid
 γ -chloro- γ -(t-butylphenyl)butyric acid
 γ -chloro- γ -(pentylphenyl)butyric acid
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 γ -chloro- γ -(cyclohexylphenyl)butyric acid
 γ -chloro- γ -(cyclopentylphenyl)butyric acid
 γ -chloro- γ -(p-cycloheptylphenyl)butyric acid
 γ -chloro- γ -(p-cyclopent-1-enylphenyl)butyric acid
 γ -chloro- γ -(p-cyclohex-1-enylphenyl)butyric acid
 γ -chloro- γ -(p-cyclohept-1-enylphenyl)butyric acid
 γ -chloro- γ -(p-cyclohex-3-enylphenyl)butyric acid
 γ -chloro- γ -(p-cyclohex-1,3-dienylphenyl)butyric acid
 γ -chloro- γ -(p-phenoxyphenyl)butyric acid
 γ -chloro- γ -(p-phenylthiophenyl)butyric acid
 γ -chloro- γ -(p-biphenyl)butyric acid
 γ -chloro- γ -[P-(2'-chlorobiphenyl)]butyric acid
 γ -chloro- γ -[P-(3'-chlorobiphenyl)]butyric acid
 γ -chloro- γ -[p-(4'-chlorobiphenyl)]butyric acid
 γ -chloro- γ -[p-(2'-nitrobiphenyl)]butyric acid
 γ -chloro- γ -(2-chloro-4-biphenyl)butyric acid
 γ -chloro- γ -(3-chloro-4-biphenyl)butyric acid
 γ -chloro- γ -(2,6-dichloro-4-biphenyl)butyric acid
 γ -chloro- γ -(2-methyl-4-biphenyl)butyric acid
 γ -chloro- γ -(2-bromo-4-biphenyl)butyric acid
 γ -chloro- γ -(2-fluoro-4-biphenyl)butyric acid
 γ -chloro- γ -(2-iodo-4-biphenyl)butyric acid
 γ -chloro- γ -(2-nitro-4-biphenyl)butyric acid
 γ -chloro- γ -(2-amino-4-biphenyl)butyric acid
 γ -chloro- γ -(2-acetyl-amino-4-biphenyl)butyric acid
 γ -chloro- γ -(2-ethyl-amino-4-biphenyl)butyric acid
 γ -chloro- γ -(2-dimethyl-amino-4-biphenyl)butyric acid
 γ -chloro- γ -(2-mercapto-4-biphenyl)butyric acid

γ -chloro- γ -(2-acetylthio-4-biphenyl)butyric acid
 γ -chloro- γ -(2-methylthio-4-biphenyl)butyric acid
 γ -chloro- γ -(2-methylsulfinyl-4-biphenyl)butyric acid
 γ -chloro- γ -(2-methylsulfonyl-4-biphenyl)butyric acid
 γ -chloro- γ -(2-hydroxy-4-biphenyl)butyric acid
 γ -chloro- γ -(2-methoxy-4-biphenyl)butyric acid
 γ -chloro- γ -(2-acetoxy-4-biphenyl)butyric acid
 γ -chloro- γ -(2-trifluoromethyl-4-biphenyl)butyric acid
 γ -chloro- γ -(2-cyano-4-biphenyl)butyric acid
 γ -chloro- γ -(2-acetyl-4-biphenyl)butyric acid
 γ -chloro- γ -(p-i-butylphenyl)butyric acid
 γ -chloro- γ -(p-cyclohexylphenyl)butyric acid
 γ -chloro- γ -(3-chloro-4-cyclohexylphenyl)butyric acid
 γ -chloro- γ -(3-chloro-4-i-butylphenyl)butyric acid
 γ -chloro- α -methyl- γ -(p-biphenyl)butyric acid
 γ -chloro- β -methyl- γ -(p-biphenyl)butyric acid
 γ -chloro- γ -methyl- γ -(p-biphenyl)butyric acid
 γ -chloro- α,β -dimethyl- γ -(p-biphenyl)butyric acid
 γ -chloro- α,γ -dimethyl- γ -(p-biphenyl)butyric acid
 γ -chloro- β,γ -dimethyl- γ -(p-biphenyl)butyric acid
 γ -chloro- α,β,γ -trimethyl- γ -(p-biphenyl)butyric acid
 γ -chloro- α -methyl- γ -(m-phenoxyphenyl)butyric acid
 γ -bromo- γ -(p-biphenyl)butyric acid
 γ -fluoro- γ -(p-biphenyl)butyric acid
 γ -iodo- γ -(p-biphenyl)butyric acid
 γ -mercapto- γ -(p-biphenyl)butyric acid
 γ -methylthio- γ -(p-biphenyl)butyric acid
 γ -acetylthio- γ -(p-biphenyl)butyric acid
 γ -benzoylthio- γ -(p-biphenyl)butyric acid
 γ -sulfo- γ -(p-biphenyl)butyric acid
 γ -sulfin- γ -(p-biphenyl)butyric acid
 γ -methylsulfinyl- γ -(p-biphenyl)butyric acid
 γ -methylsulfonyl- γ -(p-biphenyl)butyric acid
 γ -thioacetylthio- γ -(p-biphenyl)butyric acid
 γ -thiosulfo- γ -(p-biphenyl)butyric acid
 γ -thiocyanato- γ -(p-biphenyl)butyric acid
 γ -amidinothio- γ -(p-biphenyl)butyric acid
 γ -carbamylthio- γ -(p-biphenyl)butyric acid
 γ -ethylcarbamylthio- γ -(p-biphenyl)butyric acid
 γ -diethylcarbamylthio- γ -(p-biphenyl)butyric acid
 γ -methoxythiocarbonylthio- γ -(p-biphenyl)butyric acid
 γ -dimethylthiocarbamylthio- γ -(p-biphenyl)butyric acid
 γ -benzyloxycarbonylthio- γ -(p-biphenyl)butyric acid
 γ -(o-carboxybenzoylthio)- γ -(p-biphenyl)butyric acid
 γ -cyano- γ -(p-biphenyl)butyric acid
 γ -dimethylamino- γ -(p-biphenyl)butyric acid
 γ -(4-carboxybutyryloxy)- γ -(p-biphenyl)butyric acid
 γ -(4-carboxybut-2-enyloxy)- γ -(p-biphenyl)butyric acid
 γ -acetylthio- γ -(p-i-butylphenyl)butyric acid
 γ -acetylthio- γ -(3-chloro-4-i-butylphenyl)butyric acid
 γ -acetylthio- γ -(p-cyclohexylphenyl)butyric acid
 γ -acetylthio- γ -(3-chloro-4-cyclohexylphenyl)butyric acid
 γ -acetylthio- γ -[p-(2'-chlorobiphenyl)]butyric acid
 γ -acetylthio- γ -(2-chloro-4-biphenyl)butyric acid

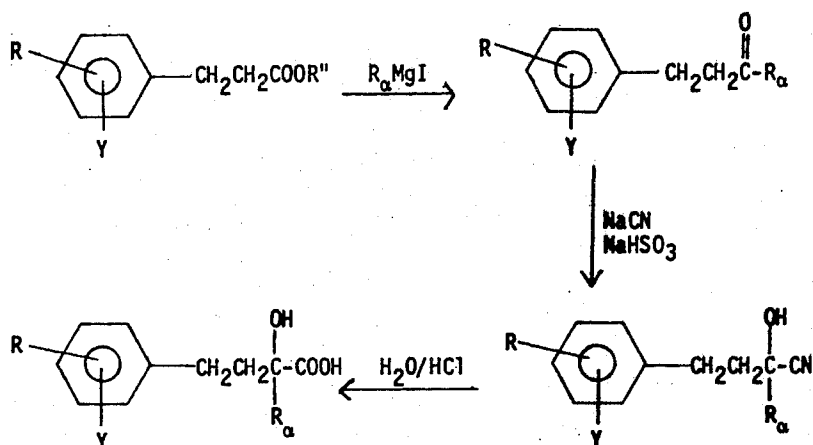
γ -acetylthio- α -methyl- γ -(p-biphenyl)butyric acid
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 γ -acetylthio- β -methyl- γ -(p-biphenyl)butyric acid
 γ -acetylthio- γ -methyl- γ -(p-biphenyl)butyric acid
 γ -acetylthio- α -methyl- γ -(3-chloro-4-i-butylphenyl)butyric acid
methyl γ -chloro- γ -(p-biphenyl)butyrate
ethyl γ -chloro- γ -(p-biphenyl)butyrate
benzyl γ -chloro- γ -(p-biphenyl)butyrate
N-methyl γ -chloro- γ -(p-biphenyl)butyramide
N,N-dimethyl γ -chloro- γ -(p-biphenyl)butyramide
N-cyclopropyl γ -chloro- γ -(p-biphenyl)butyramide
N,N-pentamethylene γ -chloro- γ -(p-biphenyl)butyramide
N,N-oxydiethylene γ -chloro- γ -(p-biphenyl)butyramide
N,N-thiotrimethylene γ -chloro- γ -(p-biphenyl)butyramide
 γ -chloro- γ -(p-biphenyl)butyric acid, sodium salt
 γ -chloro- γ -(p-biphenyl)butyric acid, potassium salt
 γ -chloro- γ -(p-biphenyl)butyric acid, calcium salt
 γ -chloro- γ -(p-biphenyl)butyric acid, aluminum salt
 γ -chloro- γ -(p-biphenyl)butyric acid, diethylammonium salt
 γ -chloro- γ -(p-biphenyl)butyric acid, cyclohexylammonium salt
 γ -chloro- γ -(p-biphenyl)butyric acid, β -hydroxyethylammonium salt
 γ -chloro- γ -(p-biphenyl)butyric acid, piperazinium salt
 γ -chloro- γ -(p-biphenyl)butyric acid, methylbenzylammonium salt
methyl γ -acetylthio- γ -(p-biphenyl)butyrate
ethyl γ -acetylthio- γ -(p-biphenyl)butyrate
benzyl γ -acetylthio- γ -(p-biphenyl)butyrate
N-methyl γ -acetylthio- γ -(p-biphenyl)butyramide
N,N-dimethyl γ -acetylthio- γ -(p-biphenyl)butyramide
N-cyclopropyl γ -acetylthio- γ -(p-biphenyl)butyramide
N,N-pentamethylene γ -acetylthio- γ -(p-biphenyl)butyramide
N,N-oxydiethylene γ -acetylthio- γ -(p-biphenyl)butyramide
N,N-thiotrimethylene γ -acetylthio- γ -(p-biphenyl)butyramide
 γ -acetylthio- γ -(p-biphenyl)butyric acid, sodium salt
 γ -acetylthio- γ -(p-biphenyl)butyric acid, potassium salt
 γ -acetylthio- γ -(p-biphenyl)butyric acid, calcium salt
 γ -acetylthio- γ -(p-biphenyl)butyric acid, aluminum salt
 γ -acetylthio- γ -(p-biphenyl)butyric acid, diethylammonium salt
 γ -acetylthio- γ -(p-biphenyl)butyric acid, cyclohexylammonium salt
 γ -acetylthio- γ -(p-biphenyl)butyric acid, β -hydroxyethylammonium salt
 γ -acetylthio- γ -(p-biphenyl)butyric acid, piperazinium salt
 γ -acetylthio- γ -(p-biphenyl)butyric acid, methylbenzylammonium salt

Claisen condensation of a substituted benzaldehyde with an active acid ester (preferably a loweralkyl or benzyl ester) in the presence of a metal alkoxide results in a β -acrylic acid ester. The aldehyde may also be subjected to a Perkin reaction with acetic anhydride and an acetic acid salt or through a Knoevenagel condensation using malonic acid and ammonia in an amine base

to obtain a substituted β -acrylic acid. Hydrogenation of the double bond in the presence of a heterogeneous catalyst results in the propionic acid or ester. Conversion of the propionic acid to the acid halide followed by Rosenmund reduction in the presence of a supported catalyst results in the propionaldehyde. This in turn is treated with cyanohydrin to afford the propionaldehyde cyanohydrin which is then hydrolyzed to the α -hydroxybutyric acid. The ester or amide may also be prepared in the same manner.



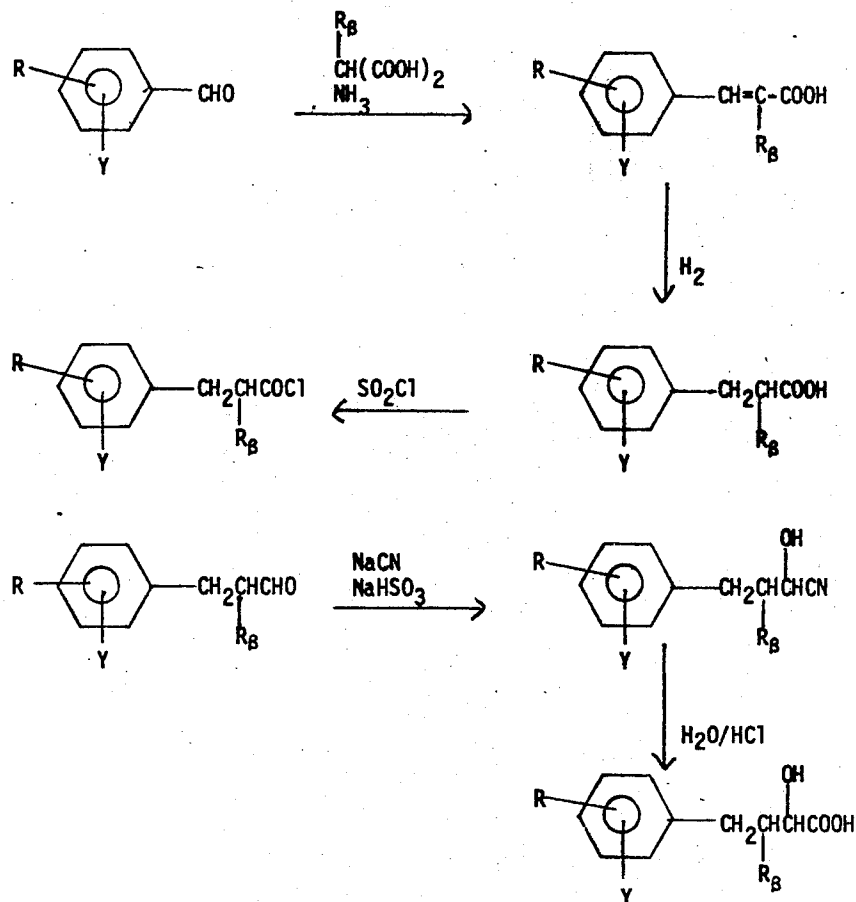
The α -alkyl- α -hydroxy- γ -substituted phenyl butyric acid may be prepared by reacting a β -substituted phenyl propionic acid ester with an alkyl Grignard reagent to obtain a 1-substituted phenyl-3-butanone which on reaction with sodium cyanide in the presence of sodium bisulfite yields the 1-substituted phenyl-3-butanone cyanohydrin. Hydrolysis gives the desired acid, ester or amide.



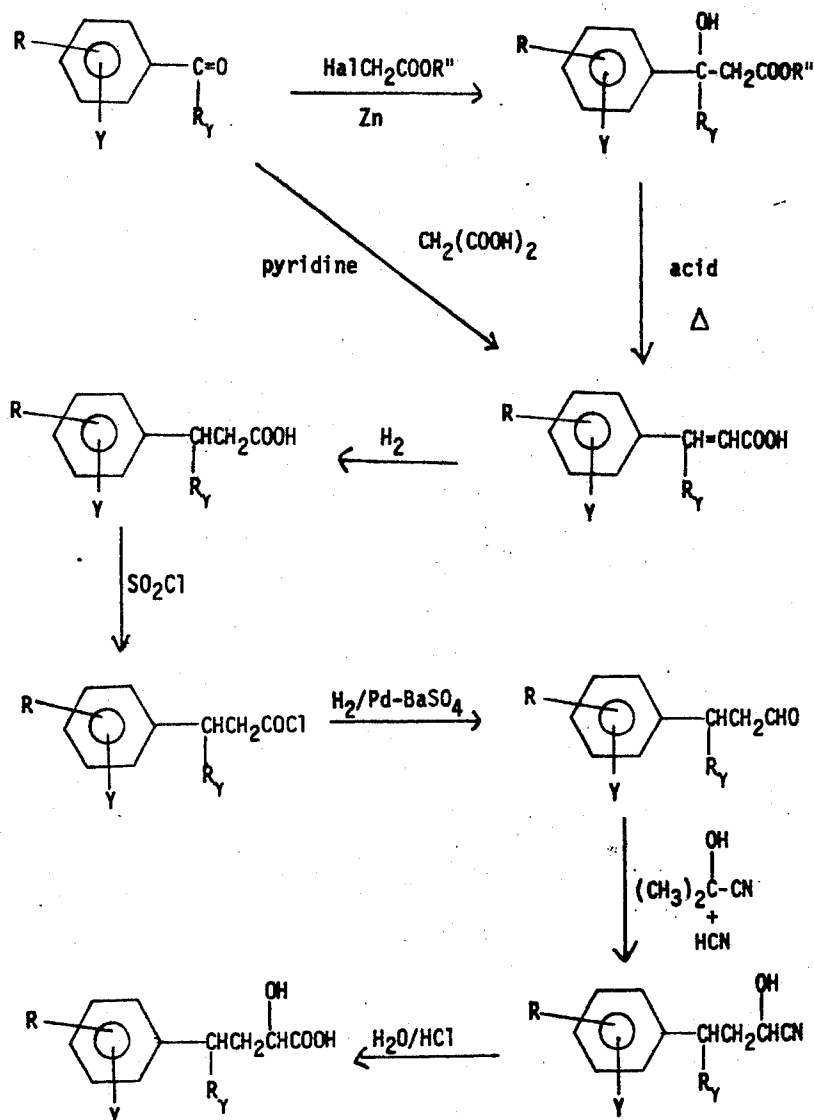
The β -alkyl- α -hydroxy- γ -substituted phenyl butyric acids may be prepared as previously described for the α -hydroxy- γ -substituted phenyl butyric acid compounds by starting with an α -alkylmalonic acid in the Knoevenagel condensation to obtain an α -alkyl- β -substituted acrylic acid.

The γ -alkyl- α -hydroxy- γ -substituted phenyl butyric acids may be prepared as previously described for the α -hydroxy- γ -substituted phenyl butyric acid compounds. The reaction sequence starting material is a substituted phenyl alkyl ketone upon which a Reformatsky reaction is performed with an α -halo acetate in the presence of zinc. The resultant β -hydroxy- β -alkyl- β -substituted phenyl propionate is then dehydrated

with acid at raised temperatures to the β -alkyl- β -substituted phenylacrylic acid. This may also be accomplished by carrying out a Doebner modification of the Perkin reaction on a substituted phenyl alkyl ketone with malonic acid in the presence of pyridine to obtain the β -alkyl- β -substituted phenyl acrylic acid.



This, in turn, is then reacted as previously described to obtain the desired γ -alkyl- α -hydroxy- γ -substituted phenyl butyric acid.



Grignard conditions results in the substituted phenyl magnesium bromide. When this is condensed with 2,3-epoxypropyl chloride the resultant product is 1-chloro-

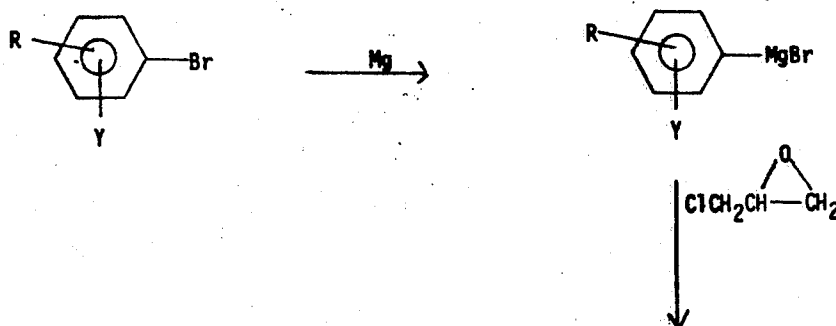
A combination of the previously described reactions affords di- and tri-substitution in the side chain.

The β -position

Reaction of a substituted bromobenzene under

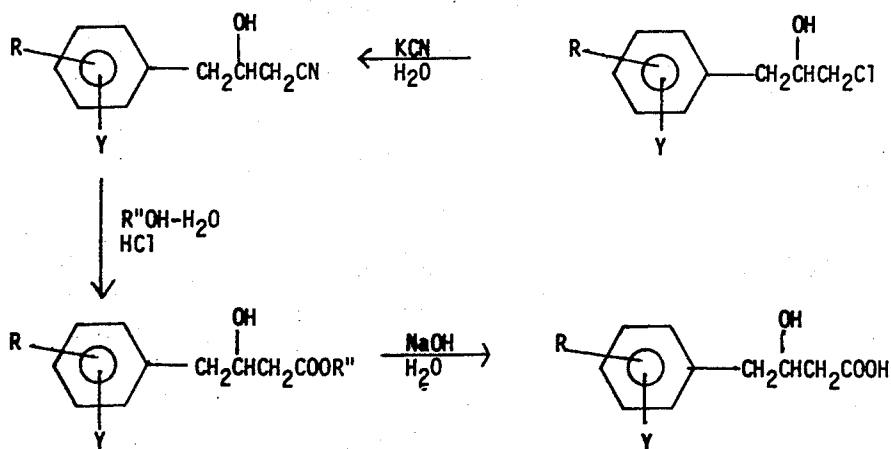
3-substituted phenylpropan-2-ol. Reaction of the latter chlorohydrin with an aqueous solution of potassium cyanide affords the 1-cyano-3-substituted phenylpropan-2-ol which on hydrolysis and esterification results in the γ -substituted phenyl- β -hydroxybutyrate. Acid hydrolysis of this ester gives the γ -substituted phenyl- β -hydroxybutyric acid.

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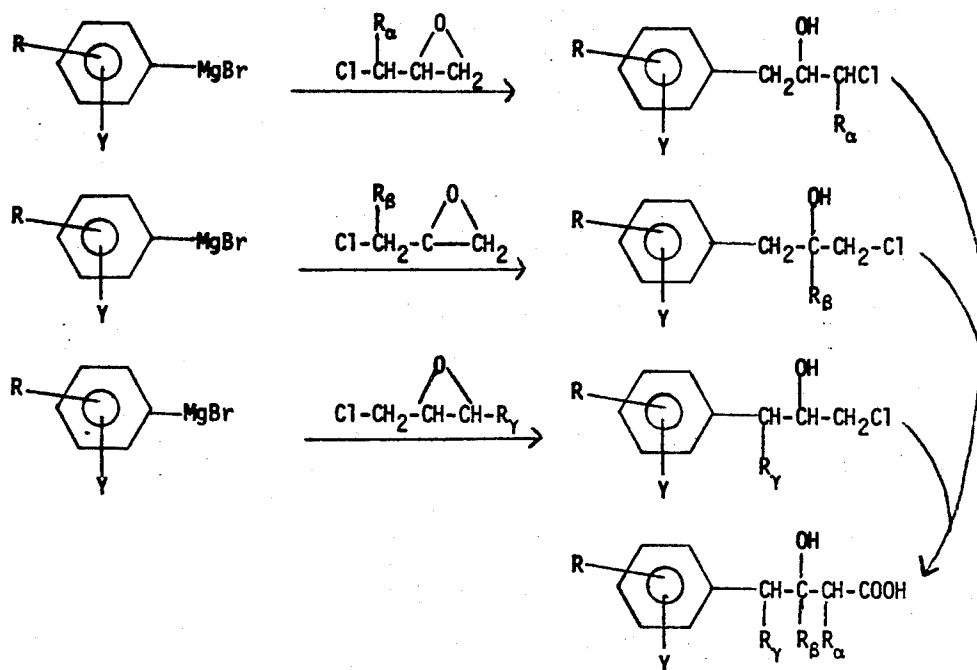


When the α -alkyl- β -hydroxy- γ -substituted phenyl butyric acid is desired 1-methyl-2,3-epoxypropyl chloride is used. The corresponding β -alkyl compound is prepared when the starting material is 2-methyl-2,3-epoxypropyl chloride and the γ -alkyl compound results when the starting material is 2,3-epoxybutyl chloride.

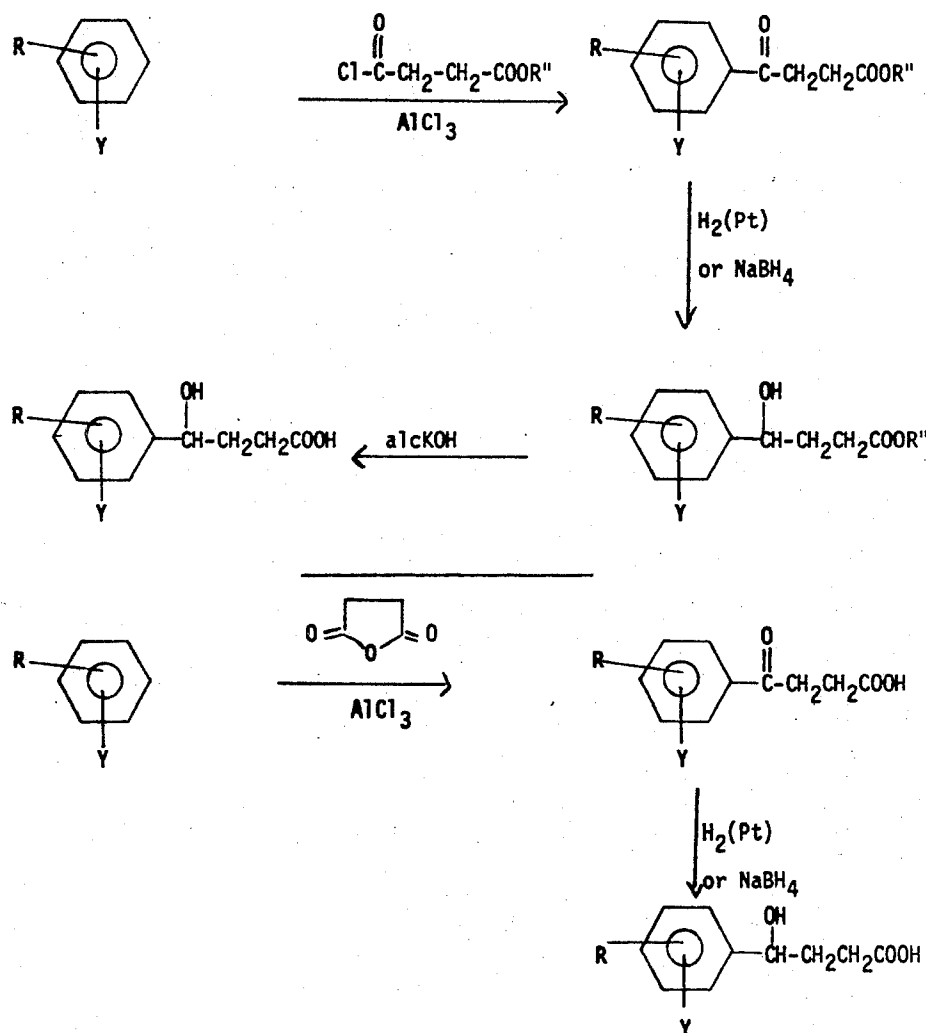
Again, using the desired epoxyalkylchloride the corresponding di or tri alkyl substituted compound results.

The γ -position

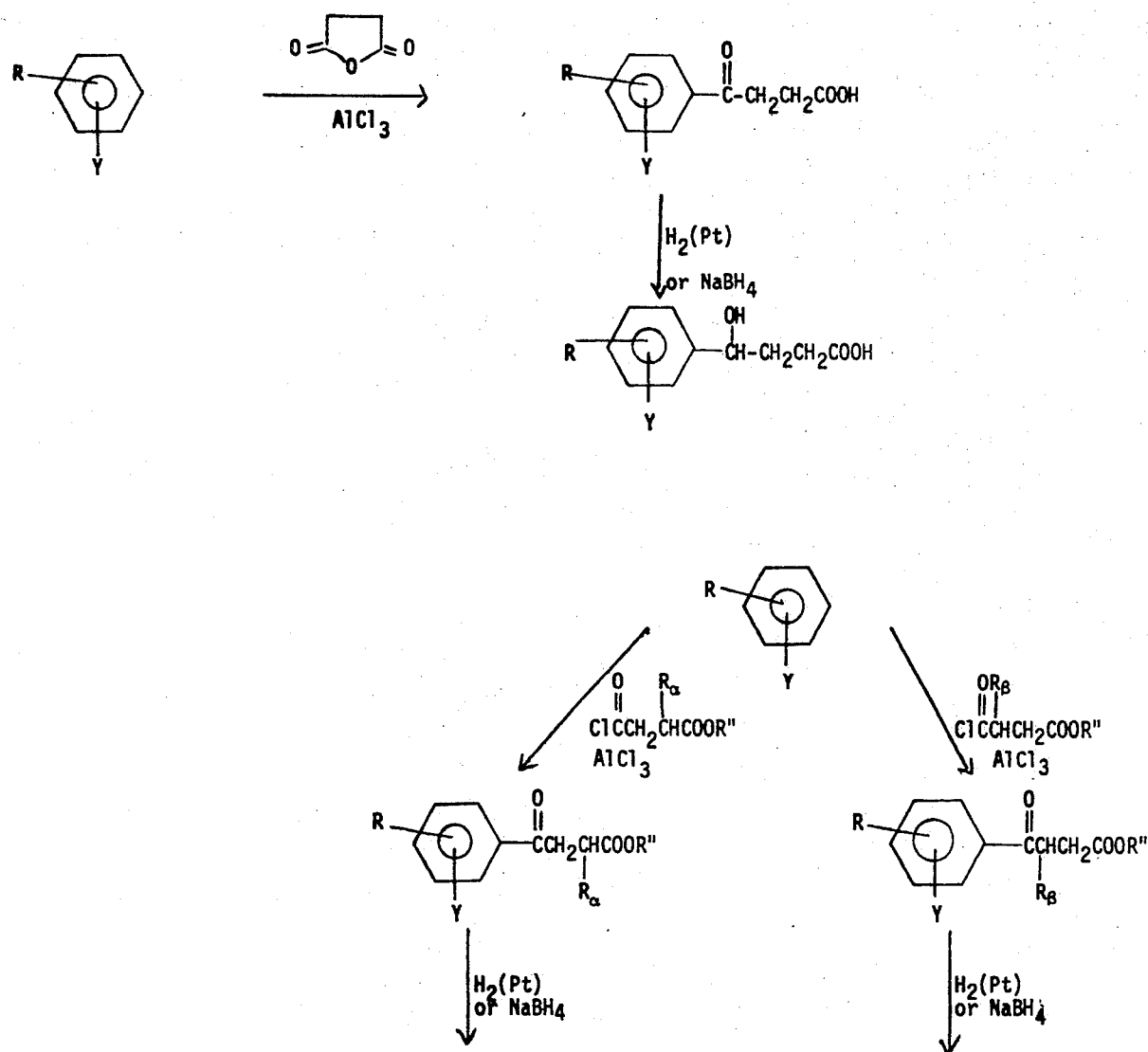
Friedel-Crafts reaction of a substituted benzene with alkyl succinyl chloride or succinic anhydride results in



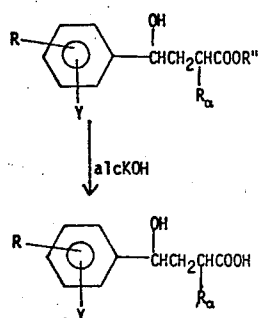
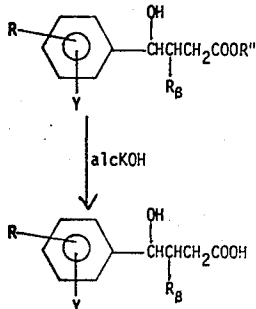
formation of a γ -substituted phenyl- γ -keto butyric acid ester or the acid. Reduction of the γ -keto group may then be carried out in the presence of a metal catalyst or sodium borohydride to obtain the γ -substituted phenyl- γ -hydroxy butyric acid ester with is then hydrolyzed to the corresponding acid.



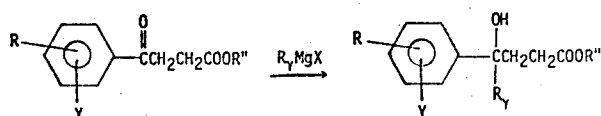
The α -alkyl- γ -substituted phenyl- γ -hydroxybutyric acid or β -alkyl- γ -substituted phenyl- γ -hydroxybutyric acid may be prepared by analogous procedures using the appropriately substituted alkyl succinyl chloride or succinic anhydride.



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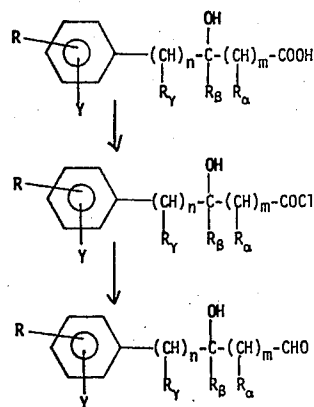


The γ -alkyl- γ -substituted- γ -hydroxybutyric acid is prepared from the γ -keto butyric acid and an alkyl Grignard reagent.



The hydroxybutyric acids may further be reduced to an aldehyde through a Rosenmund reduction in the

24



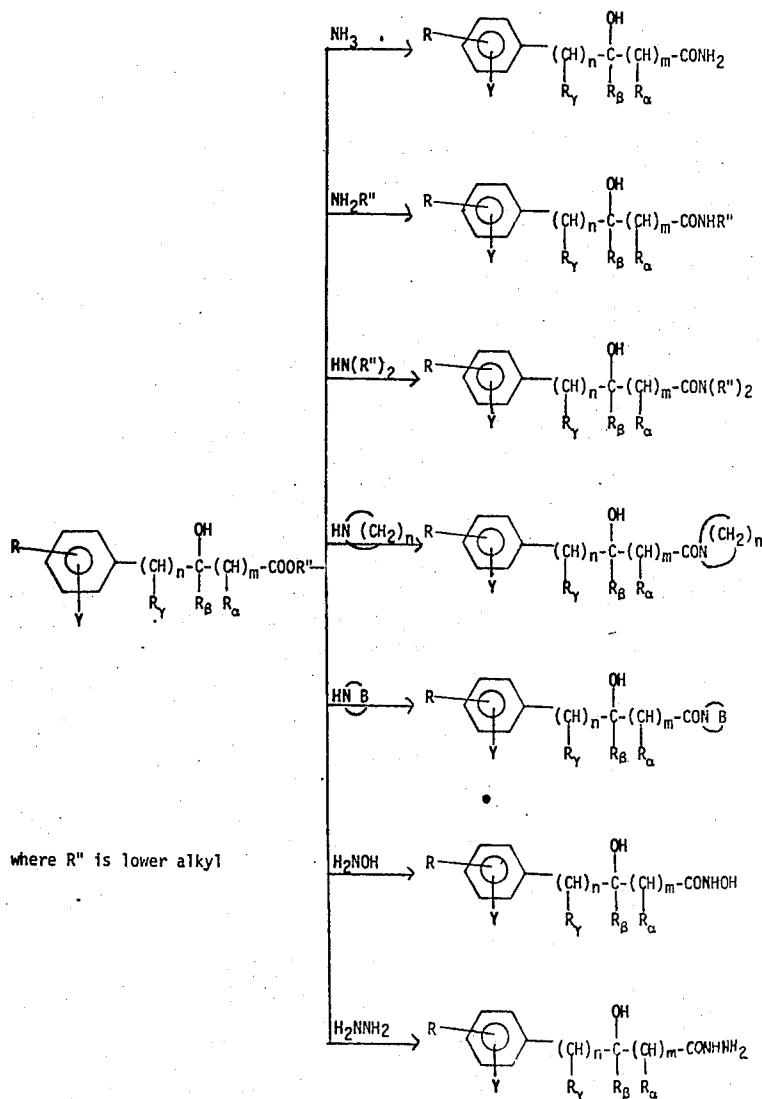
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Reaction of a substituted phenylbutyric acid ester with a nitrogen base such as ammonia, loweralkylamine, diloweralkylamine, cycloweralkylamine, a nitrogen containing hetero compound such as piperidine, morpholine, piperazine, hydroxylamine and hydrazine gives the corresponding amide, hydroxamic acid, or hydrazide.

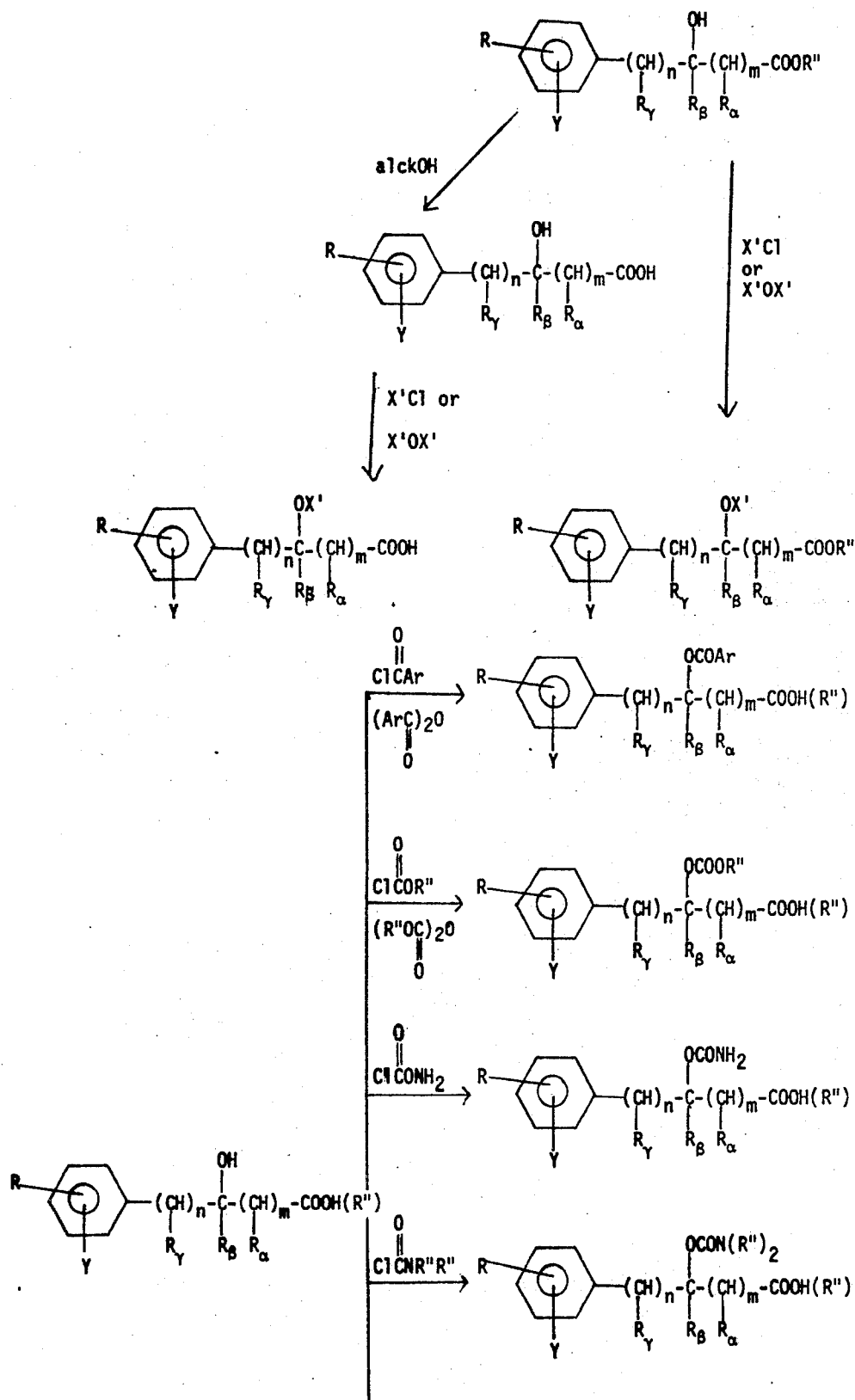


conventional manner. The acid halide is first formed as above and this is then catalytically reduced in the pres-

The butyric acid esters may be hydrolyzed to the corresponding acids. Reaction of the hydroxybutyrate or hydroxybutyric acid with an acid chloride Y/Cl or acid

anhydride $X'OX'$ in the presence of a tertiary amine such as pyridine, picoline, or quinoline results in the formation of an hydroxy derivative of the butyrate. Examples of $X'Cl$ and $X'OX'$ include acetyl chloride, acetic anhydride, propionyl chloride, butyryl chloride, 5

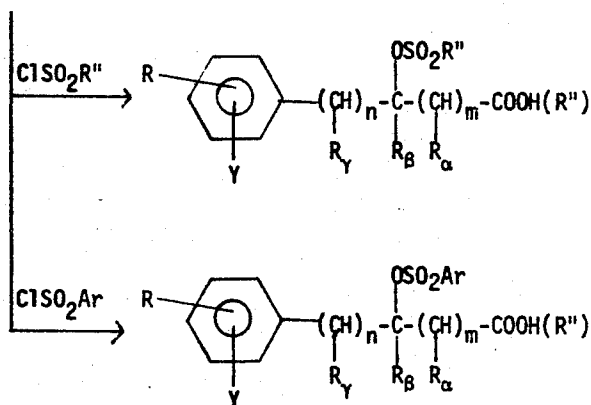
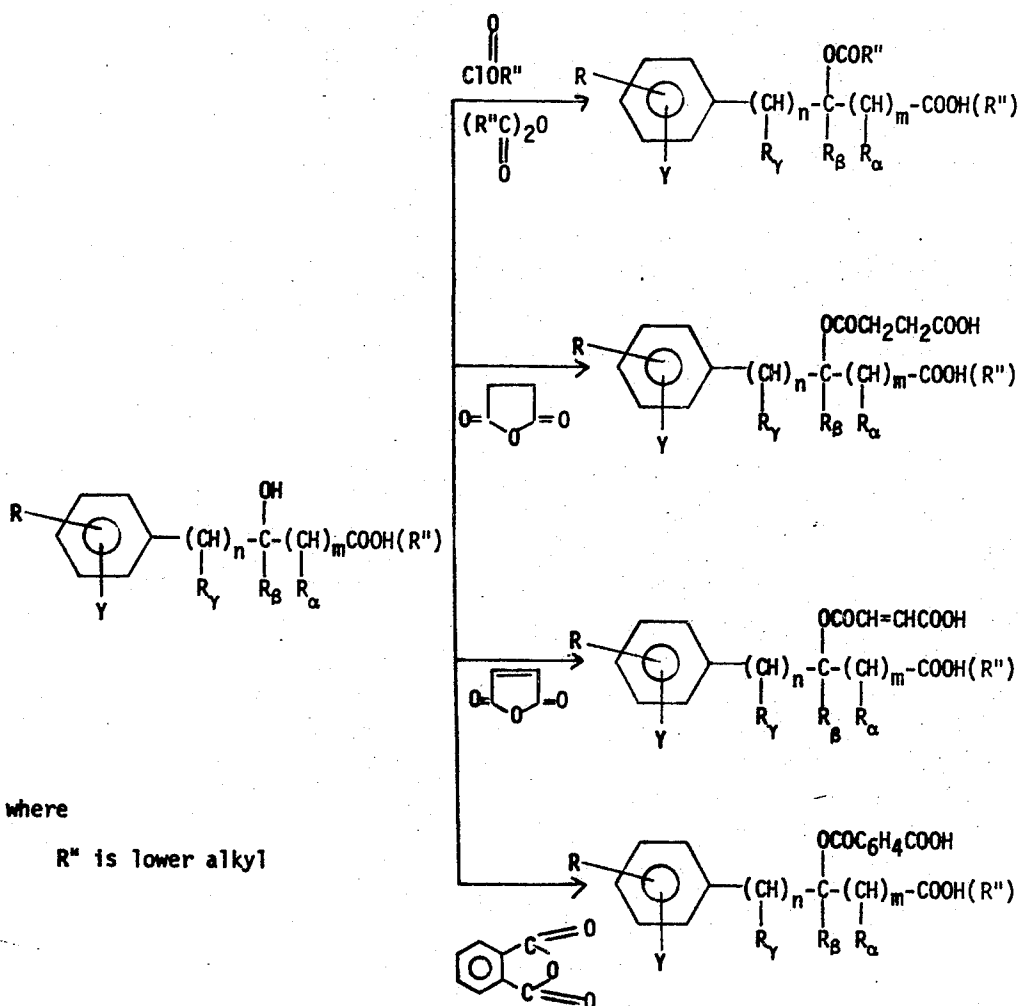
succinic anhydride, maleic anhydride, phthalic anhydride, benzoyl chloride, benzoic anhydride, benzyl chlorocarbonate, ethyl chlorocarbonate, dimethylcarbamyl chloride, dibutylcarbamyl chloride, benzenesulfonyl chloride, methanesulfonyl chloride.



where

R'' is loweralkyl and

Ar is phenyl or
substituted phenyl



where

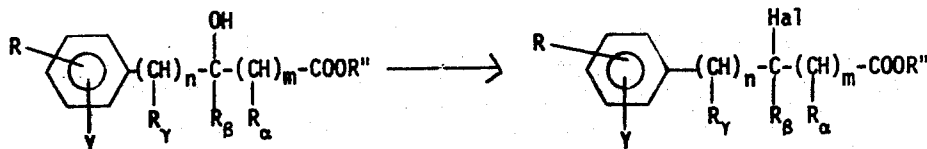
R'' is lower alkyl

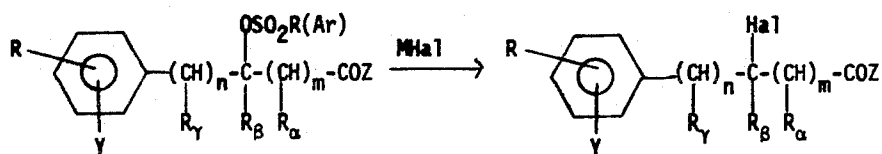
When a substituted hydroxybutyrate is reacted with a phosphorus trihalide, phosphorus pentahalide, phosphorus oxyhalide, sulfurylhalide, thionyl halide, or sulfur halide, the corresponding substituted halo butyrate is prepared.

where R'' is lower alkyl;

where Hal is chloro, bromo or iodo.

Reaction of a sulfonate derivative with a metal halide (preferably an alkali halide) results in the corresponding halo compound.

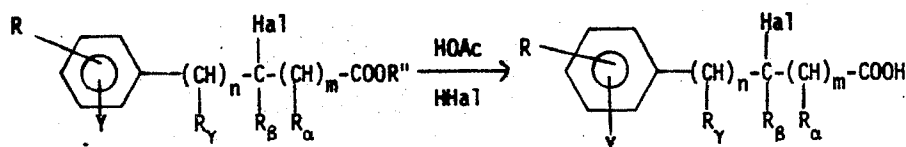




where Z is as described on page 4.

The corresponding halo butyric acid may be prepared by heating the ester with acetic acid containing the corresponding hydrogen halide.

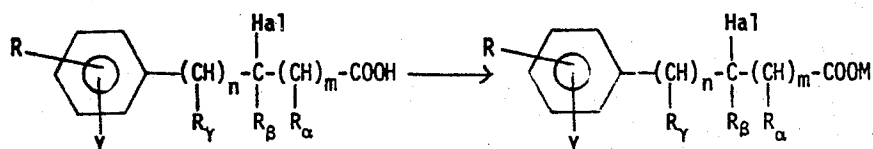
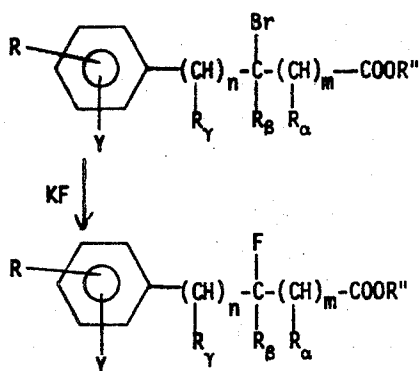
ide, potassium carbonate, sodium bicarbonate, magnesium bicarbonate, etc.). Also, the aluminum salts of the instant products may be obtained by treating the corresponding sodium salt with an appropriate aluminum



where R'' is lower alkyl.

The substituted fluoro compounds may also be obtained from the corresponding iodo, bromo or chloro compounds by reaction with potassium fluoride at about 130–200°C.

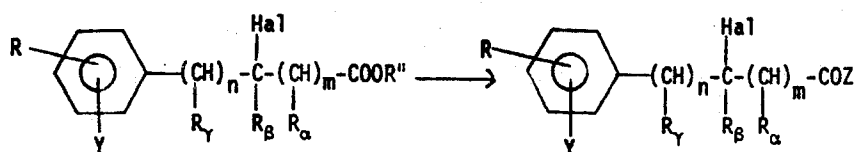
complex such as aluminum hydroxy chloride hexahydrate, etc. The ammonium salts may be made by reaction with the corresponding amine such as methylamine, diethylamine, β -hydroxyethylamine, piperazine, piperidine, α -methylbenzylamine, cyclohexylamine,



triethylamine, phenethylamine, etc.

Reaction of a substituted halo butyrate ester with a nitrogen base such as ammonia, loweralkylamine, diloweralkylamine, cycloloweralkylamine, a nitrogen containing hetero compound such as piperidine, morpholine, piperazine results in the corresponding amide.

The butyrate ester with hydroxylamine gives the corresponding hydroxamic acid, and with hydrazine gives the corresponding hydrazide.



The acid addition salts may be formed by the action of one equivalent of a suitable base with the substituted halo butyric acid. Suitable bases thus include for example the alkali metal alkoxides such as sodium methoxide, etc., and the alkali metal and alkaline earth metal hydroxides, carbonates, bicarbonates, etc. (such as sodium hydroxide, potassium hydroxide, calcium hydrox-

Where:

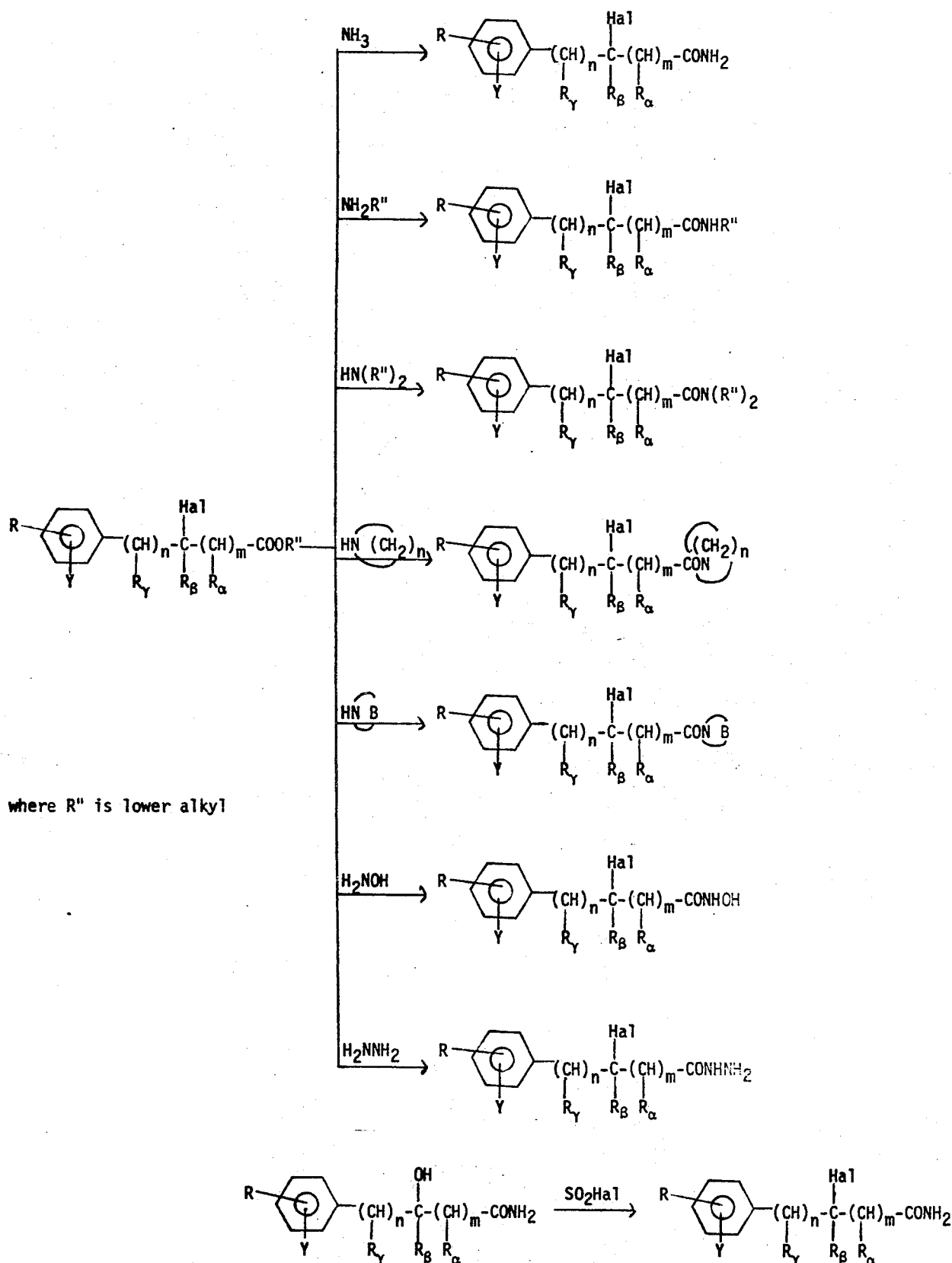
Z is —NH₂,
loweralkylamine,
diloweralkylamino,
cycloloweralkylamino,

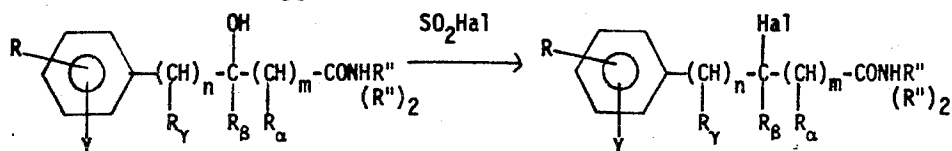
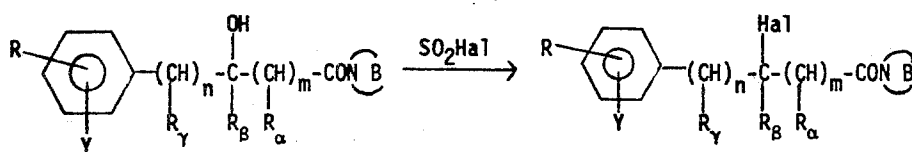
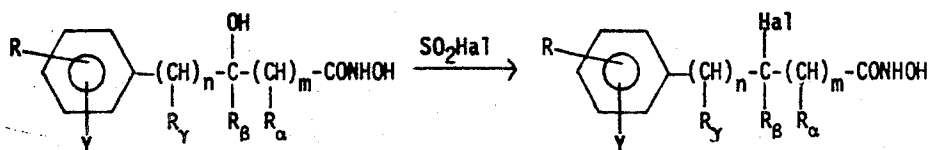
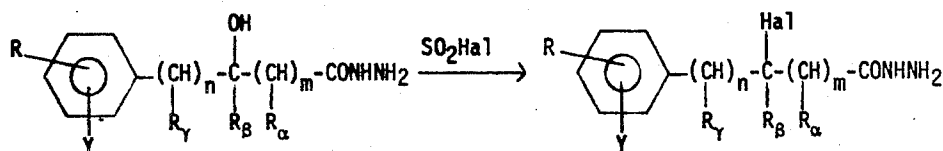
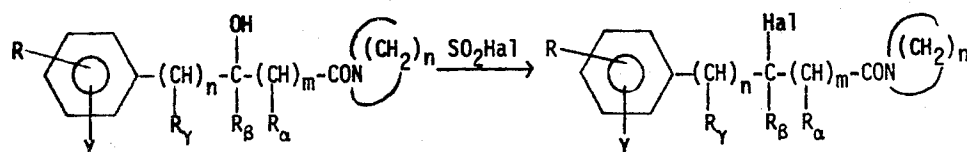


(where B is loweralkyldienyl or heteroloweralkyldienyl),

—NHOH or
—NHNH₂.

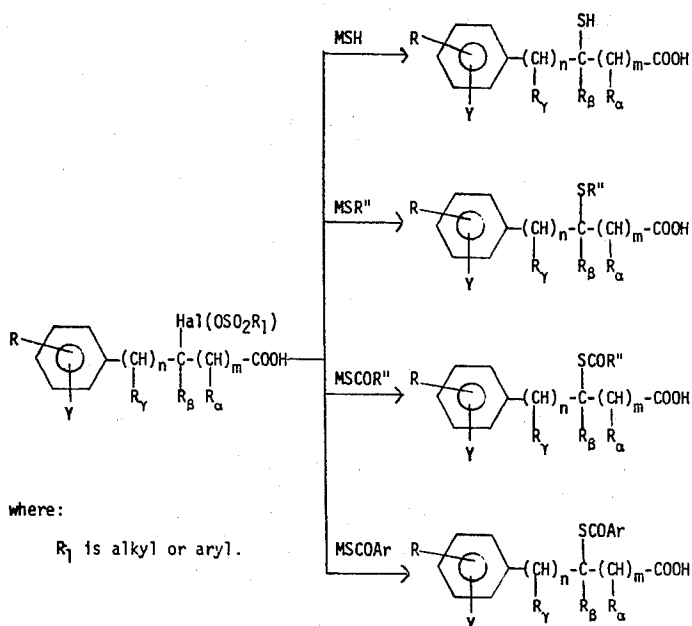
The halo butyramides, butyrylhydroxamic acids or butyrylhydrazides can be prepared from the corresponding hydroxy butyramides with thionyl halides according to the method of I. A. Smith, Chem. Berichte 71B:634 5 (1938).

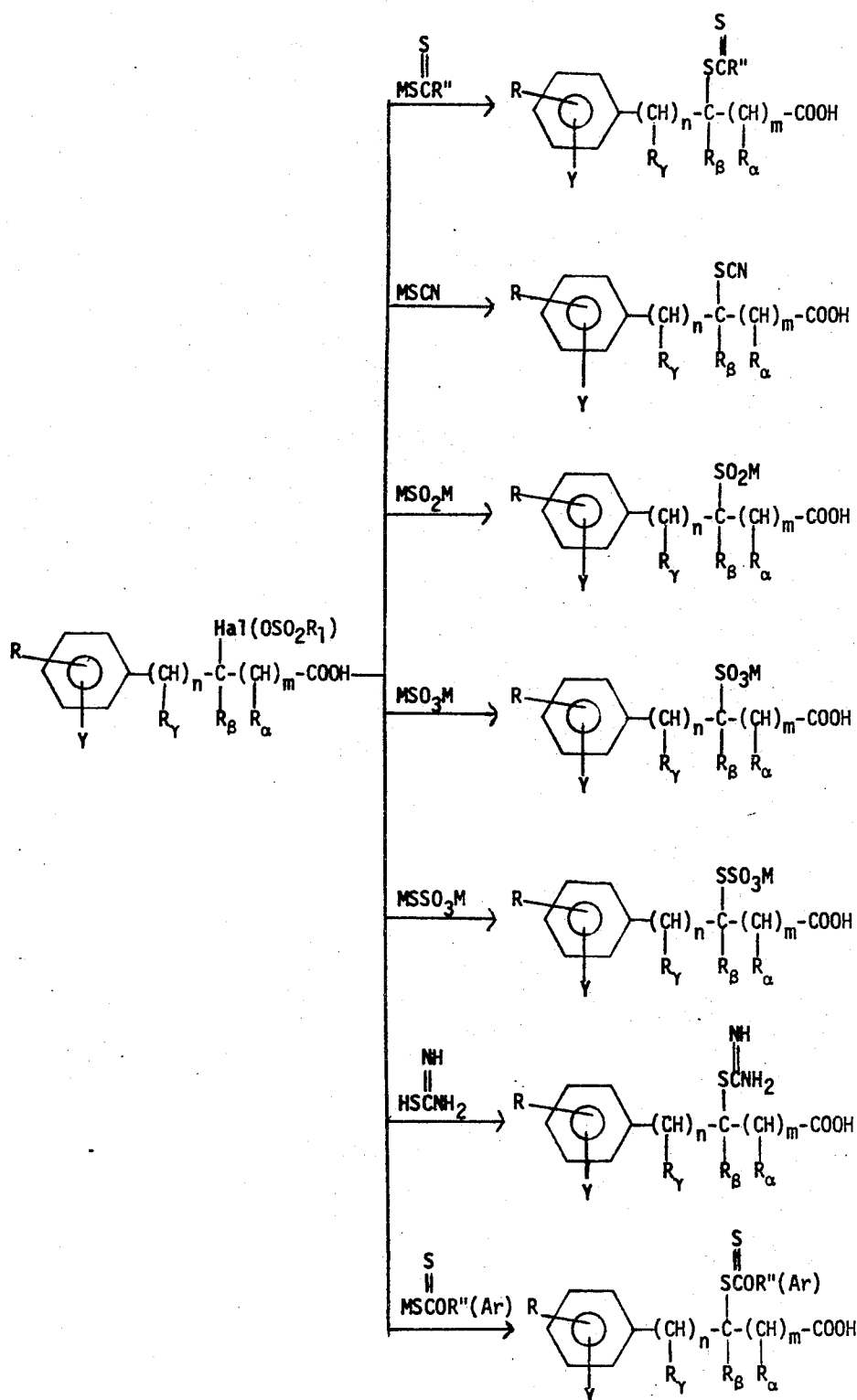




The substituted halo butyric acids and acid derivatives such as their salts, amides or esters may be reacted with various nucleophilic reagents which will replace the halogen group. Thus, for example, an alkali hydrosulfide, alkali thioalkanoate, alkali thiobenzoate, alkali loweralkylxanthate, thiourea, alkali thio-

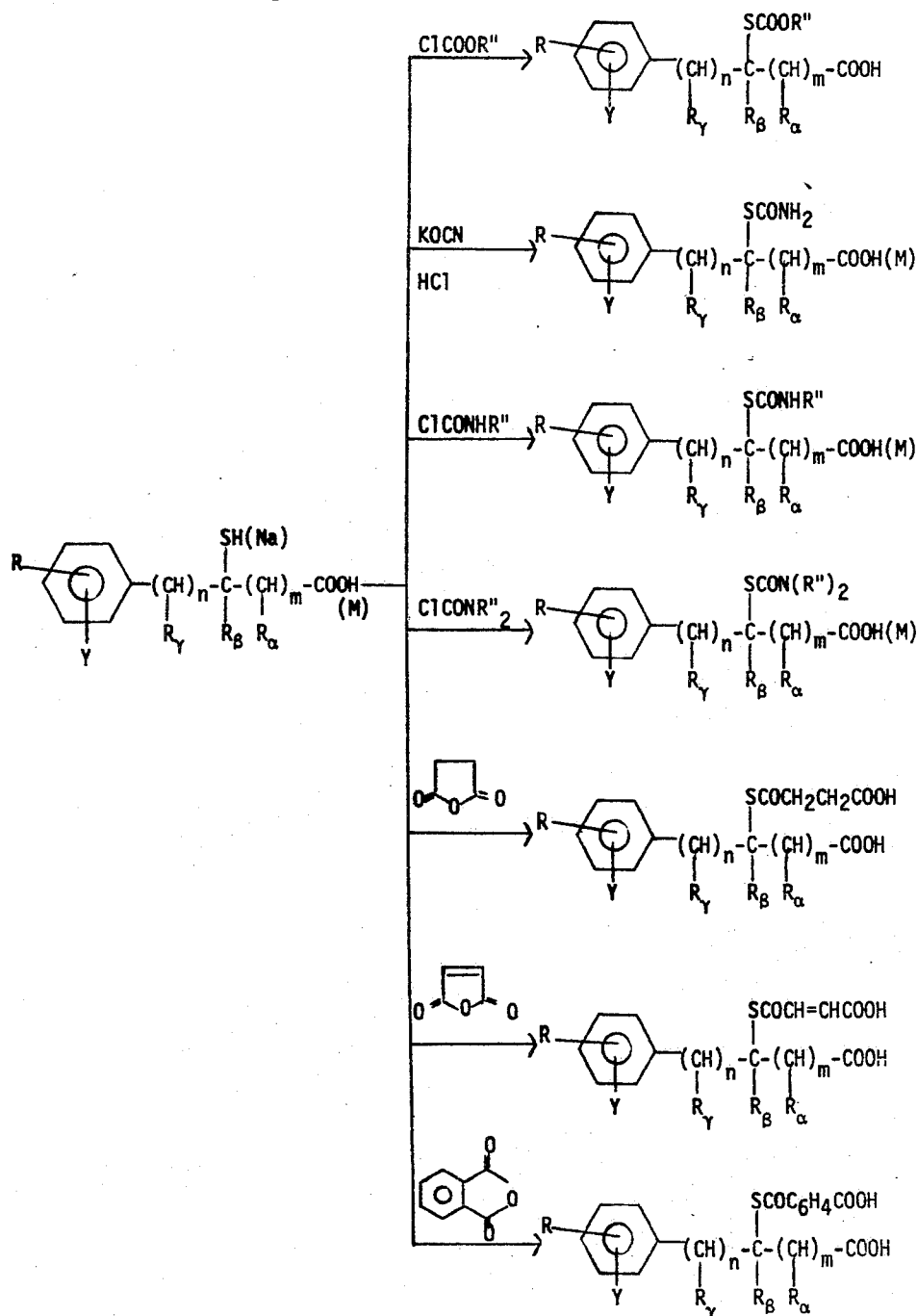
cyanate, alkali thiosulfate, alkali loweralkylmercaptide, alkali sulfite or an alkali sulfinate may be reacted with the chloro, bromo or iodo butyric acid to form the corresponding derivative of the mercapto butyric acid. This may also be carried out on the sulfonate compounds.



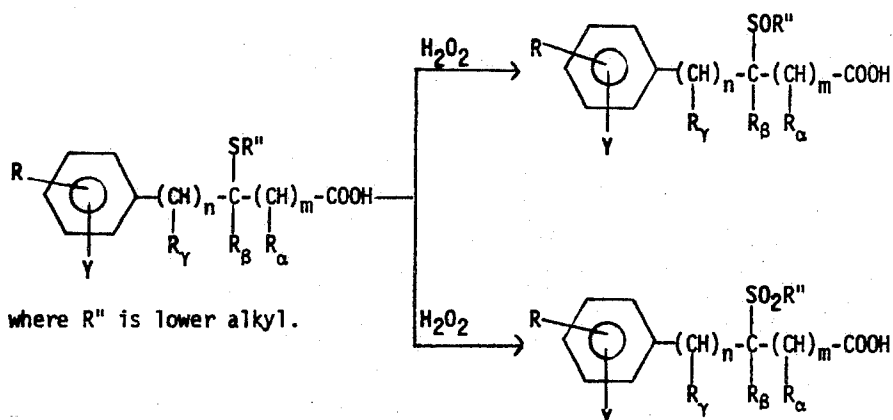


The mercapto butyric acids may then be reacted with a loweralkyl chlorocarbonate, an alkali isocyanate in the presence of hydrogen chloride, a loweralkylcarbamyl chloride, a diloweralkylcarbamyl chloride or converted to the metal salt which will react with a carba-

60 myl chloride to form the corresponding mercapto-
 butyric acid derivatives. The mercapto-
 butyric acid may also be reacted with succinic anhydride, maleic
 anhydride or phthalic anhydride to form the corre-
 65 sponding derivative.

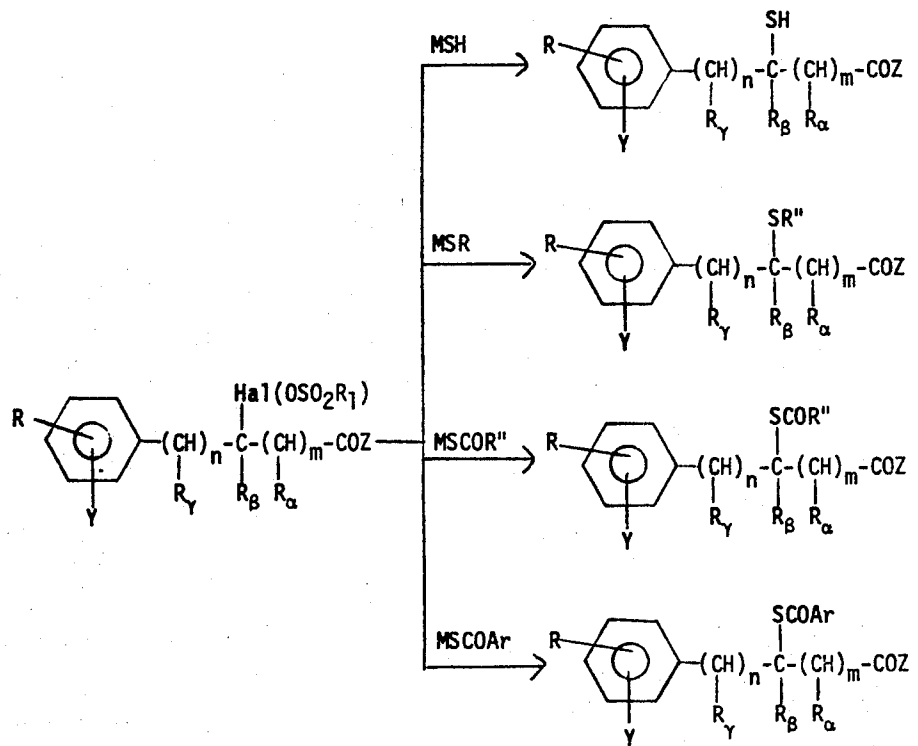


The loweralkylmercapto butyric acid may further be oxidized to the loweralkylsulfinyl and loweralkylsulfonyl groups.



In an analogous manner the various mercaptobuty-
rates, mercaptobutyramides and mercaptobutyric acid

salts may be prepared from the corresponding halobu-
tyrates, halobutyramides and halobutyric acid salts.



where
35 R_1 is alkyl or aryl.

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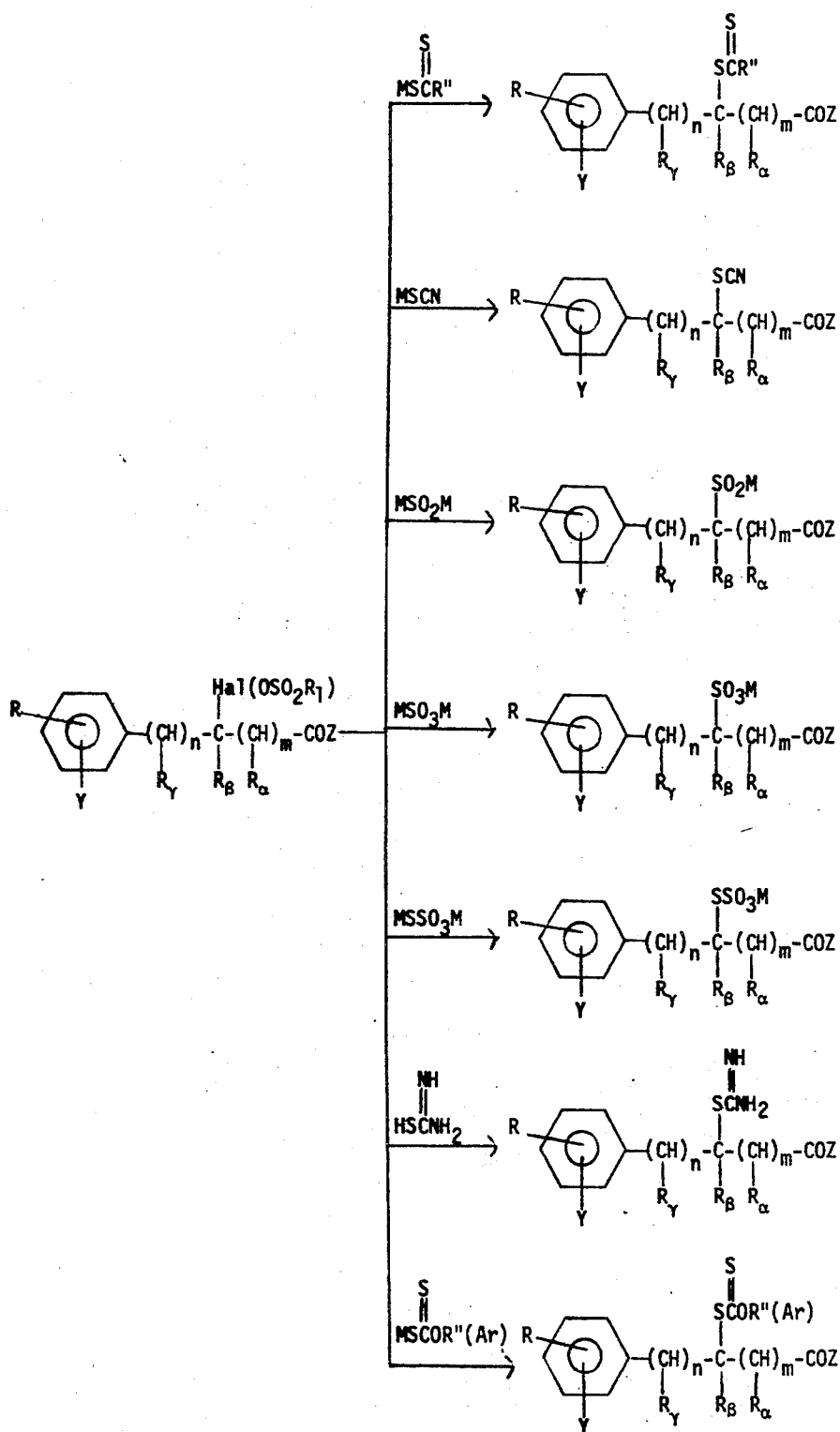
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wherein:

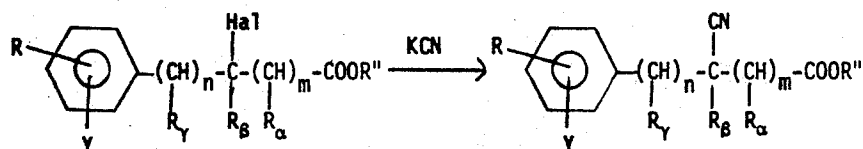
M is an alkali metal salt;

R'' is lower alkyl;

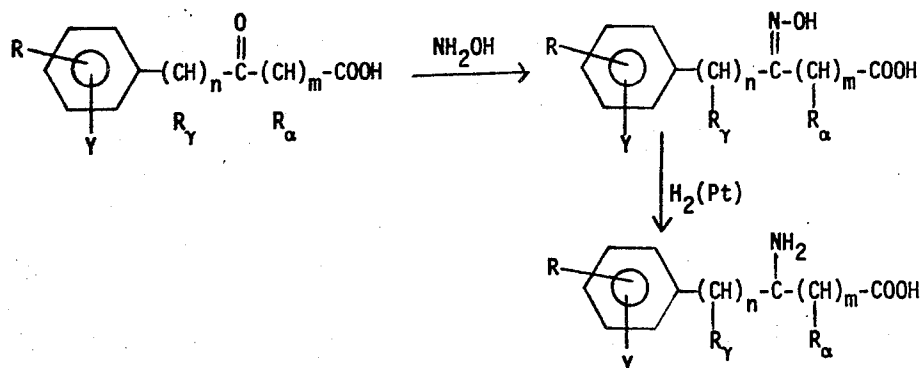
Ar is phenyl or tolyl;

R₁ is alkyl or aryl.

60 Reaction of a substituted halo butyric acid derivative with an alkali cyanide produces the corresponding substituted cyano butyric acid derivative.

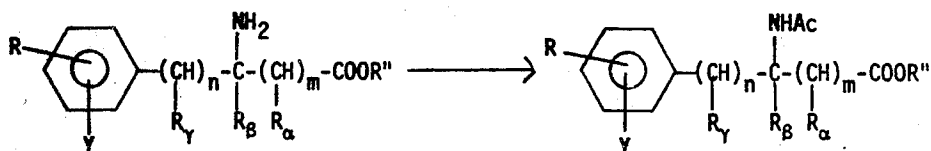


The corresponding acids, acid salts, esters and amides of the foregoing cyano butyric acids may be prepared according to the previously described proce-



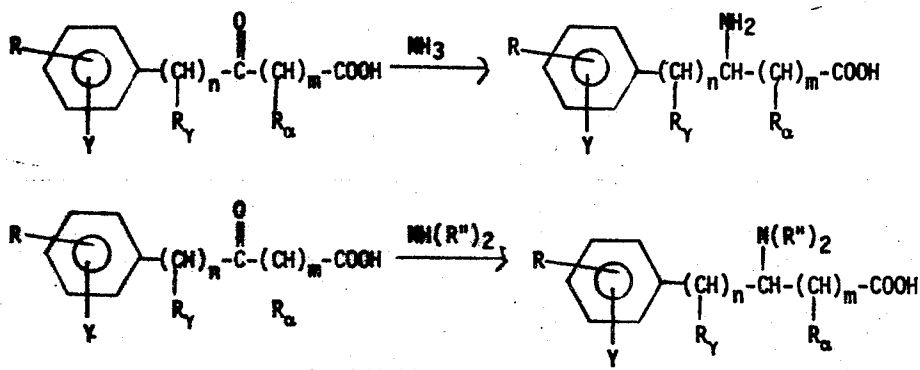
dures or the replacement of the halo group with the cyano group may be carried out on the desired acid 20 salt, ester or amide.

Treatment of the amino butyric acid or acid derivatives with an acyl halide results in the corresponding acyl-amino butyric acid or corresponding derivative.



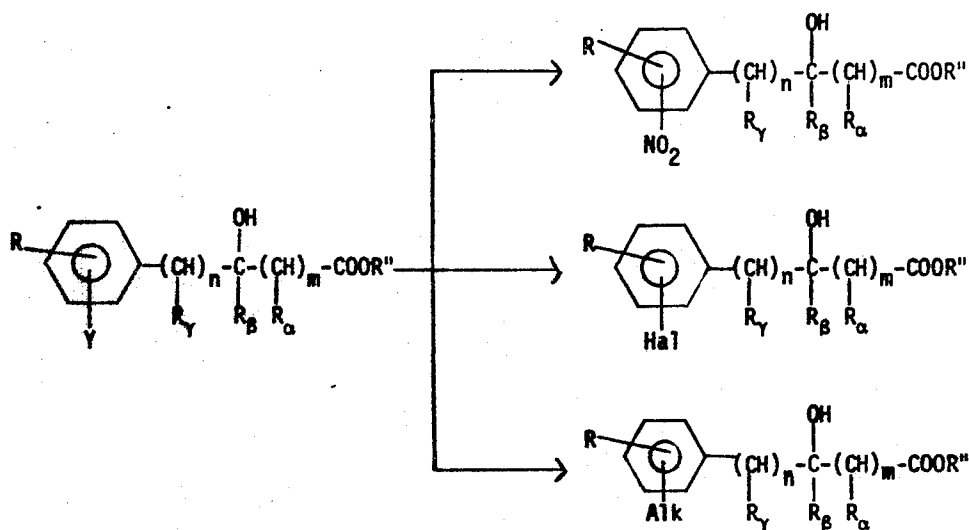
Substituted amino butyric acids and their acid derivatives are prepared from substituted ketobutyric acids by reaction with ammonia or a loweralkylamine and hydrogen over a Raney nickel or platinum catalyst.

Appropriately desired end products having various Y substituents can be prepared by using suitable reactions in order to convert one group to another. Thus, for example, the hydroxybutyrates may be alkylated, halogenated or nitrated to obtain substitution in the phenyl rings as desired.



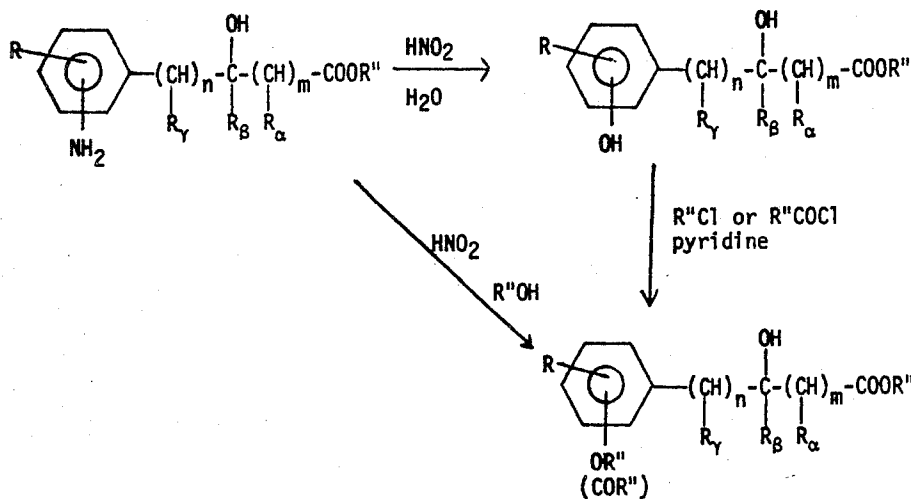
Substituted amino butyric acids may also be prepared by hydrogenation of a substituted ketobutyric acid

nated or nitrated to obtain substitution in the phenyl rings as desired.

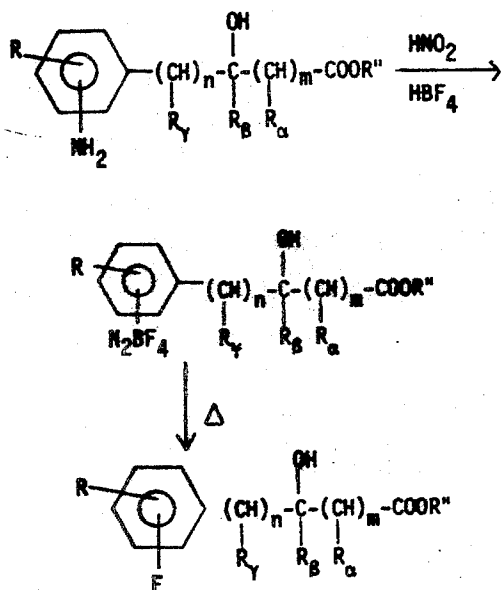


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An aminophenyl-hydroxybutyrate may also be diazotized to the diazonium fluoroborate which is then ther-



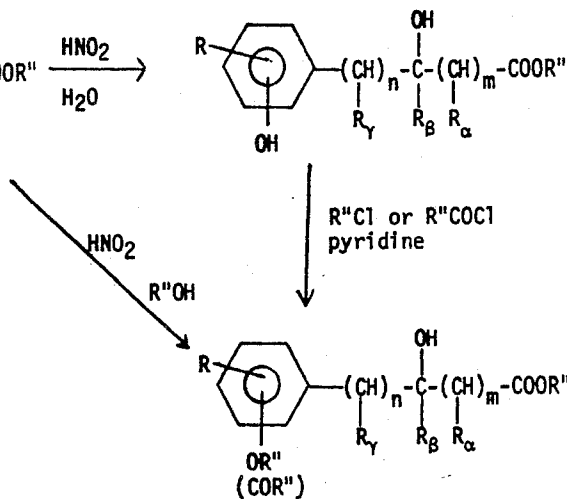
mally decomposed to the fluorophenyl-hydroxybutyrate.



The aminophenylhydroxybutyrate may be diazotized and heated in an aqueous medium to form the hydroxyphenyl compound or heated in an alcohol to form the alkoxyphenyl compound. The hydroxyl group may also be alkylated with loweralkyl halides or sulfates to the alkoxy group or acylated with loweracyl chlorides or

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anhydrides to the acyloxy compound in the presence of a tertiary amine such as pyridine.



A nitrophenyl-hydroxybutyrate may be hydrogenated to the corresponding amine.

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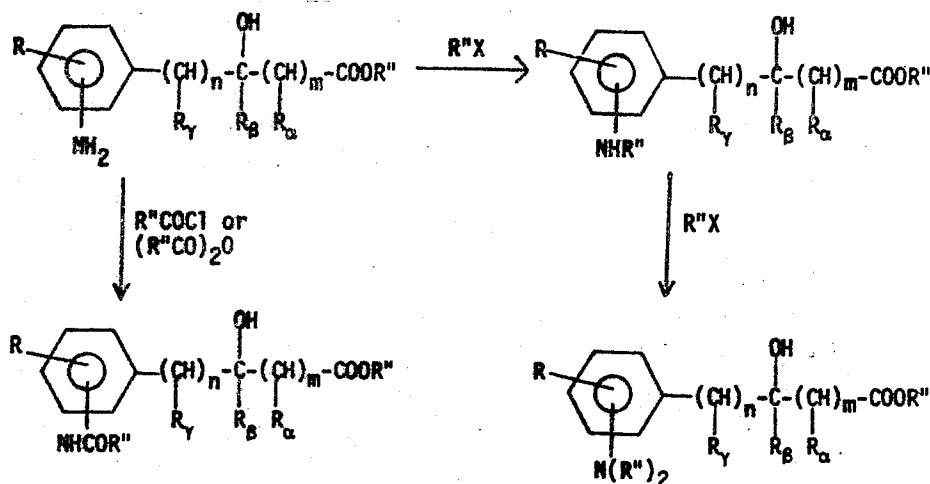
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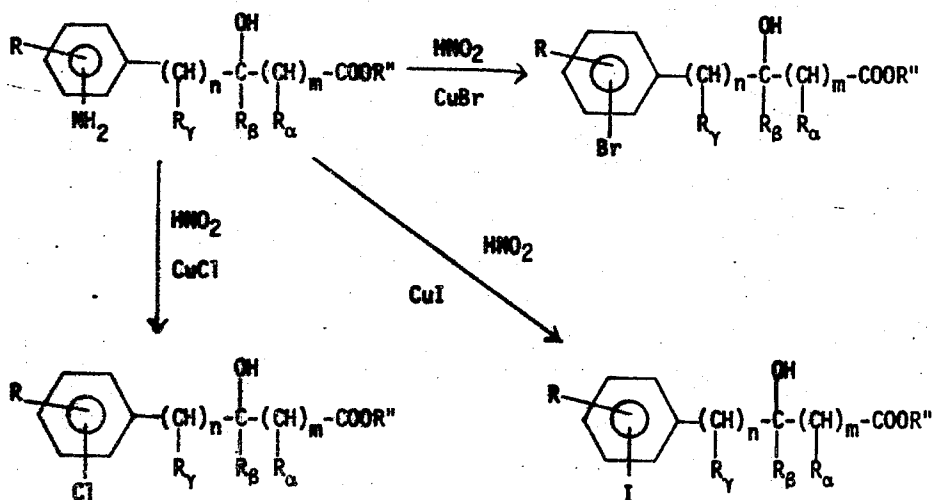
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An aminophenyl-hydroxybutyrate may then be mono- or dialkylated with loweralkyl halides or sulfates or acylated with loweracyl chlorides or anhydrides.



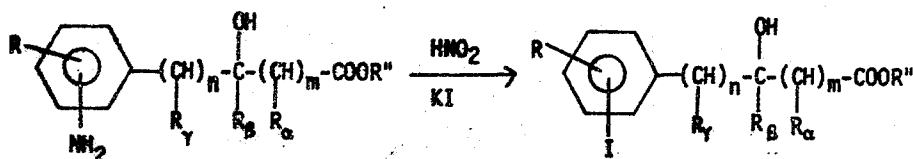
An aminophenyl-hydroxybutyrate may be diazotized 20 followed by a Sandmeyer type reaction to yield the halo group.

The aminophenyl-hydroxybutyrate may be diazo- 21 tized followed by reaction with potassium ethylxanthate followed by hydrolysis to obtain mercaptophenyl-



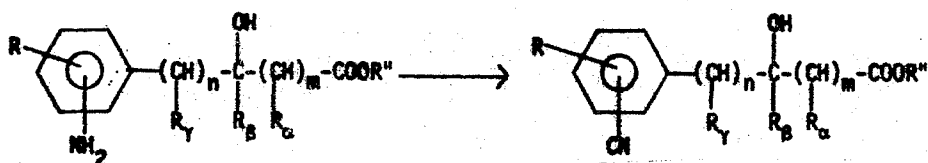
or diazotized and heated with an aqueous solution of 45 potassium iodide to prepare the iodo-substituted hydroxybutyrate.

hydroxybutyric acid which can be esterified to a buty- 46 rate. This in turn can be lower alkylated to the lower alkylthio and oxidized to the loweralkylsulfinyl and



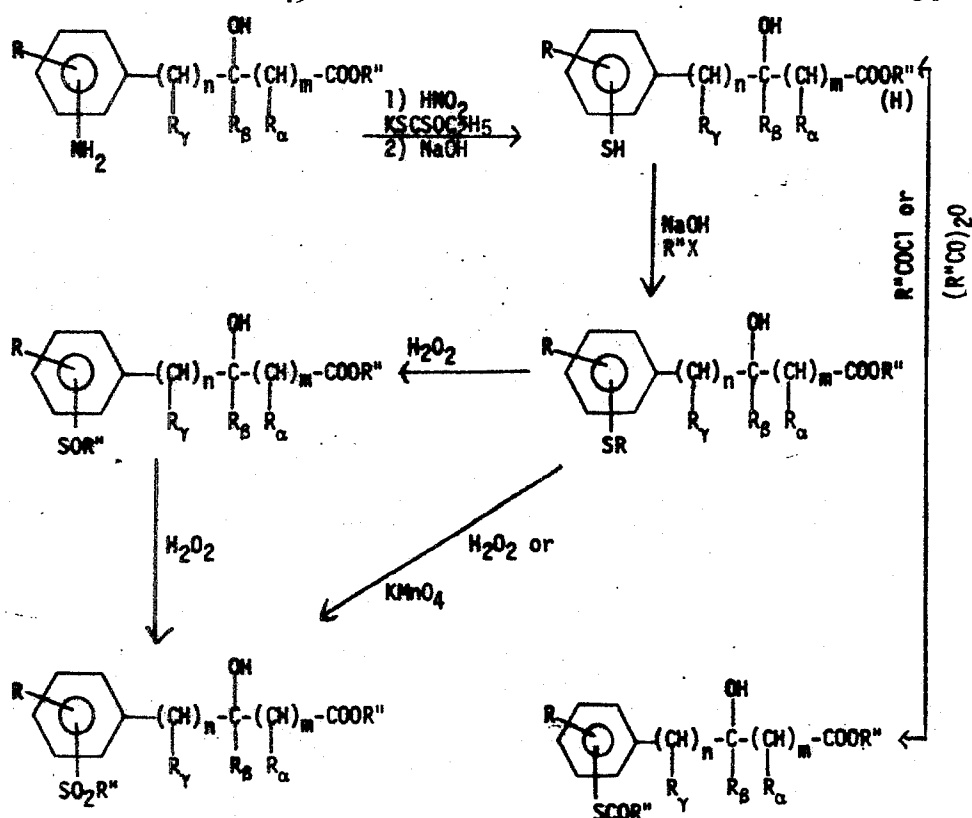
It may further be diazotized and followed by addition 47 of cuprous cyanide to obtain the cyanophenyl-hydroxybutyrate.

loweralkylsulfonyl groups or acylated to the acylthio 48 compounds.



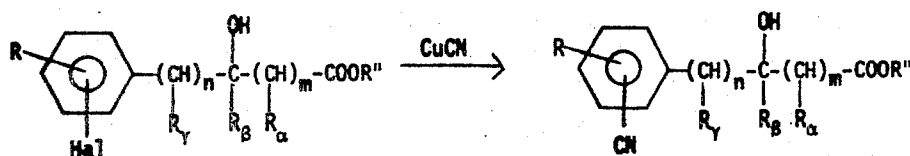
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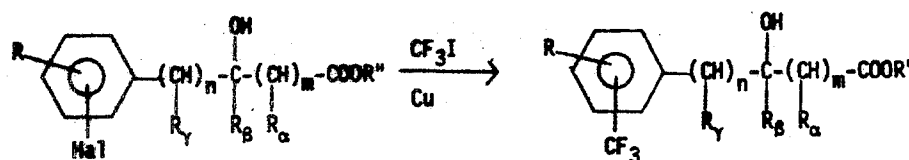
A halo compound in which halo is chloro or bromo or iodo may be reacted with cuprous cyanide in quinoline at about 150°C to produce a cyano compound:

When R' is phenyl then nitration, halogenation and alkylation may be carried out as above which in turn may be converted from one group to another as previously described.

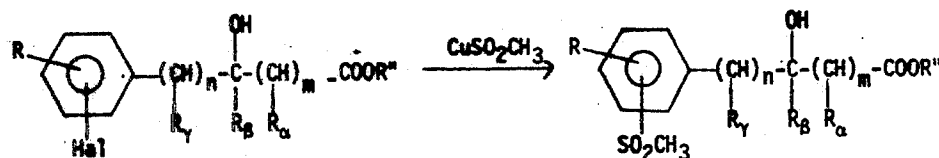


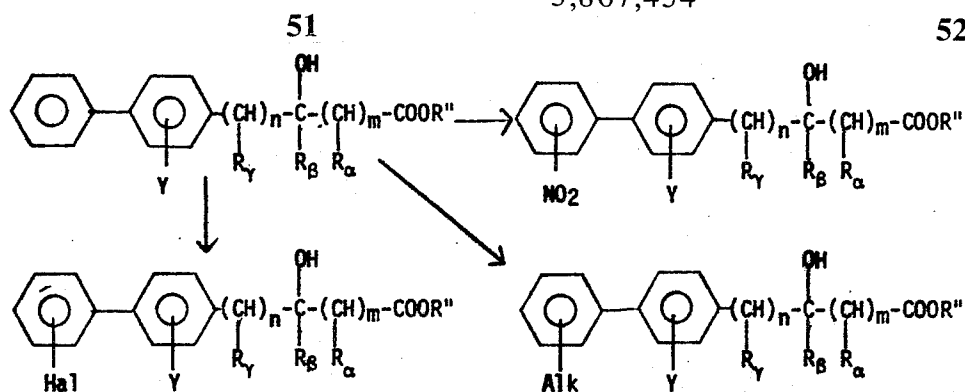
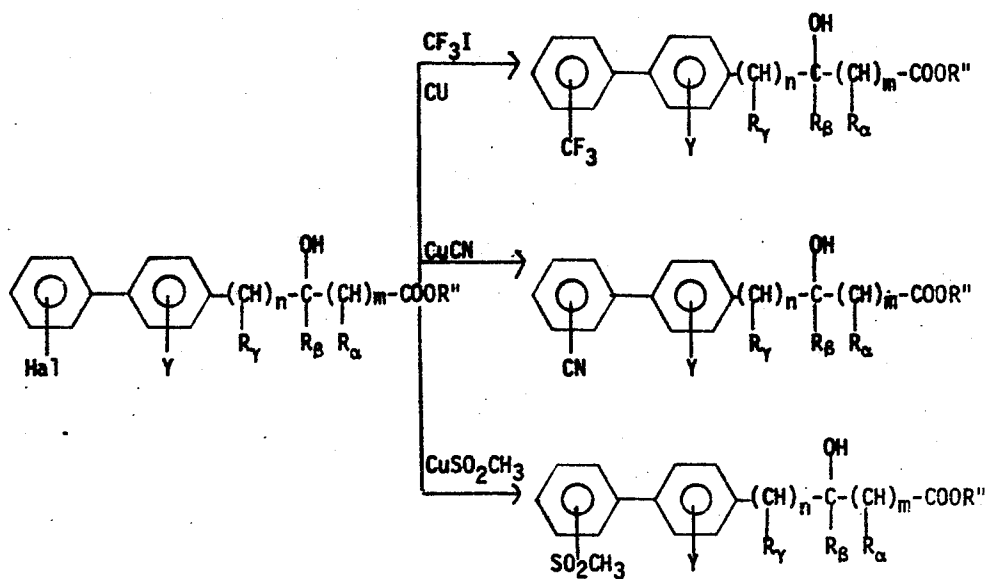
or reacted with trifluoromethyl iodide and copper powder at about 150°C in dimethylformamide to obtain a trifluoromethyl compound: [as described in Tetrahedron Letters: 47, 4095 (1959)]

Thus, for example, when R' is phenyl the following reactions may take place:



A halo compound may also be reacted with cuprous methanesulfonate in quinoline at about 150°C to obtain a methylsulfonyl compound.



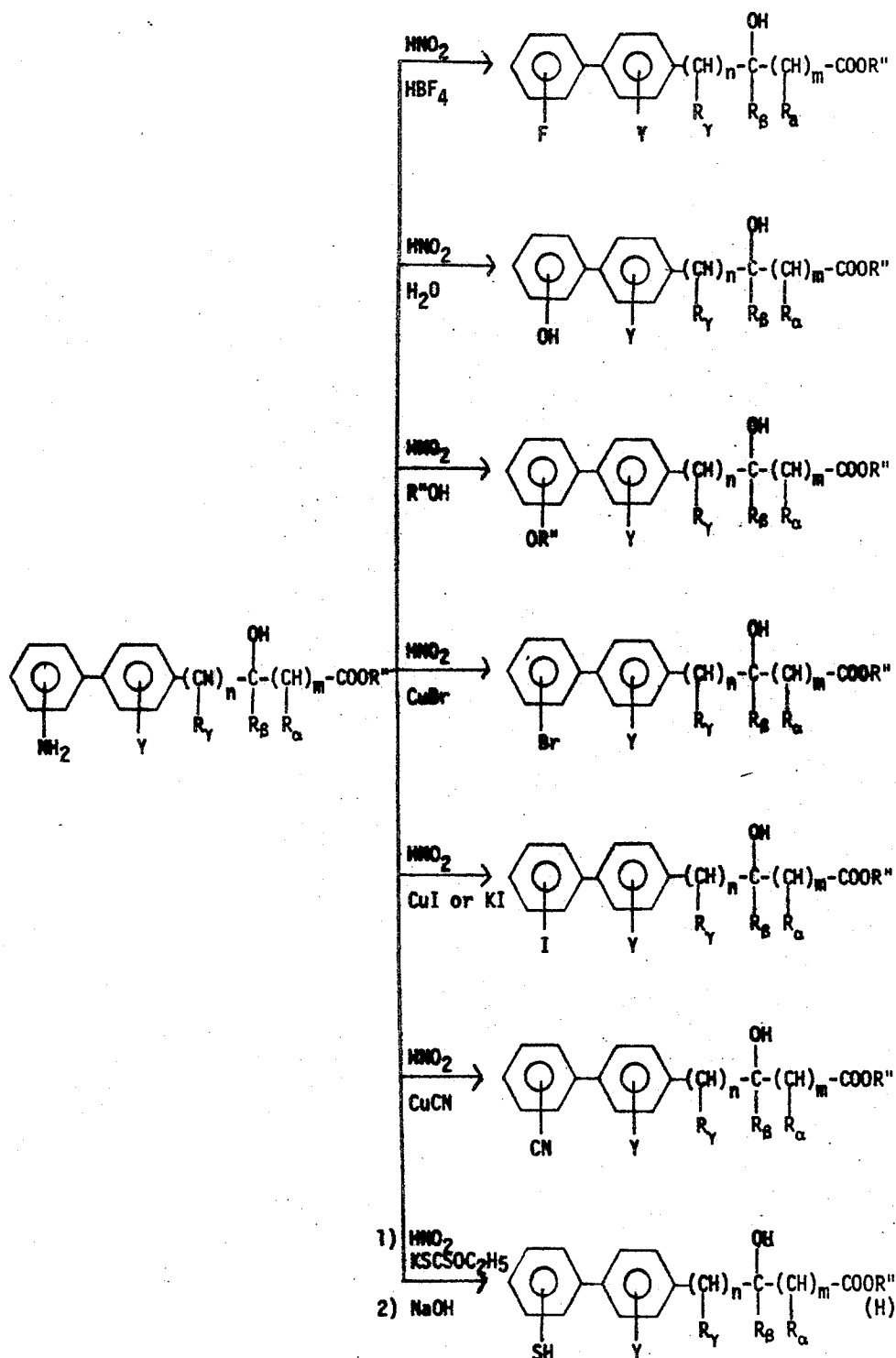


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where:

R'' is loweralkyl

Of course it will be understood by one skilled in the art that variations in the above procedures can be employed which will give that sequence of reactions which will result in the desired substituents.

The products of this invention are obtained as racemic mixtures of their dextro and levorotatory isomers since at least one carbon is asymmetric. When, the α , β or γ -carbon is also substituted with an alkyl group, two or three asymmetric carbon atoms may be present and the product may exist as a mixture of these diastereomers, each based on syn and anti configurations.

These diastereomers may be separated by fractional crystallization. Each diastereomer may then be resolved into dextro and levorotatory optical isomers by conventional methods.

One method of resolution that may be employed is combining the racemic compound with an optically active compound by salt formation, ester formation, or amide formation to form two diastereomeric products. If the instant acids are added to an optically active base, then two diastereomeric salts are produced which possess different properties and different solubilities

and can be separated by fractional crystallization. When the salts have been completely separated by repeated crystallization, the base is split off by acid hydrolysis and the pure *d* or *l* acids are obtained. Preferably, the butyric acid is reacted in alcoholic or acetone solution with an equivalent amount of the optically active primary, secondary or tertiary amine such as cinchonidine, cinchonine, quinine, ephedrine, α -methylbenzylamine, sec-butylamine, sec-amylamine, etc. The diastereomeric amine salts produced thereby, are separated by fractional crystallization and each optically active salt is hydrolyzed with dilute mineral acid to produce the dextro or levo form of the butyric acid. Each optical isomer may be reacted then with X'-Cl or XOX' to produce the corresponding optically active alcoholic derivative. Alternatively, an butyrate ester may be reacted with an optically active primary or secondary amine such as ephedrine, α -methylbenzylamine, sec-butylamine, etc., to produce a mixture of diastereomeric butyrates which may be separated by fraction crystallization. Each optically active amide may be hydrolyzed with mineral acid to its respective optically active acid.

Alternatively, a butyrate may be reacted with an optically active alcohol such as 1-menthol or d-borneol, or 1- α -methylbenzylalcohol, to produce a mixture of diastereomeric butyrate esters which may be separated by fractional crystallization. Each optically active ester may be hydrolyzed with mineral acid or alkali to its respective optically active acid. The optically active acids can also be recovered from the α -methylbenzyl esters by hydrogenolysis in the presence of palladium. In this manner the α , β or γ -oxy, halo, thio, cyano or amino isomers may be prepared.

I have found that the compounds of this invention exercise a useful degree of anti-inflammatory activity in mammals and are effective in the treatment of associated pain and fever and in like conditions which are responsive to treatment with anti-inflammatory agents. In general, the compounds of this invention are indicated for a wide variety of mammalian conditions where the symptoms of inflammation and associated fever and pain are manifested. Exemplary of such conditions are: rheumatic diseases such as rheumatoid arthritis, osteoarthritis and other degenerative joint diseases; soft-tissue rheumatism such as tendinitis; muscular rheumatism such as sciatica; pain and inflammation associated with dental surgery and similar human and veterinary disease conditions exhibiting the foregoing symptoms requiring the use of an anti-inflammatory, analgesic and/or an antipyretic agent.

For these purposes, the compounds of this invention are normally administered orally, topically, parenterally or rectally. Orally, these may be administered in tablets, capsules, suspensions or syrups; the optimum dosage, of course, depending on the particular compound being used and the type and severity of the condition being treated. In any specific case the appropriate dosage selected will further depend on factors of the patient which may influence response to the drug; for example, general health, age, weight, etc. Although the optimum quantities of the compounds of this invention to be used in such manner will depend on the compound employed and the particular type of disease condition treated, oral dose levels of prepared compounds when administered to a mammal in dosages of 0.5 to 100 milligrams per kilogram of body weight per day are particularly useful. The preferred range is 0.5 to 15

mg/Kg. Comparative dosages may be used in topical, parenteral or rectal administration.

Dosage forms may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents; for example, sweetening agents, flavoring agents, coloring agents, preserving agents, etc. Further, the active butyric acids or their derivatives may be administered alone or in admixture with antacids such as sodium bicarbonate, magnesium carbonate, magnesium hydroxide, aluminum hydroxide, magnesium silicate, etc., and non-toxic pharmaceutically acceptable excipients. Such excipients may be, for example, inert diluents such as calcium carbonate, lactose, etc., granulating and disintegrating agents; for example, magnesium stearate, talc, etc., binding agents; for example, starch gelatin, etc., suspending agents; for example, methylcellulose, vegetable oil, etc., dispersing agents; for example, lecithin, etc., thickening agents; for example, beeswax, hard paraffin, etc., emulsifying agents; for example, naturally-occurring gums, etc., and non-irritating excipients; for example, cocoa butter and polyethylene glycols.

Various tests in animals can be carried out to show the ability of the butyric acids and derivatives of this invention to exhibit reactions that can be correlated with anti-inflammatory activity in humans. One such test is the Carrageenan paw edema test, which shows the ability of the instant compounds to inhibit edema induced by injection of an inflammatory agent such as carrageenan into the tissues of the paw of a rat against non-inflamed controls. This carrageenan testing method is known to correlate well with anti-inflammatory activity in humans and is a standard test used to determine anti-inflammatory activity. This correlation can be shown by the activities of compounds known to be clinically active including such as aspirin, phenylbutazone, cortisone, hydrocortisone and prednisolone. In view of the results of this test, the butyric acids and derivatives can be considered to be active anti-inflammatory agents.

One method for measuring the pain threshold of the butyric acids and derivatives is the Randall-Selitto test. Analgesic activity is shown by antinociceptive testing of the inflamed foot of rats and a measurement of their pain response.

Antipyretic assay is carried out by yeast-induced fever tests of subcutaneously injected rats. The measurement of rectal temperature is carried out to determine the response by the test compounds.

In view of the results of the above tests, the butyric acids and derivatives of this invention are considered to have valuable analgesic and antipyretic properties.

Other tests which can be correlated to show significant activities are the "phenylquinone writhing" test for analgesia, "polyarthritis in rats" and "ultra-violet erythema in guinea pigs".

The following are detailed examples which show the preparation of the compounds of this invention. They are to be construed as illustrations of said compounds and are not intended to be limitations thereof.

EXAMPLE I

4-(2'-Chlorophenyl)cinnamic acid

A mixture of 21.6 g. (0.1 mole) of 4-(2'-chlorophenyl)benzaldehyde is heated on a steam bath with 13.2 g. of malonic acid and 95 ml. of pyridine contain-

ing 5 drops of piperidine. The mixture is heated for four hours until the liberation of carbon dioxide ceases. The cooled mixture is poured into a mixture of 110 ml. concentrated hydrochloric acid and 500 ml. of ice water. The solid which separates is filtered, washed and 15 ml. portions of cold water and then resuspended in 200 ml. of cold water, filtered, washed with cold water and dried at 40°C. The residue is then recrystallized from ethanol to obtain 4-(2'-chlorophenyl)cinnamic acid.

A. When malonic acid is replaced in the above example by methylmalonic acid or ethylmalonic acid then the products prepared are

α -methyl-4-(2'-chlorophenyl)cinnamic acid

α -ethyl-4-(2'-chlorophenyl)cinnamic acid

B. When 4-(2'-chlorophenyl)benzaldehyde in the above example is replaced by the compounds of Table I below, then the corresponding product of Table II below is prepared.

TABLE I

4-(4'-chlorophenyl)benzaldehyde
4-(2'-nitrophenyl)benzaldehyde
4-(4'-nitrophenyl)benzaldehyde
4-(2'-methylphenyl)benzaldehyde
4-(4'-methylphenyl)benzaldehyde
4-(2'-bromophenyl)benzaldehyde
4-(4'-bromophenyl)benzaldehyde
2-chloro-4-biphenylcarboxaldehyde
2-nitro-4-biphenylcarboxaldehyde
2-methyl-4-biphenylcarboxaldehyde
2-bromo-4-biphenylcarboxaldehyde
4-tolualdehyde
4-i-propylbenzaldehyde
4-t-butylbenzaldehyde
4-cyclopentylbenzaldehyde
4-cyclohexylbenzaldehyde
4-cycloheptylbenzaldehyde
4-cyclohex-1-enylbenzaldehyde
4-phenoxybenzaldehyde
4-phenylthiobenzenaldehyde
4-anilinobenzenaldehyde
4-benzoylbenzaldehyde
4-(2-thienyl)benzaldehyde
4-(3-furyl)benzaldehyde
4-(2-pyridyl)benzaldehyde
4-(4-pyridyl)benzaldehyde
4-(2-pyrazinyl)benzaldehyde
4-(2-pyrimidinyl)benzaldehyde
4-(3-pyridazinyl)benzaldehyde
4-(2-triazinyl)benzaldehyde
4-(3-isoxazolyl)benzaldehyde
4-(3-isothiazolyl)benzaldehyde
4-(2H-pyrrol-3-yl)benzaldehyde
4-(2-imidazolyl)benzaldehyde
4-(1-pyrazolyl)benzaldehyde
4-(2H-pyran-2-yl)benzaldehyde
4-(1-pyrrolyl)benzaldehyde
4-(2-imidazolin-4-yl)benzaldehyde
4-(2-imidazolidinyl)benzaldehyde
4-(1-pyrazolidinyl)benzaldehyde
4-(2-pyrrolidinyl)benzaldehyde
4-(2-pyrrolin-3-yl)benzaldehyde
4-(2-piperidinyl)benzaldehyde
4-(4-piperidinyl)benzaldehyde
4-(1-piperazinyl)benzaldehyde
4-(2-piperazinyl)benzaldehyde
4-(3-morpholinyl)benzaldehyde
4-(4-morpholinyl)benzaldehyde

TABLE II

4-(4'-chlorophenyl)cinnamic acid
4-(2'-nitrophenyl)cinnamic acid
4-(4'-nitrophenyl)cinnamic acid
4-(2'-methylphenyl)cinnamic acid
4-(4'-methylphenyl)cinnamic acid
4-(2'-bromophenyl)cinnamic acid
4-(4'-bromophenyl)cinnamic acid
4-(2-chlorophenyl)cinnamic acid
4-(2-nitrophenyl)cinnamic acid
4-(2-methylphenyl)cinnamic acid
4-(2-bromophenyl)cinnamic acid
4-methylcinnamic acid
4-i-propylcinnamic acid
4-t-butylcinnamic acid
4-cyclopentylcinnamic acid
4-cycloheptylcinnamic acid
4-cyclohexylcinnamic acid
4-cyclohex-1-enylcinnamic acid
4-phenoxycinnamic acid
4-phenylthiocinnamic acid
4-anilino cinnamic acid
2-anilino cinnamic acid
4-benzoylcinnamic acid
4-(2-thienyl)cinnamic acid
4-(3-furyl)cinnamic acid
4-(2-pyridyl)cinnamic acid
4-(4-pyridyl)cinnamic acid
4-(2-pyrazinyl)cinnamic acid
4-(2-pyrimidinyl)cinnamic acid
4-(3-pyridazinyl)cinnamic acid
4-(2-triazinyl)cinnamic acid
4-(3-isoxazolyl)cinnamic acid
4-(3-isothiazolyl)cinnamic acid
4-(2H-pyrrol-3-yl)cinnamic acid
4-(2-imidazolyl)cinnamic acid
4-(1-pyrazolyl)cinnamic acid
4-(2H-pyran-2-yl)cinnamic acid
4-(1-pyrrolyl)cinnamic acid
4-(2-imidazolin-4-yl)cinnamic acid
4-(2-imidazolidinyl)cinnamic acid
4-(1-pyrazolidinyl)cinnamic acid
4-(2-pyrrolidinyl)cinnamic acid
4-(2-pyrrolin-3-yl)cinnamic acid
4-(2-piperidinyl)cinnamic acid
4-(4-piperidinyl)cinnamic acid
4-(1-piperazinyl)cinnamic acid
4-(2-piperazinyl)cinnamic acid
4-(3-morpholinyl)cinnamic acid
4-(4-morpholinyl)cinnamic acid

When 4-(2'-chlorophenyl)benzaldehyde is replaced in the above example by the compounds of Table I and malonic acid is replaced by the compounds of part A then the corresponding product is prepared.

EXAMPLE 2

β -(2'-Chloro-4-biphenyl)propionic acid

A suspension of 100 g of p-(2-chlorophenyl)cinnamic acid in 1 l. of 95% ethanol is hydrogenated at atmospheric pressure using platinum oxide catalyst (1 g). The uptake of hydrogen ceases when approximately 9-10 l. of hydrogen is consumed. The catalyst is then filtered off and the reaction evaporated to dryness to give β -(2'-chloro-4-biphenyl)propionic acid.

A. When p-(2-chlorophenyl)cinnamic acid is replaced by the cinnamic acid compounds of Table II.

Example 1 then the corresponding propionic acid is prepared.

EXAMPLE 3

β -(2'-Chloro-4-biphenyl)propionyl chloride

β -(2'-chloro-4-biphenyl)propionic acid (26 g.) is treated with thionyl chloride (18 g.) at 0°-5°C. After 10 mins the temperature is raised to 60°C for 30 mins, then the residue is distilled at 0.05 mm to give β -(2'-chloro-4-biphenyl)propionyl chloride.

A. When β -(2'-chloro-4-biphenyl)propionic acid in the above reaction is replaced by the propionic acids of Example 2, then the corresponding propionyl chloride is prepared.

EXAMPLE 4

β -(2'-Chloro-4-biphenyl)propionaldehyde

β -(2'-chloro-4-biphenyl)propionyl chloride (28 g.) in 500 ml glyme is treated dropwise with a solution of lithium tri-*t*-butoxyaluminum hydroxide (25.5 g.) in 500 ml. diglyme while maintaining the reaction temperature at -70°C with dry ice. When addition is complete, the mixture is allowed to come to room temperature, is diluted with ether, and washed with water, dilute HCl and brine. The solvent is dried over sodium sulfate, evaporated under vacuo and the residue distilled to give β -(2'-chloro-4-biphenyl)propionaldehyde.

A. When β -(2'-chloro-4-biphenyl)propionyl chloride in the above reaction is replaced by propionyl chloride of Example 3, then the corresponding propionaldehyde is prepared.

EXAMPLE 5

4-(2'-Chloro-4-biphenyl)butan-2-one

A solution of β -(2'-chloro-4-biphenyl)propionyl chloride (28 g.) in anhydrous ether 1 l. is cooled to -70°C. To it is added dropwise a solution of 3M methylmagnesium bromide in ether (34 ml.). The reaction is stirred vigorously throughout. When addition of the grignard is complete (approx. 1 hr), the mixture is allowed to come to room temperature and is decomposed by adding carefully a saturated ammonium chloride solution (approx. 500 ml). The ether phase is washed with brine, dried over sodium sulfate, evaporated in vacuo and the residue distilled to yield 4-(2'-chloro-4-biphenyl)butan-2-one.

A. When β -(2'-chloro-4-biphenyl)propionyl chloride in the above reaction is replaced by propionyl chloride of Example 3, then the corresponding products are obtained.

EXAMPLE 6

α -Hydroxy- γ -(2'-chloro-4-biphenyl)butyronitrile

β -(2'-chloro-4-biphenyl)propionaldehyde (10 g.) is treated with 50 ml aqueous saturated sodium bisulfite solution in 80 ml. absolute ethanol. The addition complex is filtered off, washed with water, ethanol, then ether. The dry material is added to 40 ml. dimethylsulfide and treated with excess (cu 5 g.) of powdered sodium cyanide. After 3 hours the mixture is poured into water and extracts are washed with brine, dried over sodium sulfate and evaporated to dryness after a trace of sulfuric acid is added to obtain α -hydroxy- γ -(2'-chloro-4-biphenyl)butyronitrile.

A. When β -(2'-chloro-4-biphenyl)propionaldehyde in the above procedure is

replaced by the propionaldehydes or ketones of Examples 4 and 5, then the corresponding products are obtained.

EXAMPLE 7

p-(2-Chlorophenyl)phenylmagnesium bromide

4-bromo-2'-chlorobiphenyl (54 g) in ether (70 ml) is added in portions to clean magnesium turnings (4.8 g.). After the first 5 ml. of the solution, a crystal of iodine is added and 3 drops of ethyl iodide to initiate the reaction. When reaction is proceeding, the remainder of the solution is added as rapidly as possible without quenching the reaction. When addition is complete, the mixture is refluxed with stirring until only a trace of metal remains, when formation of the grignard reagent is adjudged complete.

1-Chloro-3-(2'-chloro-4-biphenyl)-2-propanol

The grignard solution of the above procedure is cooled to 0°C in an ice bath and to it is added dropwise with stirring a solution of freshly distilled epichlorohydrin (18.0 g.) in ether (100 ml.) at such a rate the temperature does not rise about 5°C. When addition is complete, the reaction is allowed to come to room temperature then excess saturated ammonium chloride solution is added. The ether phase is separated, washed with brine, dried and the solvent evaporated to give the crude product 1-chloro-3-(2'-chloro-4-biphenyl)-2-propanol which may be reacted directly or distilled at very low pressures to obtain 1-chloro-3-(2'-chloro-4-biphenyl)-2-propanol.

A. When epichlorohydrin in the above example is replaced with 2-chloro-3,4-epoxybutane, 1-chloro-2-methyl-2,3-epoxypropane or 1-chloro-2,3-epoxybutane then the products obtained are 2-chloro-4-(2'-chloro-4-biphenyl)-3-butanol 1-chloro-2-methyl-3-(2'-chloro-4-biphenyl)-2-propanol 1-chloro-3-methyl-3-(2'-chloro-4-biphenyl)-2-propanol.

B. When 2'-chloro-4-biphenylmagnesium bromide in the above procedure is replaced by the Grignard reagents of Table I, below then the corresponding product of Table II, below is prepared.

TABLE I

4'-chloro-4-biphenylmagnesium bromide
2'-nitro-4-biphenylmagnesium bromide
4'-nitro-4-biphenylmagnesium bromide
2'-methyl-4-biphenylmagnesium bromide
4'-methyl-4-biphenylmagnesium bromide
4'-bromo-4-biphenylmagnesium bromide
2-chloro-4-biphenylmagnesium bromide
2-nitro-4-biphenylmagnesium bromide
2-methyl-4-biphenylmagnesium bromide
4-tolylmagnesium bromide
4-i-propylphenylmagnesium bromide
4-cyclopentylphenylmagnesium bromide
4-cyclohexylphenylmagnesium bromide
4-cycloheptylphenylmagnesium bromide
4-cyclohex-1-enylphenylmagnesium bromide
4-phenoxyphenylmagnesium bromide
4-phenylthiophenylmagnesium bromide
4-(2-thienyl)phenylmagnesium bromide
4-(3-furyl)phenylmagnesium bromide
4-(2-pyrazinyl)phenylmagnesium bromide
4-(3-pyridazinyl)phenylmagnesium bromide

4-(3-isoxazolyl)phenylmagnesium bromide
 4-(3-isothiazolyl)phenylmagnesium bromide
 4-(2-imidazolyl)phenylmagnesium bromide
 4-(1-pyrazolyl)phenylmagnesium bromide
 4-(2H-pyran-2-yl)phenylmagnesium bromide
 4-(2-imidazolin-4-yl)phenylmagnesium bromide
 4-(2-imidazolidinyl)phenylmagnesium bromide
 4-(1-pyrazolidinyl)phenylmagnesium bromide
 4-(4-morpholinyl)phenylmagnesium bromide

TABLE II

1-chloro-3-(4'-chloro-4-biphenyl)-2-propanol
 1-chloro-3-(2'-nitro-4-biphenyl)-2-propanol
 1-chloro-3-(4'-nitro-4-biphenyl)-2-propanol
 1-chloro-3-(2'-methyl-4-biphenyl)-2-propanol
 1-chloro-3-(4'-methyl-4-biphenyl)-2-propanol
 1-chloro-3-(2'-bromo-4-biphenyl)-2-propanol
 1-chloro-3-(4'-bromo-4-biphenyl)-2-propanol
 1-chloro-3-(2-chloro-4-biphenyl)-2-propanol
 1-chloro-3-(2-nitro-4-biphenyl)-2-propanol
 1-chloro-3-(2-methyl-4-biphenyl)-2-propanol
 1-chloro-3-(2-bromo-4-biphenyl)-2-propanol
 1-chloro-3-(4-tolyl)-2-propanol
 1-chloro-3-(4-i-propylphenyl)-2-propanol
 1-chloro-3-(4-t-butylphenyl)-2-propanol
 1-chloro-3-(4-cyclopentylphenyl)-2-propanol
 1-chloro-3-(4-cycloheptylphenyl)-2-propanol
 1-chloro-3-(4-cyclohexylphenyl)-2-propanol
 1-chloro-3-(4-cyclohex-1-enylphenyl)-2-propanol
 1-chloro-3-(4-phenoxyphenyl)-2-propanol
 1-chloro-3-(4-phenylthiophenyl)-2-propanol
 1-chloro-3-[4-(2-thienyl)phenyl]-2-propanol
 1-chloro-3-[4-(3-furyl)phenyl]-2-propanol
 1-chloro-3-[4-(2-pyrazinyl)phenyl]-2-propanol
 1-chloro-3-pyridazinylphenyl]-2-propanol
 1-chloro-3-[4-(3-isoxazolyl)phenyl]-2-propanol
 1-chloro-3-[4-(3-isothiazolyl)phenyl]-2-propanol
 1-chloro-3-[4-(2-imidazolyl)phenyl]-2-propanol
 1-chloro-3-[4-(1-pyrazolyl)phenyl]-2-propanol
 1-chloro-3-[4-(2H-pyran-2-yl)phenyl]-2-propanol
 1-chloro-3-[4-(2-imidazolin-4-yl)phenyl]-2-propanol
 1-chloro-3-[4-(2-imidazolidinyl)phenyl]-2-propanol
 1-chloro-3-[4-(1-pyrazolidinyl)phenyl]-2-propanol
 1-chloro-3-[4-(4-morpholinyl)phenyl]-2-propanol
 C. When the above procedure is followed using the Grignard reagent of Table I and the epoxy compounds of Part A, then the corresponding product is prepared.

EXAMPLE 8

β -Hydroxy- γ -(2'-chloro-4-biphenyl)butyronitrile

The crude 1-chloro-3-(2'-chloro-4-biphenyl)-2-propanol from Example 12 is dissolved in dimethylsulfoxide (100 g.) and treated with powdered sodium cyanide (20 g.). After stirring at room temperature for 24 hours, the mixture is warmed to 60°C for 4 hours then poured into water and extracted with ether. The ether extracts are washed thoroughly with water, sodium bicarbonate solution, brine, and dried over sodium sulfate. Evaporation of the solvent and distillation of the residue at 0.01 to 0.05 m.m. yields β -hydroxy- γ -(2'-chloro-4-biphenyl)butyronitrile.

A. When 1-chloro-3-(2'-chloro-4-biphenyl)-2-propanol in the above reaction is replaced by 2-chloro-4-(2'-chloro-4-biphenyl)-3-butanol, 1-chloro-2-methyl-3-(2'-chloro-4-biphenyl)-2-propanol and 1-chloro-3-methyl-3-(2'-chloro-4-biphenyl)-2-

propanol, then the products prepared are:

- α -methyl- β -hydroxy- γ -(2'-chloro-4-biphenyl)butyronitrile,
 β -methyl- β -hydroxy- γ -(2'-chloro-4-biphenyl)butyronitrile and
 β -hydroxy- γ -methyl- γ -(2'-chloro-4-biphenyl)butyronitrile.

B. When the propanol and butanol compounds of Example 7 are used in the foregoing procedure, then the corresponding butyronitrile product is obtained.

EXAMPLE 9

α -Hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid

- A mixture of α -hydroxy- γ -(2'-chloro-4-biphenyl)butyronitrile from Example 14 (10 g. crude) is treated with 250 ml. acetic acid and 150 ml. conc. HCl. The mixture is stirred on the steam bath for 4 hours, cooled, diluted with water (500 ml.) and extracted with benzene. The benzene extract is washed with brine, dried (Na₂SO₄) and evaporated to dryness. The residue is dissolved in ether, and the organic phase extracted with sodium bicarbonate (three washes). Acidification of the bicarbonate extracts affords a precipitate of the biphenyl butyric acid, which is dissolved in ether, washed with brine and on evaporation of the solvent results in α -hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid.

- A. When α -hydroxy- γ -(2'-chloro-4-biphenyl)butyronitrile in the above procedure is replaced by the nitriles of Examples 6 and 8, then the corresponding carboxylic acid products are obtained. A representative list of the compounds thus prepared is shown below.

- α -hydroxy- γ -(4'-chloro-4-biphenyl) butyric acid
 -biphenyl)butyric
 α -hydroxy- γ -(2'-nitro-4-biphenyl)butyric acid
 α -hydroxy- γ -(4'-nitro-4-biphenyl)butyric acid
 α -hydroxy- γ -(2'-methyl-4-biphenyl)butyric acid
 α -hydroxy- γ -(4'-methyl-4-biphenyl)butyric acid
 α -hydroxy- γ -(2'-bromo-4-biphenyl)butyric acid
 α -hydroxy- γ -(4'-bromo-4-biphenyl)butyric acid
 α -hydroxy- γ -(2-chloro-4-biphenyl)butyric acid
 α -hydroxy- γ -(2-nitro-4-biphenyl)butyric acid
 α -hydroxy- γ -(2-methyl-4-biphenyl)butyric acid
 α -hydroxy- γ -(2-bromo-4-biphenyl)butyric acid
 α -hydroxy- γ -(4-tolyl)butyric acid
 α -hydroxy- γ -(4-i-propylphenyl)butyric acid
 α -hydroxy- γ -(4-t-butylphenyl)butyric acid
 α -hydroxy- γ -(4-cyclopentylphenyl)butyric acid
 α -hydroxy- γ -(4-cycloheptylphenyl)butyric acid
 α -hydroxy- γ -(4-cyclohexylphenyl)butyric acid
 α -hydroxy- γ -(4-cyclohex-1-enylphenyl)butyric acid
 α -hydroxy- γ -(4-phenoxyphenyl)butyric acid
 α -hydroxy- γ -(4-phenylthiophenyl)butyric acid
 α -hydroxy- γ -(4-anilinophenyl)butyric acid
 α -hydroxy- γ -(2-anilinophenyl)butyric acid
 α -hydroxy- γ -(4-benzoylphenyl)butyric acid
 α -hydroxy- γ -[4-(2-thienyl)phenyl]butyric acid
 α -hydroxy- γ -[4-(3-furyl)phenyl]butyric acid
 α -hydroxy- γ -[4-(2-pyridyl)phenyl]butyric acid
 α -hydroxy- γ -[4-(4-pyridyl)phenyl]butyric acid
 α -hydroxy- γ -[4-(2-pyrazinyl)phenyl]butyric acid
 α -hydroxy- γ -[4-(2-pyrimidinyl)phenyl]butyric acid
 α -hydroxy- γ -[4-(3-pyridazinyl)phenyl]butyric acid
 α -hydroxy- γ -[4-(2-triazinyl)phenyl]butyric acid
 α -hydroxy- γ -[4-(3-isoxazolyl)phenyl]butyric acid
 α -hydroxy- γ -[4-(3-isothiazolyl)phenyl]butyric acid

α -hydroxy- γ -[4-(2H-pyrrol-3-yl)phenyl]butyric acid
 α -hydroxy- γ -[4-(2-imidazolyl)phenyl]butyric acid
 α -hydroxy- γ -[4-(1-pyrazolyl)phenyl]butyric acid
 α -hydroxy- γ -[4-(2H-pyran-2-yl)phenyl]butyric acid
 α -hydroxy- γ -[4-(1-pyrrolyl)phenyl]butyric acid 5
 α -hydroxy- γ -[4-(2-imidazolin-4-yl)phenyl]butyric acid
 α -hydroxy- γ -[4-(2-imidazolindinyl)phenyl]butyric acid
 α -hydroxy- γ -[4-(1-pyrazolidinyl)phenyl]butyric acid 10
 α -hydroxy- γ -[4-(2-pyrrolidinyl)phenyl]butyric acid
 α -hydroxy- γ -[4-(2-pyrrolin-3-yl)phenyl]butyric acid
 α -hydroxy- γ -[4-(2-piperidinyl)phenyl]butyric acid
 α -hydroxy- γ -[4-(4-piperidinyl)phenyl]butyric acid
 α -hydroxy- γ -[4-(1-piperazinyl)phenyl]butyric acid 15
 α -hydroxy- γ -[4-(2-piperazinyl)phenyl]butyric acid
 α -hydroxy- γ -[4-(3-morpholinyl)phenyl]butyric acid
 α -hydroxy- γ -[4-(4-morpholinyl)phenyl]butyric acid
 α -hydroxy- α -methyl- γ -(2'-chloro-4-biphenyl)butyric acid 20
 α -hydroxy- α -methyl- γ -(2'-nitro-4-biphenyl)butyric acid
 α -hydroxy- α -methyl- γ -(2'-bromo-4-biphenyl)butyric acid
 α -hydroxy- α -methyl- γ -(4'-nitro-4-biphenyl)butyric acid 25
 α -hydroxy- α -methyl- γ -(4'-chloro-4-biphenyl)butyric acid
 α -hydroxy- α -methyl- γ -(4'-bromo-4-biphenyl)butyric acid
 α -hydroxy- α -methyl- γ -(2-chloro-4-biphenyl)butyric acid
 α -hydroxy- α -methyl- γ -(2-nitro-4-biphenyl)butyric acid
 α -hydroxy- α -methyl- γ -(2-bromo-4-biphenyl)butyric acid
 α -hydroxy- α -methyl- γ -(4-i-propylphenyl)butyric acid
 α -hydroxy- α -methyl- γ -(4-cyclohexylphenyl)butyric acid 40
 α -hydroxy- α -methyl- γ -[4-(1-pyrrolyl)phenyl]butyric acid
 α -hydroxy- β -methyl- γ -(2'-chloro-4-biphenyl)butyric acid
 α -hydroxy- β -methyl- γ -(2'-nitro-4-biphenyl)butyric acid
 α -hydroxy- γ -methyl- γ -(2'-bromo-4-biphenyl)butyric acid
 α -hydroxy- β -methyl- γ -(4'-nitro-4-biphenyl)butyric acid 50
 α -hydroxy- β -methyl- γ -(4'-chloro-4-biphenyl)butyric acid
 α -hydroxy- β -methyl- γ -(4'-bromo-4-biphenyl)butyric acid
 α -hydroxy- β -methyl- γ -(2-chloro-4-biphenyl)butyric acid
 α -hydroxy- β -methyl- γ -(2-nitro-4-biphenyl)butyric acid
 α -hydroxy- β -methyl- γ -(2-bromo-4-biphenyl)butyric acid
 α -hydroxy- β -methyl- γ -(4-i-propylphenyl)butyric acid
 α -hydroxy- β -methyl- γ -(4-cyclohexylphenyl)butyric acid
 α -hydroxy- β -methyl- γ -[4-(1-pyrrolyl)phenyl]butyric acid 65

α -hydroxy- γ -methyl- γ -(2'-nitro-4-biphenyl)butyric acid
 α -hydroxy- γ -methyl- γ -(2'-bromo-4-biphenyl)butyric acid
 α -hydroxy- γ -methyl- γ -(4'-nitro-4-biphenyl)butyric acid
 α -hydroxy- γ -methyl- γ -(4'-chloro-4-biphenyl)butyric acid
 α -hydroxy- γ -methyl- γ -(4'-bromo-4-biphenyl)butyric acid 10
 α -hydroxy- γ -methyl- γ -(2-chloro-4-biphenyl)butyric acid
 α -hydroxy- γ -methyl- γ -(2-nitro-4-biphenyl)butyric acid
 α -hydroxy- γ -methyl- γ -(2-bromo-4-biphenyl)butyric acid 15
 α -hydroxy- γ -methyl- γ -(4-i-propylphenyl)butyric acid
 α -hydroxy- γ -methyl- γ -(4-cyclohexylphenyl)butyric acid
 α -hydroxy- γ -methyl- γ -[4-(1-pyrrolyl)phenyl]butyric acid
 β -hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid
 β -hydroxy- γ -(4'-chloro-4-biphenyl)butyric acid
 β -hydroxy- γ -(2'-nitro-4-biphenyl)butyric acid 25
 β -hydroxy- γ -(4'-nitro-4-biphenyl)butyric acid
 β -hydroxy- γ -(2'-methyl-4-biphenyl)butyric acid
 β -hydroxy- γ -(4'-methyl-4-biphenyl)butyric acid
 β -hydroxy- γ -(2-bromo-4-biphenyl)butyric acid
 β -hydroxy- γ -(4'-bromo-4-biphenyl)butyric acid 30
 β -hydroxy- γ -(2-chloro-4-biphenyl)butyric acid
 β -hydroxy- γ -(2-nitro-4-biphenyl)butyric acid
 β -hydroxy- γ -(2-methyl-4-biphenyl)butyric acid
 β -hydroxy- γ -(2-bromo-4-biphenyl)butyric acid 35
 β -hydroxy- γ -(4-tolyl)butyric acid
 β -hydroxy- γ -(4-i-propylphenyl)butyric acid
 β -hydroxy- γ -(4-t-butylphenyl)butyric acid
 β -hydroxy- γ -(4-cyclopentylphenyl)butyric acid
 β -hydroxy- γ -(4-cycloheptylphenyl)butyric acid
 β -hydroxy- γ -(4-cyclohexylphenyl)butyric acid 40
 β -hydroxy- γ -(4-cyclohex-1-enylphenyl)butyric acid
 β -hydroxy- γ -(4-phenoxylphenyl)butyric acid
 β -hydroxy- γ -(4-phenylthiophenyl)butyric acid
 β -hydroxy- γ -(4-anilinophenyl)butyric acid 45
 β -hydroxy- γ -(2-anilinophenyl)butyric acid
 β -hydroxy- γ -(4-benzoylphenyl)butyric acid
 β -hydroxy- γ -[4-(2-thienyl)phenyl]butyric acid
 β -hydroxy- γ -[4-(3-furyl)phenyl]butyric acid
 β -hydroxy- γ -[4-(2-pyridyl)phenyl]butyric acid 50
 β -hydroxy- γ -[4-(4-pyridyl)phenyl]butyric acid
 β -hydroxy- γ -[4-(2-pyrazinyl)phenyl]butyric acid
 β -hydroxy- γ -[4-(2-pyrimidinyl)phenyl]butyric acid
 β -hydroxy- γ -[4-(3-pyridazinyl)phenyl]butyric acid
 β -hydroxy- γ -[4-(2-triazinyl)phenyl]butyric acid 55
 β -hydroxy- γ -[4-(3-isoxazolyl)phenyl]butyric acid
 β -hydroxy- γ -[4-(3-isothiazolyl)phenyl]butyric acid
 β -hydroxy- γ -[4-(2H-pyrrol-3-yl)phenyl]butyric acid
 β -hydroxy- γ -[4-(2-imidazolyl)phenyl]butyric acid
 β -hydroxy- γ -[4-(1-pyrazolyl)phenyl]butyric acid 60
 β -hydroxy- γ -[4-(2H-pyran-2-yl)phenyl]butyric acid
 β -hydroxy- γ -[4-(1-pyrrolyl)phenyl]butyric acid
 β -hydroxy- γ -[4-(2-imidazolin-4-yl)phenyl]butyric acid
 β -hydroxy- γ -[4-(2-imidazolindinyl)phenyl]butyric acid 65
 β -hydroxy- γ -[4-(1-pyrazolidinyl)phenyl]butyric acid
 β -hydroxy- γ -[4-(2-pyrrolidinyl)phenyl]butyric acid
 β -hydroxy- γ -[4-(2pyrrolin-3-yl)phenyl]butyric acid

β -hydroxy- γ -[4-(2-piperidinyl)phenyl]butyric acid
 β -hydroxy- γ -[4-(4-piperidinyl)phenyl]butyric acid
 β -hydroxy- γ -[4-(1-piperazinyl)phenyl]butyric acid
 β -hydroxy- γ -[4-(2-piperazinylphenyl)]butyric acid
 β -hydroxy- γ -[4-(3-morpholinyl)phenyl]butyric acid 5
 β -hydroxy- γ -[4-(4-morpholinyl)phenyl]butyric acid
 α -methyl- β -hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid
 α -methyl- β -hydroxy- γ -(2'-nitro-4-biphenyl)butyric acid 10
 α -methyl- β -hydroxy- γ -(2'-bromo-4-biphenyl)butyric acid
 α -methyl- β -hydroxy- γ -(4'-nitro-4-biphenyl)butyric acid
 α -methyl- β -hydroxy- γ -(4'-chloro-4-biphenyl)butyric acid 15
 α -methyl- β -hydroxy- γ -(4'-bromo-4-biphenyl)butyric acid
 α -methyl- β -hydroxy- γ -(2-chloro-4-biphenyl)butyric acid 20
 α -methyl- β -hydroxy- γ -(2-nitro-4-biphenyl)butyric acid
 α -methyl- β -hydroxy- γ -(2-bromo-4-biphenyl)butyric acid
 α -methyl- β -hydroxy- γ -(4-i-propylphenyl)butyric acid 25
 α -methyl- β -hydroxy- γ -(4-cyclohexylphenyl)butyric acid
 α -methyl- β -hydroxy- γ -[4-(1-pyrrolyl)phenyl]butyric acid 30
 β -methyl- β -hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid
 β -methyl- β -hydroxy- γ -(2'-nitro-4-biphenyl)butyric acid
 β -methyl- β -hydroxy- γ -(2'-bromo-4-biphenyl)butyric acid 35
 β -methyl- β -hydroxy- γ -(4'-nitro-4-biphenyl)butyric acid
 β -methyl- β -hydroxy- γ -(4'-chloro-4-biphenyl)butyric acid 40
 β -methyl- β -hydroxy- γ -(4'-bromo-4-biphenyl)butyric acid
 β -methyl- β -hydroxy- γ -(2-chloro-4-biphenyl)butyric acid
 β -methyl- β -hydroxy- γ -(2-nitro-4-biphenyl)butyric acid 45
 β -methyl- β -hydroxy- γ -(2-bromo-4-biphenyl)butyric acid
 β -methyl- β -hydroxy- γ -(4-i-propylphenyl)butyric acid 50
 β -methyl- β -hydroxy- γ -(4-cyclohexylphenyl)butyric acid
 β -methyl- β -hydroxy- γ -[4-(1-pyrrolyl)phenyl]butyric acid
 β -hydroxy- γ -methyl- γ -(2'-chloro-4-biphenyl)butyric acid
 β -hydroxy- γ -methyl- γ -(2'-nitro-4-biphenyl)butyric acid
 β -hydroxy- γ -methyl- γ -(2'-bromo-4-biphenyl)butyric acid 60
 β -hydroxy- γ -methyl- γ -(4'-nitro-4-biphenyl)butyric acid
 β -hydroxy- γ -methyl- γ -(4'-chloro-4-biphenyl)butyric acid
 β -hydroxy- γ -methyl- γ -(4'-bromo-4-biphenyl)butyric acid 65
 β -hydroxy- γ -methyl- γ -(2-chloro-4-biphenyl)butyric acid

β -hydroxy- γ -methyl- γ -(2-nitro-4-biphenyl)butyric acid
 β -hydroxy- γ -methyl- γ -(2-bromo-4-biphenyl)butyric acid
 β -hydroxy- γ -methyl- γ -(4-i-propylphenyl)butyric acid
 β -hydroxy- γ -methyl- γ -(4-cyclohexylphenyl)butyric acid
 β -hydroxy- γ -methyl- γ -[4-(1-pyrrolyl)phenyl]butyric acid

EXAMPLE 10

Ethyl γ -keto- γ -(2'-chloro-4-biphenyl)butyrate

2-Chlorobiphenyl 57 g. (0.33 mole) and (0.37 mole) of succinyl chloride ethyl ester are dissolved in 200 ml. of dry 1,1,2,2-tetrachloroethane. Anhydrous aluminum chloride 52 g. (0.39 mole) is added in small portions to the reaction mixture with stirring over 2 hours. During the addition, the temperature of the mixture is maintained between 16°–18°C. The mixture is stirred for an additional hour and allowed to stand overnight. The solution is then slowly poured into 1500 ml. of iced saline solution with stirring. After standing, two layers form. The aqueous layer is extracted with 500 ml. of ether and the ether extract is combined with the organic layer which is dissolved in 1500 ml. of ether and separated. The ether solution is washed with 10 $\times$ 100 ml. portions of a 1:1 mixture of saturated sodium chloride solution and 10% HCl solution, and 5 $\times$ 100 ml. portions of water. The ether solution is then dried over anhydrous magnesium sulfate for 1 hour and filtered. The solvents are removed by distillation under reduced pressure and the residue distilled to obtain ethyl γ -keto- γ -(2'-chloro-4-biphenyl)butyrate.

A. When succinyl chloride ethyl ester is replaced in the above example by the compounds of Table I below, then the corresponding product of Table II below is prepared.

TABLE I

α -methylsuccinyl chloride ethylester
 β -methylsuccinyl chloride ethylester
 α,β -dimethylsuccinyl chloride ethylester

TABLE II

ethyl α -methyl- γ -keto- γ -(2'-chloro-4-biphenyl)butyrate
 ethyl β -methyl- γ -keto- γ -(2'-chloro-4-biphenyl)butyrate 50
 ethyl α,β -dimethyl- γ -keto- γ -(2'-chloro-4-biphenyl)butyrate

B. When 2-chlorophenyl is replaced in the above example by the compounds of Table III below, then the corresponding product of Table IV below is prepared.

TABLE III

2-nitrobiphenyl
 2-bromobiphenyl
 2-methylbiphenyl
 4-nitrobiphenyl
 4-chlorobiphenyl
 4-bromobiphenyl
 4-methylbiphenyl
 toluene
 i-propylbenzene
 t-butylbenzene
 cyclopentylbenzene

cyclohexylbenzene
 cycloheptylbenzene
 cyclohex-1-enylbenzene
 phenoxybenzene
 diphenylsulfide
 diphenylamine
 benzophenone
 2-phenylthiophenone
 3-phenylfuran
 2-phenylpyridine
 4-phenylpyridine
 2-phenylpyrize
 2-phenylpyrimidine
 3-phenylpyridazine
 2-phenyltriazine
 2-phenylimidazole
 1-phenylpyrazole
 3-phenyl-2H-pyran
 4-phenyl-2-imidazoline
 2-phenylimidazolidine
 1-phenylpyrazolidine
 2-phenylpyrrolidinyl
 2-phenylpiperidine
 4-phenylpiperidine
 1-phenylpiperazine
 2-phenylpiperazine
 3-phenylmorpholine
 4-phenylmorpholine

TABLE IV

ethyl γ -keto- γ -(2'-nitro-4-biphenyl)butyrate
 ethyl γ -keto- γ -(2'-bromo-4-biphenyl)butyrate
 ethyl γ -keto- γ -(2'-methyl-4-biphenyl)butyrate
 ethyl γ -keto- γ -(4'-nitro-4-biphenyl)butyrate
 ethyl γ -keto- γ -(4'-chloro-4-biphenyl)butyrate
 ethyl γ -keto- γ -(4'-bromo-4-biphenyl)butyrate
 ethyl γ -keto- γ -(4'-methyl-4-biphenyl)butyrate
 ethyl γ -keto- γ -(p-tolyl)butyrate
 ethyl γ -keto- γ -(p-i-propylphenyl)butyrate
 ethyl γ -keto- γ -(p-t-butylphenyl)butyrate
 ethyl γ -keto- γ -(p-cyclopentylphenyl)butyrate
 ethyl γ -keto- γ -(p-cyclohexylphenyl)butyrate
 ethyl γ -keto- γ -(p-cycloheptylphenyl)butyrate
 ethyl γ -keto- γ -(p-cyclohex-1-enylphenyl)butyrate
 ethyl γ -keto- γ -(p-phenoxyphenyl)butyrate
 ethyl γ -keto- γ -(p-phenylthiophenyl)butyrate
 ethyl γ -keto- γ -(o-phenylaminophenyl)butyrate
 ethyl γ -keto- γ -(p-phenylaminophenyl)butyrate
 ethyl γ -keto- γ -(p-benzoylphenyl)butyrate
 ethyl γ -keto- γ -[p-(2-thienyl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(3-furyl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(2-pyridyl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(4-pyridyl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(2-pyrazinyl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(2-pyrimidinyl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(3-pyridazinyl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(2-triazinyl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(2-imidazolyl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(1-pyrazolyl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(2-imidazolin-4-yl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(2-imidazolidinyl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(1-pyrazolidinyl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(2-pyrrolidinyl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(2-piperidinyl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(4-piperidinyl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(1-piperazinyl)phenyl]butyrate

ethyl γ -keto- γ -[p-(2-piperazinyl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(3-morpholinyl)phenyl]butyrate
 ethyl γ -keto- γ -[p-(4-morpholinyl)phenyl]butyrate

C. When 2-chlorobiphenyl is replaced in the above example by the compounds of Table III and malonyl chloride methyl ester is replaced by the compounds of Table II then the corresponding product is prepared.

EXAMPLE 11

10 Ethyl γ -keto- γ -(2'-chloro-4-biphenyl)butyrate

Reaction of γ -keto- γ -(2'-chloro-4-biphenyl)butyric acid with absolute ethanol containing a small amount of anhydrous hydrochloric acid results in ethyl γ -keto- γ -(2'-chloro-4-biphenyl)butyrate.

20 Ethyl γ -hydroxy- γ -methyl- γ -(2'-chloro-4-biphenyl)butyrate

A solution of methylmagnesium iodide is prepared from 6.7 g. (0.047 mole) of methyl iodide, 1.24 g. (0.051 g-atom) of magnesium turnings and 40 ml. of anhydrous ether. This solution is added over a period of 1 hour to a solution of (0.05 mole) of ethyl γ -keto- γ -(2'-chloro-4-biphenyl) butyrate. The addition is carried out with vigorous stirring at 0°-5°C. The mixture is then allowed to warm to room temperature over 10 hours. The mixture is poured into an ice-cold solution of 0.2 M-sulfuric acid. The ether layer is separated, extracted with 1% sulfuric acid, dried over magnesium sulfate, filtered and evaporated to obtain ethyl γ -hydroxy- γ -methyl- γ -(2'-chloro-4-biphenyl)butyrate.

35 A. When γ -hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid in the above example is replaced by the keto butyric acids or esters of this invention, then the corresponding products are obtained.

40 B. When the Grignard reagent used is ethylmagnesium iodide, propylmagnesium iodide or butylmagnesium iodide then the corresponding product is prepared.

EXAMPLE 12

45 γ -Hydroxy-(2'-chloro-4-biphenyl)butyric acid

To a suspension of γ -keto-(2'-chloro-4-biphenyl)butyric acid 8.64 g. (0.031 mole) in 300 ml. of 90% ethanol is added 1 ml. of 0.1M ferrous sulfate solution followed by 0.5 g. of platinum oxide catalyst. The mixture is shaken with hydrogen for 3½ hours. The catalyst is filtered off. The filtrate is distilled under reduced pressure to yield γ -hydroxy(2'-chloro-4-biphenyl)butyric acid.

55 Ethyl γ -hydroxy- γ -(2'-nitro-4-biphenyl)butyrate

A sodium borohydride solution (1.142 g., 0.302 mole in 13 ml. of water containing 1 drop of 10 N sodium hydroxide) is added dropwise to a stirred solution of 0.06 mole of ethyl γ -keto- γ -(2'-nitro-4-biphenyl) butyrate, methanol (50 ml.) and water (5 ml.) cooled in an ice-water mixture. The solution is partially neutralized with urea-active acid solution (15 ml. each of acetic acid and urea 0.041 mole). The pH after the addition is near neutral. The pH is then adjusted to acidic by addition of 18 N sulfuric acid (2.8 ml.). The product is extracted with ether, washed with 2 × 25 ml. of saturated sodium bisulfite and then dried over anhydrous sodium sulfite for 2 hours. The drying agent is removed and the

solvent is then removed to obtain ethyl γ -hydroxy- γ -(2'-nitro-4-biphenyl)butyrate.

A. When γ -keto- γ -(2'-chloro-4-biphenyl)butyric acid and γ -keto- γ -(2'-nitro-4-biphenyl)butyric acid are replaced in the above procedures by the ketobutyric acids or esters of Examples 10 and 11, then the corresponding products are obtained. A representative list of the products thus prepared is shown in Table I, below.

TABLE I

γ -hydroxy- γ -(4'-chloro-4-biphenyl)butyric acid
 γ -hydroxy- γ -(4'-nitro-4-biphenyl)butyric acid
 γ -hydroxy- γ -(4'-methyl-4-biphenyl)butyric acid
 γ -hydroxy- γ -(2'-methyl-4-biphenyl)butyric acid
 γ -hydroxy- γ -(2-chloro-4-biphenyl)butyric acid
 γ -hydroxy- γ -(2-nitro-4-biphenyl)butyric acid
 γ -hydroxy- γ -(2-bromo-4-biphenyl)butyric acid
 α -methyl- γ -hydroxy- γ -(2'-chloro-4-biphenyl)propionic acid
 β -methyl- γ -hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid
 γ -methyl- γ -hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid
 α,β -dimethyl- γ -hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid
 γ -hydroxy- γ -(4-tolyl)butyric acid
 γ -hydroxy- γ -(4-i-propylphenyl)butyric acid
 γ -hydroxy- γ -(4-t-butylphenyl)butyric acid
 γ -hydroxy- γ -(4-cyclopentylphenyl)butyric acid
 γ -hydroxy- γ -(4-cycloheptylphenyl)butyric acid
 γ -hydroxy- γ -(4-cyclohexylphenyl)butyric acid
 γ -hydroxy- γ -(4-cyclohex-1-enylphenyl)butyric acid
 γ -hydroxy- γ -(4-phenoxyphenyl)butyric acid
 γ -hydroxy- γ -(4-phenylthiophenyl)butyric acid
 γ -hydroxy- γ -(4-anilinophenyl)butyric acid
 γ -hydroxy- γ -(2-anilinophenyl)butyric acid
 γ -hydroxy- γ -(4-benzoylphenyl)butyric acid
 γ -hydroxy- γ -[4-(2-thienyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(3-furyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(2-pyridyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(4-pyridyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(2-pyrazinyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(2-pyrimidinyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(3-pyridazinyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(2-triazinyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(3-isoxazolyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(3-isothiazolyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(2H-pyrrol-3-yl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(2-imidazolyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(1-pyrazolyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(2H-pyran-2-yl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(1-pyrrolyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(2-imidazolin-4-yl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(2-imidazolidinyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(1-pyrazolidinyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(2-pyrrolidinyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(2-pyrrolin-3-yl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(2-piperidinyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(4-piperidinyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(1-piperazinyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(2-piperazinyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(3-morpholinyl)phenyl]butyric acid
 γ -hydroxy- γ -[4-(4-morpholinyl)phenyl]butyric acid

γ -hydroxy- γ -methyl- γ -(2'-chloro-4-biphenyl)butyric acid
 γ -hydroxy- γ -methyl- γ -(2'-nitro-4-biphenyl)butyric acid
 γ -hydroxy- γ -methyl- γ -(2'-bromo-4-biphenyl)butyric acid
 γ -hydroxy- γ -methyl- γ -(4'-nitro-4-biphenyl)butyric acid
 γ -hydroxy- γ -methyl- γ -(4'-chloro-4-biphenyl)butyric acid
 γ -hydroxy- γ -methyl- γ -(4'-bromo-4-biphenyl)butyric acid
 γ -hydroxy- γ -methyl- γ -(2-chloro-4-biphenyl)butyric acid
 γ -hydroxy- γ -methyl- γ -(2-nitro-4-biphenyl)butyric acid
 γ -hydroxy- γ -methyl- γ -(2-bromo-4-biphenyl)butyric acid
 γ -hydroxy- γ -methyl- γ -(4-i-propylphenyl)butyric acid
 γ -hydroxy- γ -methyl- γ -(4-cyclohexylphenyl)butyric acid
 γ -hydroxy- γ -methyl- γ -[4-(1-pyrrolyl)phenyl]butyric acid

EXAMPLE 13

Ethyl

α -hydroxy- γ -(3-chloro-4-cyclohexylphenyl)butyrate

Ethyl α -hydroxy- γ -(4-cyclohexylphenyl)butyrate 0.38 mole and 6.1 g. of iodine (0.048 mole) and dissolved in 100 ml. of carbon tetrachloride. To this solution is added a solution of 40.4 g. (0.57 mole) of chlorine dissolved in 365 ml. of carbon tetrachloride over a period of 2 hours. During the addition, the temperature of the reaction mixture is maintained at 0°C. The mixture is stirred for 3 hours and allowed to stand with gradual warming to room temperature over 15 hours. The solvent is removed by distillation under reduced pressure. The residue is fractionally distilled to obtain ethyl α -hydroxy- γ -(3-chloro-4-cyclohexylphenyl)butyrate.

A. When bromine is used in place of chlorine in the above example then the product obtained is ethyl α -hydroxy- γ -(3-bromo-4-cyclohexylphenyl)butyrate.

B. In a similar manner the compounds of this invention may be chlorinated or brominated.

EXAMPLE 14

Ethyl

α -hydroxy- γ -(3-nitro-4-cyclohexylphenyl)butyrate

Ethyl α -hydroxy- γ -(4-cyclohexylphenyl)butyrate 0.066 mole is added to ice-cold concentrated sulfuric acid (18 ml.) and stirred with cooling for 5 minutes. Concentrated nitric acid (Sp. G. 1.51) (2.5 ml.) is added dropwise, maintaining the temperature between 30° and 40° by water cooling if necessary. After addition of the nitric acid is complete, the mixture is stirred for ½ hour, then poured into water. The mixture is made alkaline with sodium hydroxide, then extracted with ether. The ether extract is washed, dried over sodium sulfate, evaporated and the residue is fractionally distilled to obtain ethyl α -hydroxy- γ -(3-nitro-4-cyclohexylphenyl)butyrate.

A. In a similar manner the compounds of this invention may be nitrated.

71

EXAMPLE 15

Ethyl

α -hydroxy- γ -(3-trifluoromethyl-4-cyclohexylphenyl)-butyrate.

To a solution of 0.01 moles of ethyl α -hydroxy- γ -(3-bromo-4-cyclohexylphenyl)butyrate in 50 ml. of dimethylformamide is added 0.15 moles of trifluoromethyl iodide and 0.02 g. of copper powder. The reaction is shaken in a sealed tube for 5 hours at 140°C, cooled and then filtered and evaporated in vacuo. 200 ml. of water is added to the residue and extracted with ether. The ether extract is dried, evaporated to dryness and distilled to obtain ethyl α -hydroxy- γ -(3-trifluoromethyl-4-cyclohexylphenyl)butyrate.

A. In a similar manner the trifluoromethyl compounds of this invention may be prepared.

EXAMPLE 16

Ethyl

α -hydroxy- γ -(3-amino-4-cyclohexylphenyl)butyrate

A mixture of 0.05 moles of ethyl α -hydroxy- γ -(3-nitro-4-cyclohexylphenyl)butyrate in 100 ml. methanol containing 0.05 mole citric acid and 1.5 g. of 5% palladium-on-carbon is shaken with hydrogen at 2 atm. pressure and 27°C until 3 moles of hydrogen are absorbed. The mixture is filtered, washed with methanol and the filtrate concentrated in vacuo to obtain ethyl α -hydroxy- γ -(3-amino-4-cyclohexylphenyl)butyrate, isolated as the citrate salt.

A. In a similar manner the amino compounds of this invention may be prepared.

EXAMPLE 17

Ethyl α -hydroxy- γ -(3-methylamino-4-cyclohexylphenyl)butyrate

To a solution of 0.01 moles of ethyl α -hydroxy- γ -(3-amino-4-cyclohexylphenyl)butyrate in 100 ml. of pyridine is added 0.1 moles of methyl iodide. The reaction mixture is stirred overnight at room temperature, filtered and concentrated. The residue is distilled to obtain ethyl α -hydroxy- γ -(3-methylamino-4-cyclohexylphenyl)butyrate.

A. When 0.01 moles of acetyl chloride is used in place of methyl iodide in the above example, then the product prepared is ethyl α -hydroxy- γ -(3-acetylamino-4-cyclohexylphenyl)butyrate.

B. In a similar manner the methylamino and acetylamino compounds of this invention may be prepared.

EXAMPLE 18

Ethyl

α -hydroxy- γ -(3-dimethylamino-4-cyclohexylphenyl)-butyrate

A solution of 0.005 moles of ethyl α -hydroxy- γ -(3-nitro-4-cyclohexylphenyl)butyrate and 1.6 ml. of 37% formaldehyde in 50 ml. of methanol is shaken with hydrogen over 0.5 g. of 5% palladium-on-charcoal at 42 lbs. and 27°C until 5 moles of hydrogen are absorbed. The catalyst is filtered off and the filtrate is evaporated in vacuo. The residue is then distilled to obtain ethyl α -hydroxy- γ -(3-dimethylamino-4-cyclohexylphenyl)-butyrate.

72

A. In a similar manner the dimethylamino compounds of this invention may be prepared.

EXAMPLE 19

Benzyl

α -hydroxy- γ -(3-cyano-4-cyclohexylphenyl)butyrate

To 0.1 moles of benzyl α -hydroxy- γ -(3-amino-4-cyclohexylphenyl) butyrate in 35 ml. of 28% hydrochloric acid and 100 ml. of cracked ice to maintain the temperature at 0°C is added a solution of 7.1 g. (0.102 moles) of sodium nitrite in 20 ml. of water. The reaction mixture is then neutralized with sodium carbonate. This diazonium mixture is added to a cuprous cyanide solution (prepared from 31.5 g. of copper sulfate and 16.2 of sodium cyanide in 75 ml. of water). 250 ml of toluene is also added and the mixture is stirred for ½ hour. The reaction is then allowed to stir an additional 2 hours while warming gradually to 50°C. This is then cooled and the toluene separated, dried over sodium sulfate and evaporated to dryness to obtain benzyl α -hydroxy- γ -(3-cyano-4-cyclohexylphenyl)butyrate.

A. In a similar manner the cyano compounds of this invention may be prepared.

EXAMPLE 20

Ethyl

α -hydroxy- γ -(3-fluoro-4-cyclohexylphenyl)butyrate

To 0.15 moles of ethyl α -hydroxy- γ -(3-amino-4-cyclohexylphenyl) butyrate is added at 0°C 44 ml. of 1.5 moles of concentrated hydrochloric acid. The reaction mixture is maintained at 0°C and the diazonium salt is prepared with 23.2 g. (0.32 moles) of 95% sodium nitrite in 80 ml. of water. To this mixture is rapidly added a solution of 10.4 g. (0.17 moles) of boric acid dissolved in 22 g. (0.66 moles) of 60% hydrofluoric acid. The reaction mixture is then stirred for 1/2 hour and filtered, washed with 3 × 25 ml. of water, 2 × 25 ml. of methanol and 25 ml. of ether. The residual cake is then treated in vacuo. The treated cake is then placed in a distilling flask and heated to permit spontaneous decomposition. After the decomposition, the residue is then fractionally distilled to obtain ethyl α -hydroxy- γ -(3-fluoro-4-cyclohexylphenyl)butyrate.

A. In a similar manner the fluoro compounds of this invention may be prepared.

EXAMPLE 21

α -Hydroxy- γ -(3-hydroxy-4-cyclohexylphenyl)butyric acid

To 4.9 g. of ethyl α -hydroxy- γ -(3-amino-4-cyclohexylphenyl)butyrate suspension in 125 ml. of 80% hydrochloric acid and cooled to 0°C is added dropwise a solution of 1.2 g. of sodium nitrite in 15 ml. of water. After about 10 min., 200 ml. of 50% hydrochloric acid is added portion wise and stirred for 15 hours. The reaction mixture is then poured onto ice water and extracted with chloroform, dried over sodium sulfate and concentrated in vacuo. The residue is crystallized to obtain α -hydroxy- γ -(3-hydroxy-4-cyclohexylphenyl)butyric acid.

The ethyl ester of the product is formed by reaction with absolute ethanol containing a small amount of anhydrous hydrochloric acid.

a. In a similar manner the hydroxy compounds of this invention may be prepared.

EXAMPLE 22

Ethyl

 α -hydroxy- γ -(3-methoxy-4-cyclohexylphenyl)butyrate

To a stirred solution of 0.01 moles of sodium hydride in 25 ml. of dry dimethylformamide which has been cooled to 0°C is added dropwise a solution of 0.01 moles of ethyl α -hydroxy- γ -(3-hydroxy-4-cyclohexylphenyl)butyrate in 10 ml. of dimethylformamide. The reaction is stirred for 15 minutes and 0.015 moles of methyl iodide is then added dropwise. The mixture is allowed to stir overnight at room temperature. 200 ml. of water is added and the resulting mixture is extracted well with ether. The ether extract is washed with water, dried over sodium sulfate, evaporated to dryness and distilled to obtain ethyl α -hydroxy- γ -(3-methoxy-4-cyclohexylphenyl)butyrate.

When the benzyl ester is used above and 0.01 moles of acetyl chloride is used in place of methyl iodide, then the product prepared is benzyl α -hydroxy- γ -(3-acetyloxy-4-cyclohexylphenyl)butyrate.

B. In a similar manner the methoxy and acetyloxy compounds of this invention may be prepared.

EXAMPLE 23

 α -Hydroxy- γ -(3-bromo-4-cyclohexylphenyl)butyric acid

To 0.044 moles of ethyl α -hydroxy- γ -(3-amino-4-cyclohexylphenyl)butyrate suspension in 225 ml. of 40% hydrobromic acid and cooled to 0°C is added dropwise a solution of 2.34 g. of sodium nitrite in 30 ml. of water. To this mixture is added a solution of 20 g. of cuprous bromide in 350 ml. of 40% hydrobromic acid added portion wise and stirred for 15 hours. The reaction mixture is then poured onto ice water, extracted with chloroform, dried over sodium sulfate and concentrated in vacuo. The residue is then crystallized to obtain α -hydroxy- γ -(3-bromo-4-cyclohexylphenyl)butyric acid.

The ethyl ester of the product is formed by reaction with absolute ethanol containing a small amount of anhydrous hydrochloric acid.

A. In a similar manner the bromo compounds of this invention may be prepared.

EXAMPLE 24

 α -Hydroxy- γ -(3-iodo-4-cyclohexylphenyl)butyric acid

To 0.05 moles of ethyl α -hydroxy- γ -(3-amino-4-cyclohexylphenyl)butyrate dissolved in a mixture of 50 g. of ice water and .06 moles of concentrated sulfuric acid at 0°C is added a solution of 0.05 moles of 95% sodium nitrite in 8 ml. of water. Stirring is continued for ½ hour and then 1.5 ml. of concentrated sulfuric acid is added. This solution is poured into an ice-cold solution of 0.06 moles of potassium iodide in 10 ml. of water. To this is added 0.075 g. copper bronze with stirring and the solution is warmed slowly on a water bath to about 80°C for 2 hours. After cooling to room temperature the reaction mixture is extracted thrice with 15 ml. portions of chloroform. This is then washed with dilute thiosulfate solution, water, dried over sodium sulfate and evaporated in vacuo. The residue is crystallized to obtain α -hydroxy- γ -(3-iodo-4-cyclohexylphenyl)butyric acid.

The ethyl ester of the product is formed by reaction with absolute ethanol containing a small amount of an-

hydrous hydrochloric acid.

A. In a similar manner the iodo compounds of this invention may be prepared.

EXAMPLE 25

 α -Hydroxy- γ -(3-mercapto-4-cyclohexylphenyl)butyric acid

To 19.5 g. of ethyl α -hydroxy- γ -(3-amino-4-cyclohexylphenyl)butyrate in 11.1 ml. of concentrated hydrochloric acid and 20 g. of ice is added 4.1 g. of sodium nitrite in 2 ml. of water. This mixture is stirred for 10 min. and then added gradually to an ice cold solution of 10.3 g. of potassium ethyl xanthate in 14 ml. of water. The reaction is gradually heated over 45 min. to 50°C and stirred an additional 45 minutes. The mixture is then cooled, extracted with ether which is then washed with water, dilute sodium hydroxide and water, dried over sodium sulfate and evaporated in vacuo. The residue is dissolved in 35 ml. of boiling ethanol to which is added gradually 13 g. of potassium hydroxide. The reaction is refluxed an additional hour and then evaporated to dryness in vacuo. The residue is dissolved in water and extracted with ether. The alkaline phase is acidified with 6N sulfuric acid and extracted with ether. The ether is washed with water, dried over sodium sulfate and evaporated to dryness to obtain α -hydroxy- γ -(3-mercapto-4-cyclohexylphenyl)butyric acid.

The ethyl ester of the product is formed by reaction with absolute ethanol containing a small amount of anhydrous hydrochloric salt.

A. In a similar manner the mercapto compounds of this invention may be prepared.

EXAMPLE 26

Ethyl

 α -hydroxy- γ -(3-methylthio-4-cyclohexylphenyl)butyrate

To 3.9 g. of ethyl α -hydroxy- γ -(3-mercapto-4-cyclohexylphenyl)butyrate in 40 ml. of water containing 0.65 g. of sodium hydroxide is added 2 ml. of dimethyl sulfate with stirring. The reaction mixture is gradually warmed to 40°C and stirred for 2 hours. The mixture is cooled and extracted with ether which is washed with water, dried and evaporated in vacuo. The residue is distilled to obtain ethyl α -hydroxy- γ -(3-methylthio-4-cyclohexylphenyl)butyrate.

A. When the benzyl ester of α -hydroxy- γ -(3-methylthio-4-cyclohexylphenyl)butyrate is treated with 30% H₂O₂, then the resultant product is benzyl α -hydroxy- γ -(3-methylsulfinyl-4-cyclohexylphenyl)butyrate or benzyl α -hydroxy- γ -(3-methylsulfonyl-4-cyclohexylphenyl)butyrate.

B. When an equimolar amount of acetyl chloride is used in place of dimethyl sulfate in the above reaction along with the benzyl ester, then the product prepared is benzyl α -hydroxy- γ -(3-acetylthio-4-cyclohexylphenyl)butyrate.

C. In a similar manner the methylthio, methylsulfinyl, methylsulfonyl and acetylthio compounds of this invention may be prepared.

EXAMPLE 27

 α -Hydroxy- γ -(3-chloro-4-cyclohexylphenyl)butyric acid

To a solution of 0.144 moles of ethyl α -hydroxy-(3-chloro-4-cyclohexylphenyl)butyrate dissolved in 220

ml. of isopropanol is added 38 g. (0.7 mole) of potassium hydroxide. This mixture is then heated at reflux temperature in a nitrogen atmosphere. The solution is concentrated in vacuo to a viscous oil, which is then dissolved in 500 ml. of water and filtered. The filtrate is acidified with 10% HCl and the precipitate is taken up in ether. The ether layer is dried, filtered and the filtrate concentrated to dryness. Recrystallization of residue from benzene-cyclohexane 1:1 gives α -hydroxy- γ -(3-chloro-4-cyclohexylphenyl)butyric acid.

A. In a similar manner the esters of this invention may be converted to the corresponding acids.

EXAMPLE 28

α -Hydroxy- γ -(3-cyano-4-cyclohexylphenyl)butyric acid

A solution of 0.01 moles of benzyl α -hydroxy- γ -(3-cyano-4-cyclohexylphenyl)butyrate dissolved in 100 ml. of acetic acid and containing 0.01 mole of hydrogen chloride is shaken with hydrogen over a 5% Pd carbon catalyst until 0.01 moles of hydrogen is absorbed. The catalyst is then filtered and the solution is evaporated to dryness and crystallized to obtain α -hydroxy- γ -(3-cyano-4-cyclohexylphenyl)butyric acid.

A. In a similar manner the acid may be formed from the benzyl ester of the various cyano, acetamino, acetylthio, acetyloxy, methylsulfinyl and methylsulfonyl compounds of this invention.

EXAMPLE 29

1 α -Hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid

To a boiling solution of 0.10 mole of cinchonidine in 1 liter of absolute ethanol is added a boiling solution of 0.10 mole of dl α -hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid in 500 ml. of absolute ethanol. The solution is stirred briefly then allowed to cool to room temperature overnight. The precipitate is collected and washed with 2 $\times$ 25 ml. of ethanol and air dried. Recrystallization from isopropanol gives white needle crystals. This material is hydrolyzed with 200 ml. of 1.2 N-HCl. The white solid is collected, washed with 3 $\times$ 50 ml. water and dried at 55°C. overnight. Recrystallization from benzene-cyclohexane 3:2 gives 1 α -hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid.

A. When modifications of the above resolution procedure is followed but dl α -hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid is replaced by an equimolar amount of the dl alkanic acids of this invention, then the corresponding 1-isomer is prepared.

EXAMPLE 30

d- α -Hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid

The combined ethanol and isopropanol filtrates from Example 29 are evaporated to dryness. This material is triturated with 1 liter of boiling acetone. The material which does not go into solution is filtered off. The filtrate is evaporated to dryness and hydrolyzed with 100 ml. of 1.2 N-HCl. The precipitate is collected, washed with 3 $\times$ 25 ml. of water, and dried at 55°C. Recrystallization from benzene-cyclohexane 3:2 gives d α -hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid.

A. When modifications of the above resolution procedure is followed but dl α -hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid is replaced by an equimolar amount of the dl alkanic acids of this invention, then the corresponding d-isomer is prepared.

EXAMPLE 31

α -Hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid, sodium salt

A solution of 12.4 g. of sodium bicarbonate in 135 ml. of water is added dropwise to a stirred solution of 0.164 moles of α -hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid in 150 ml. of methanol. The solvent is removed in vacuo and the residue is dried by repeated distillations with anhydrous ethanol. The crystalline residue is triturated with ether (100 ml.), collected and washed with ether. The residue is dried in a vacuum desiccator to obtain α -hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid, sodium salt.

A. When sodium bicarbonate in the above reaction is replaced by an equimolar amount of the compounds listed below, then the corresponding salt is prepared.

sodium hydroxide
calcium hydroxide
magnesium bicarbonate
potassium hydroxide
potassium carbonate

B. When the acid compounds of this invention are used in the above reaction, the corresponding salt is prepared.

EXAMPLE 32

α -Hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid, diethylammonium salt

Anhydrous diethylamine (0.11 moles) is added dropwise to a stirred solution of α -hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid (0.10 moles) in 100 ml. of n-hexane at 0°C. The precipitated diethylammonium salt is collected on a filter washed with n-hexane and dried in a vacuum desiccator to obtain α -hydroxy- γ -(2'-chloro-4-biphenyl)butyric acid, diethylammonium salt.

A. When diethylamine in the above reaction is replaced by an equimolar amount of the compounds below, then the corresponding product is prepared.

dimethylamine
 β -hydroxyethylamine
piperazine
piperidine
 α -methylbenzylamine
cyclohexylamine
triethylamine
phenethylamine

B. When the acid compounds of this invention are used in the reaction, then the corresponding salt is prepared.

EXAMPLE 33

N-isopropyl

α -hydroxy- γ -(2'-chloro-4-biphenyl)butyramide

Ethyl α -hydroxy- γ -(2'-chloro-4-biphenyl)butyrate 0.1 mole is stirred with 20 ml. of isopropylamine at about 35°C with stirring overnight and the temperature is then raised to reflux for 28 hours. The reaction mixture is evaporated in vacuo and the residue distilled to obtain N-isopropyl α -hydroxy- γ -(2'-chloro-4-biphenyl)butyramide.

A. When isopropylamine in the above reaction is replaced by an equimolar amount of the compound below, then the corresponding product is prepared.

diethylamine
ethylmethanamine

t-butylamine
cyclopropylamine
isothiazolidine
piperidine
morpholine
N-methylpiperazine
N-methylhomopiperazine

When isopropylamine in the above reaction is replaced by ammonia, methylamine or dimethylamine and the reaction carried out in a bomb at 150°C, then the product prepared is α -hydroxy- γ -(2'-chloro-4-biphenyl)butyramide, N-methyl α -hydroxy- γ -(2'-chloro-4-biphenyl)butyramide or N,N-dimethyl α -hydroxy- γ -(2'-chloro-4-biphenyl)butyramide.

B. When the acid compounds of this invention are used in the above reaction, then the corresponding amide is prepared.

EXAMPLE 34

Ethyl α -chloro- γ -(2'-chloro-4-biphenyl)butyrate 20

A mixture of 0.747 mole of ethyl α -hydroxy- γ -(2'-chloro-4-biphenyl)butyrate is stirred with 106.67 g. (0.895 mole) of thionyl chloride at room temperature for 24 hours and then heated to reflux for 6 hours. The cold reaction mixture is poured into 1125 ml. of ice-cold water with stirring. The mixture is extracted with 800 ml. of ether. The ethereal solution is washed with 450 ml. of cold saturated sodium hydrocarbonate solution followed by washing twice, each time with 250 ml. of cold water. The ethereal solution is dried over anhydrous sodium sulfate and filtered. The solvent is removed in vacuo to obtain ethyl α -chloro- γ -(2'-chloro-4-biphenyl)butyrate.

A. When ethyl α -hydroxy- γ -(2'-chloro-4-biphenyl)butyrate is replaced in the above procedure by the hydroxy butyrates of Examples 10-28, then the corresponding chloro butyrates are prepared. A representative list of the products thus prepared is shown in Table I, below.

TABLE I

ethyl β -chloro- γ -(4'-chloro-4-biphenyl)butyrate
ethyl β -chloro- γ -(4'-nitro-4-biphenyl)butyrate
ethyl β -chloro- γ -(2'-chloro-4-biphenyl)butyrate
ethyl β -chloro- γ -(2'-nitro-4-biphenyl)butyrate
ethyl β -chloro- γ -(2-chloro-4-biphenyl)butyrate
ethyl β -chloro- γ -(2-nitro-4-biphenyl)butyrate
ethyl γ -chloro- γ -(4'-chloro-4-biphenyl)butyrate
ethyl γ -chloro- γ -(4'-nitro-4-biphenyl)butyrate
ethyl γ -chloro- γ -(2'-chloro-4-biphenyl)butyrate
ethyl γ -chloro- γ -(2'-nitro-4-biphenyl)butyrate
ethyl γ -chloro- γ -(2-chloro-4-biphenyl)butyrate
ethyl γ -chloro- γ -(2-nitro-4-biphenyl)butyrate
ethyl α -chloro- γ -(4'-chloro-4-biphenyl)butyrate
ethyl α -chloro- γ -(4'-nitro-4-biphenyl)butyrate
ethyl α -chloro- γ -(2'-chloro-4-biphenyl)butyrate
ethyl α -chloro- γ -(2'-nitro-4-biphenyl)butyrate
ethyl α -chloro- γ -(2-chloro-4-biphenyl)butyrate
ethyl α -chloro- γ -(2-nitro-4-biphenyl)butyrate
ethyl α -chloro- α -methyl- γ -(2'-chloro-4-biphenyl)butyrate
ethyl α -chloro- β -methyl- γ -(2'-chloro-4-biphenyl)butyrate
ethyl α -chloro- γ -methyl- γ -(2'-chloro-4-biphenyl)butyrate
ethyl α -methyl- β -chloro- γ -(2'-chloro-4-biphenyl)butyrate

ethyl β -chloro- β -methyl- γ -(2'-chloro-4-biphenyl)butyrate
ethyl β -chloro- γ -methyl- γ -(2'-chloro-4-biphenyl)butyrate
ethyl γ -chloro- γ -methyl- γ -(4'-chloro-4-biphenyl)butyrate
ethyl γ -chloro- γ -methyl- γ -(2'-chloro-4-biphenyl)butyrate
ethyl γ -chloro- γ -methyl- γ -(2-chloro-4-biphenyl)butyrate
ethyl α , γ -dimethyl- γ -chloro- γ -(2'-chloro-4-biphenyl)butyrate
ethyl β , γ -dimethyl- γ -chloro- γ -(2'-chloro-4-biphenyl)butyrate
ethyl α , β -dimethyl- γ -chloro- γ -(2'-chloro-4-biphenyl)butyrate
ethyl α , β , α -trimethyl- γ -chloro- γ -(2'-chloro-4-biphenyl)butyrate
ethyl α -methyl- β -chloro- β -(2'-chloro-4-biphenyl)butyrate
ethyl α -methyl- γ -chloro- γ -(2'-chloro-4-biphenyl)butyrate
ethyl β -methyl- γ -chloro- γ -(2'-chloro-4-biphenyl)butyrate
ethyl γ -chloro- γ -(p-i-propylphenyl)butyrate
ethyl γ -chloro- γ -(p-t-butylphenyl)butyrate
ethyl γ -chloro- γ -(p-cyclohexylphenyl)butyrate
ethyl γ -chloro- γ -(p-cyclohex-1-enylphenyl)butyrate
ethyl γ -chloro- γ -(p-phenoxyphenyl)butyrate
ethyl γ -chloro- γ -(p-phenylthiophenyl)butyrate
ethyl γ -chloro- γ -(p-phenylaminophenyl)butyrate
ethyl γ -chloro- γ -[p-(2-thienyl)phenyl]butyrate
ethyl γ -chloro- γ -[p-(3-furyl)phenyl]butyrate
ethyl γ -chloro- γ -[p-(2-pyridyl)phenyl]butyrate
ethyl γ -chloro- γ -[p-(4-pyridyl)phenyl]butyrate
ethyl γ -chloro- γ -[p-(1-pyrrolyl)phenyl]butyrate
ethyl γ -chloro- γ -[p-(1-piperazinyl)phenyl]butyrate
ethyl γ -chloro- γ -[p-(3-morpholinyl)phenyl]butyrate
ethyl α -chloro- γ -(p-t-butylphenyl)butyrate
ethyl α -chloro- γ -(p-cyclohexylphenyl)butyrate
ethyl α -chloro- γ -(p-phenylthiophenyl)butyrate
ethyl α -chloro- γ -[p-(2-thienyl)phenyl]butyrate
ethyl α -chloro- γ -[p-(4-pyridyl)phenyl]butyrate
ethyl β -chloro- γ -(p-i-propylphenyl)butyrate
ethyl β -chloro- γ -(p-cyclohexylphenyl)butyrate
ethyl β -chloro- γ -(p-benzoylphenyl)butyrate
ethyl β -chloro- γ -[p-(3-morpholinyl)phenyl]butyrate
ethyl α -chloro- α -methyl- γ -(p-cyclohexylphenyl)butyrate
ethyl α -chloro- β -methyl- γ -(p-cyclohexylphenyl)butyrate
ethyl α -chloro- γ -methyl- γ -(p-cyclohexylphenyl)butyrate
ethyl α -methyl- β -chloro- γ -(p-cyclohexylphenyl)butyrate
ethyl β -chloro- β -methyl- γ -(p-cyclohexylphenyl)butyrate
ethyl β -chloro- γ -methyl- γ -(p-cyclohexylphenyl)butyrate
ethyl α -chloro- γ -(3-chloro-4-cyclohexylphenyl)butyrate
ethyl β -chloro- γ -(3-chloro-4-cyclohexylphenyl)butyrate
ethyl α -chloro- α -methyl- γ -(3-nitro-4-t-butylphenyl)butyrate
ethyl β -chloro- β -methyl- γ -(3-fluoro-4-cyclohexylphenyl)butyrate

ethyl α -methyl- β -chloro- γ -(3-chloro-4-i-propylphenyl)butyrate
 ethyl γ -chloro- γ -methyl- γ -(p-t-butylphenyl)butyrate
 ethyl γ -chloro- γ -methyl- γ -(p-cyclohexylphenyl)butyrate
 ethyl γ -chloro- γ -methyl- γ -[p-(3-furyl)phenyl]butyrate
 ethyl α , γ -dimethyl- γ -chloro- γ -(p-cyclohexylphenyl)butyrate
 ethyl β , γ -dimethyl- γ -chloro- γ -(p-cyclohexylphenyl)butyrate
 ethyl α , β -dimethyl- γ -chloro- γ -(p-cyclohexylphenyl)butyrate
 ethyl α , β , γ -trimethyl- γ -chloro- γ -(p-cyclohexylphenyl)butyrate
 ethyl α -methyl- β -chloro- β -(p-cyclohexylphenyl)propionate
 ethyl α -methyl- γ -chloro- γ -(p-cyclohexylphenyl)butyrate
 ethyl β -methyl- γ -chloro- γ -(p-cyclohexylphenyl)butyrate
 ethyl γ -chloro- γ -(3-nitro-4-t-butylphenyl)butyrate
 ethyl γ -chloro- γ -(3-trifluoromethyl-4-cyclohexylphenyl)butyrate
 ethyl γ -chloro- γ -methyl- γ -(3-bromo-4-phenoxyphenyl)butyrate
 ethyl α -chloro-2-phenylaminophenylbutyrate
 ethyl β -chloro-2-phenylaminophenylbutyrate
 ethyl γ -chloro-2-phenylaminophenylbutyrate
 ethyl α -chloro- γ -(3-chloro-4-cyclohexylphenyl)butyrate
 ethyl α -chloro- γ -(3-bromo-4-cyclohexylphenyl)butyrate
 ethyl α -chloro- γ -(3-nitro-4-cyclohexylphenyl)butyrate
 ethyl α -chloro- γ -(3-trifluoromethyl-4-cyclohexylphenyl)butyrate
 ethyl α -chloro- γ -(3-dimethylamino-4-cyclohexylphenyl)butyrate
 ethyl α -chloro- γ -(3-cyano-4-cyclohexylphenyl)butyrate
 ethyl α -chloro- γ -(3-fluoro-4-cyclohexylphenyl)butyrate
 ethyl α -chloro- γ -(3-methoxy-4-cyclohexylphenyl)butyrate
 ethyl α -chloro- γ -(3-iodo-4-cyclohexylphenyl)butyrate
 ethyl α -chloro- γ -(3-methylthio-4-cyclohexylphenyl)butyrate
 ethyl β -chloro- γ -(3-chloro-4-cyclohexylphenyl)butyrate
 ethyl β -chloro- γ -(3-bromo-4-cyclohexylphenyl)butyrate
 ethyl β -chloro- γ -(3-nitro-4-cyclohexylphenyl)butyrate
 ethyl β -chloro- γ -(3-trifluoromethyl-4-cyclohexylphenyl)butyrate
 ethyl β -chloro- γ -(3-dimethylamino-4-cyclohexylphenyl)butyrate
 ethyl β -chloro- γ -(3-cyano-4-cyclohexylphenyl)butyrate
 ethyl β -chloro- γ -(3-fluoro-4-cyclohexylphenyl)butyrate
 ethyl β -chloro- γ -(3-methoxy-4-cyclohexylphenyl)butyrate
 ethyl β -chloro- γ -(3-iodo-4-cyclohexylphenyl)butyrate

ethyl β -chloro- γ -(3-methylthio-4-cyclohexylphenyl)butyrate
 ethyl γ -chloro- γ -(3-chloro-4-cyclohexylphenyl)butyrate
 ethyl γ -chloro- γ -(3-bromo-4-cyclohexylphenyl)butyrate
 ethyl γ -chloro- γ -(3-nitro-4-cyclohexylphenyl)butyrate
 ethyl γ -chloro- γ -(3-trifluoromethyl-4-cyclohexylphenyl)butyrate
 ethyl γ -chloro- γ -(3-dimethylamino-4-cyclohexylphenyl)butyrate
 ethyl γ -chloro- γ -(3-cyano-4-cyclohexylphenyl)butyrate
 ethyl γ -chloro- γ -(3-fluoro-4-cyclohexylphenyl)butyrate
 ethyl γ -chloro- γ -(3-methoxy-4-cyclohexylphenyl)butyrate
 ethyl γ -chloro- γ -(3-iodo-4-cyclohexylphenyl)butyrate
 ethyl γ -chloro- γ -(3-methylthio-4-cyclohexylphenyl)butyrate

EXAMPLE 35

When the procedure of Example 34 is followed but ethyl α -hydroxy- γ -(2'-chloro-4-biphenyl)butyrate is replaced by the amides of Example 33, then the corresponding chlorobutyramide product is prepared.

When the dl, d and l butyramides of this invention are used in the above reaction, then the corresponding amide is prepared.

EXAMPLE 36

α -Chloro- γ -(2'-chloro-4-biphenyl)butyric acid

A mixture of 0.167 moles of ethyl α -chloro- γ -(2'-chloro-4-biphenyl)butyrate and 160 ml. of glacial acetic acid containing 40 ml. of 37% hydrochloric acid is refluxed for 20 hours. The mixture is concentrated under reduced pressure to give a gummy residue. The latter material is dissolved in 300 ml. of n-hexane, washed with ice-cold water (100 ml. total), dried over sodium sulfate and filtered. The hexane is removed to give α -chloro- γ -(2'-chloro-4-biphenyl)butyric acid.

In a similar manner the esters of this invention may be converted to the corresponding acids.

EXAMPLE 37

α -Chloro- γ -(2'-chloro-4-biphenyl)butyric acid, sodium salt

A solution of 12.4 g. of sodium bicarbonate in 135 ml. water is added dropwise to a stirred solution of 0.164 moles of α -chloro- γ -(2'-chloro-4-biphenyl)butyric acid in 150 cc. of methanol. The solvent is removed in vacuo and the residue is dried by repeated distillations with anhydrous ethanol. The crystalline residue is triturated with ether (100 cc.), collected on a filter, and washed with ether. Drying in a vacuum desiccator affords α -chloro- γ -(2'-chloro-4-biphenyl)butyric acid, sodium salt.

A. When an equimolar amount of sodium bicarbonate in the above reaction is replaced by the compounds below, then the corresponding salt is prepared.

sodium hydroxide
 calcium hydroxide
 magnesium bicarbonate

potassium hydroxide
potassium carbonate

B. When the chloro alkanoic acid compounds of this invention are used in the above reaction, then the corresponding salt is prepared.

EXAMPLE 38

α -Chloro- γ -(2'-chloro-4-biphenyl)butric acid, dimethylammonium salt

Anhydrous diethylamine (0.11 moles) is added dropwise to a stirred solution of α -chloro- γ -(2'-chloro-4-biphenyl)butyric acid (0.10 moles) in 100 ml. of n-hexane at 0°C. The precipitate is collected on a filter, washed with n-hexane, and dried in a vacuum desiccator to obtain α -chloro- γ -(2'-chloro-4-biphenyl)butyric acid, diethylammonium salt.

A. When diethylamine in the above reaction is replaced by an equimolar amount of the compounds below, then the corresponding product is prepared.

dimethylamine
 β -hydroxyethylamine
piperazine
piperidine
 α -methylbenzylamine
cyclohexylamine
triethylamine
phenethylamine

B. When the chloro alkanoic acid compounds of this invention are used in the above reaction, then the corresponding salt is prepared.

EXAMPLE 39

N-isopropyl

α -chloro- γ -(2'-chloro-4-biphenyl)butyramide

A mixture of 5.2 g. (0.016 moles) of ethyl α -chloro- γ -(2'-chloro-4-biphenyl)butyrate and 5.5 ml. of anhydrous isopropylamine are stirred over Linde 4A molecular sieve for 16 hours at room temperature. The reaction mixture is taken up in ether and washed three times with 15 ml. of 10% hydrochloric acid. The ether layer is dried over sodium sulfate, filtered, and the ether is removed. The residue is triturated with n-hexane and the precipitate is collected to obtain N-isopropyl α -chloro- γ -(2'-chloro-4-biphenyl)butyramide.

A. When isopropylamine in the above reaction is replaced by an equimolar amount of the amines listed below, then the corresponding product is prepared.

diethylamine
ethylmethylamine
t-butylamine
cyclopropylamine
N-methylhomopiperazine
isothiazolidine
piperidine
morpholine
N-methylpiperazine

C. When the chloro butyrates of this invention are used in the above procedure, then the corresponding products are prepared.

EXAMPLE 40

Ethyl α -bromo- γ -(2'-chloro-4-biphenyl)propionate

To 15.4 g. (0.0476 moles) of ethyl α -hydroxy- γ -(2'-chloro-4-biphenyl)butyrate there is added slowly

with stirring at 40°-50°C 23 g. (0.053 moles) of phosphorus pentabromide. The mixture is stirred at room temperature for 16 hours, then diluted with 70 ml. of petroleum ether, and poured into 125 ml. of ice-cold water. The organic phase is separated, washed with saturated aqueous sodium hydrogen carbonate solution, dried over anhydrous sodium sulfate, filtered and the solvent removed in vacuo to obtain ethyl α -bromo- γ -(2'-chloro-4-biphenyl)butyrate.

A. In a similar manner the hydroxy butyrates or hydroxy butyramides of this invention may be converted to the corresponding bromo butyrates or bromo butyramides.

EXAMPLE 41

When the bromo butyrates of this invention are hydrolyzed according to the procedure of Example 36, then the corresponding bromo butyric acid compounds are prepared.

EXAMPLE 42

When the bromo butyric acid compounds of this invention are reacted according to the procedures of 37-38, then the corresponding bromo butyric acid salts are prepared.

EXAMPLE 43

Ethyl α -fluoro- γ -(2'-chloro-4-biphenyl)butyrate

A mixture of 0.33 moles of ethyl α -bromo- γ -(2'-chloro-4-biphenyl)butyrate is vigorously stirred at 130°-140°C with 29 g. (0.5 moles) of potassium fluoride in 100 ml. of ethylene glycol for 12 hours. The reaction mixture is cooled and 400 ml. of water is added and the crude product separates. The aqueous glycol mixture is extracted with ether, the ether is then dried, evaporated to dryness and upon distillation results in ethyl α -fluoro- γ -(2'-chloro-4-biphenyl)butyrate.

A. When the above procedure is followed using the various bromo butyrates and butyramides of this invention, then the corresponding fluoro butyrates and fluoro butyramides are prepared.

EXAMPLE 44

When the fluoro butyrates of Example 43 are hydrolyzed according to the procedure of Example 36, then the corresponding fluoro butyric acid compounds are prepared.

EXAMPLE 45

When the fluoro butyric acid compounds of this invention are reacted according to the procedures of Examples 37-38, then the corresponding fluoro butyric acid salts are prepared.

EXAMPLE 46

Ethyl α -iodo- γ -(2'-chloro-4-biphenyl)butyrate

A mixture of 0.1 moles of ethyl α -bromo- γ -(2'-chloro-4-biphenyl) butyrate and 150 gl. of sodium iodide in 1 liter of anhydrous acetone is refluxed for 4 hours. The reaction mixture is then evaporated to dryness and extracted with ether. The ether is then washed with water, dried and evaporated to dryness to obtain ethyl α -iodo- γ -(2'-chloro-4-biphenyl) butyrate.

A. When the above procedure is followed using the various bromo butyrates and bromo butyramides of this

invention, then the corresponding iodo butyrates and iodo butyramides are prepared.

EXAMPLE 47

When the iodo butyrates of Example 46 are hydrolyzed according to the procedure of Example 36, then the corresponding iodo butyric acid compounds are prepared.

EXAMPLE 48

When the iodo butyric acid compounds are reacted according to the procedures of Examples 37-38, then the corresponding iodo butyric acid salts are prepared.

EXAMPLE 49

α -Mercapto- γ -(2'-chloro-4-biphenyl)butyric acid

A mixture of 0.05 moles of α -chloro- γ -(2'-chloro-4-biphenyl) butyric acid and 5 g. of sodium hydrosulfide in 100 ml. of absolute ethanol and under a nitrogen atmosphere is stirred for 15 hours. The mixture is then acidified with 6 N hydrochloric acid. The solvent is removed in vacuo and the residue is extracted into ether, washed with water, saturated sodium chloride solution, dried and evaporated to dryness to obtain α -mercapto- γ -(2'-chloro-4-biphenyl)butyric acid.

A. When the chloro butyric acids, chloro butyrates and chloro butyramides of this invention are used in the above reaction, then the corresponding mercapto butyric acids, mercapto butyrates and mercapto butyramides are prepared.

EXAMPLE 50

α -Methylthio- γ -(2'-chloro-4-biphenyl)butyric acid

Methyl mercaptan is bubbled into a solution of 18.4 g. of potassium t-butoxide in 100 ml. of t-butanol for $\frac{3}{4}$ hours and under a nitrogen atmosphere. To this is added 0.041 moles of α -chloro- γ -(2'-chloro-4-biphenyl)butyric acid in 60 ml. of dry tetrahydrofuran. The mixture is then refluxed for 3 hours and allowed to stir at room temperature for 15 hrs, acidified with 30 ml. of 6 N hydrochloric acid. The solvent is removed in vacuo and the residue extracted into ether, washed with water, saturated sodium chloride solution, dried and evaporated to dryness to obtain α -methylthio- γ -(2'-chloro-4-biphenyl)butyric acid.

A. When the chloro butyric acids, chloro butyrates and chloro butyramides of this invention are used in the above reaction, then the corresponding methylthioalkanoic acids, methylthioalkanoates and methylthioalkanoamides are prepared.

EXAMPLE 51

α -Acetylthio- γ -(2'-chloro-4-biphenyl)butyric acid

To a solution of 600 ml. of anhydrous ethanol and 21 g. (0.317 moles) of potassium hydroxide is added 45 ml. of thioacetic acid dropwise. To this mixture is then added 79 g. (0.244 moles) of α -chloro- γ -(2'-chloro-4-biphenyl)butyric acid and stirring is continued for 15 hours. The solid which forms is filtered off and washed with ethanol. The filtrate is evaporated to dryness and the residue is dissolved in 500 ml. of ether and washed several times with water. Drying the ether and evaporation to dryness results in α -acetylthio- γ -(2'-chloro-4-biphenyl)butyric acid.

A. In a similar manner, the α -propionylthio- γ -(2'-

chloro-4-biphenyl) butyric acid compounds are prepared.

B. When the chloro butyric acids, chloro butyrates and chlorobutyramides of this invention are used in the above reaction, then the corresponding acetylthiobutyric acids, acetylthiobutyrate and acetylthiobutyramides are prepared.

EXAMPLE 52

α -Benzoylthio- γ -(2'-chloro-4-biphenyl)butyric acid

To 17.4 ml. of 2N alcoholic potassium hydroxide solution (0.035 mole) is added 4.84 g. (0.035 mole) of thiobenzoic acid. The solution is cooled to room temperature and to this is added in small portions 0.035 mole of α -chloro- γ -(2'-chloro-4-biphenyl)butyric acid. The reaction mixture is stirred at room temperature for 25 hours, then the solvent is removed, the residue dissolved in ether, filtered and washed with cold water. The ethereal solution is then dried over magnesium sulfate and evaporated to dryness to obtain α -benzoylthio- γ -(2'-chloro-4-biphenyl)butyric acid.

A. When the chlorobutyric acids, chlorobutyrate and chlorobutyramides of this invention are used in the above reaction, then the corresponding benzoylthiobutyric acids, benzoylthiobutyrate and benzoylthiobutyramides are prepared.

EXAMPLE 53

Ethyl

α -thioacetylthio- γ -(2'-chloro-4-biphenyl)butyrate

A mixture of 0.2 moles of sodium dithioacetate and 0.12 moles of ethyl α -chloro- γ -(2'-biphenyl)butyrate 4-biphenyl)butyrate in 300 ml. of absolute ethanol is stirred at room temperature for 15 hours. The reaction mixture is filtered, washed with absolute ethanol and evaporated to dryness in vacuo. The residue is treated with ether, filtered and evaporated to obtain ethyl α -thioacetylthio- γ -(2'-chloro-4-biphenyl)butyrate.

A. When the chlorobutyric acids, chlorobutyrate and chlorobutyramides of this invention are used in the above reaction, then the corresponding thioacetylthiobutyric acids, thioacetylthiobutyrate and thioacetylthiobutyramides are prepared.

B. When sodium dithioformate is used in the above procedure in place of sodium dithioacetate then the product prepared is ethyl α -thioformylthio- γ -(2'-chloro-4-biphenyl)butyrate.

EXAMPLE 54

α -Thiocyanato- γ -(2'-chloro-4-biphenyl)butyric acid

To a solution of 300 ml. of anhydrous ethanol and 0.15 moles of sodium thiocyanate is added 0.12 moles of α -chloro- γ -(2'-chloro-4-biphenyl)butyric acid and stirred for 15 hours. The reaction mixture is filtered and washed with absolute ethanol. The filtrate is evaporated to dryness, the residue is dissolved in 250 ml. of ether and washed several times with water. The ether is then dried and evaporated to dryness to obtain α -thiocyanato- γ -(2'-chloro-4-biphenyl)butyric acid.

A. When the chlorobutyric acids, chlorobutyrate and chlorobutyramides of this invention are used in the above reaction, then the corresponding thiocyanatobutyric acids, thiocyanatobutyrate and thiocyanatobutyramides are prepared.

EXAMPLE 55

α -Sulfo- γ -(2'-chloro-4-biphenyl)butyric acid, disodium salt

To a solution of 250 ml. of anhydrous ethanol and 0.12 moles of sodium sulfite is added 0.1 moles of α -chloro- γ -(2'-chloro-4-biphenyl) butyric acid, sodium salt. The reaction mixture is stirred for 15 hours, filtered and the residue worked with ethanol. The filtrate is evaporated to dryness to obtain α -sulfo- γ -(2'-chloro-4-biphenyl)butyric acid, disodium salt.

A. When sodium sulfinate is used in the above procedure in place of sodium sulfite, then the product obtained is α -sulfinio- γ -(2'-chloro-4-biphenyl)butyric acid, disodium salt.

B. When the chlorobutyric acids, chlorobutyramides of this invention are used in the above reactions, then the corresponding sulfo and sulfinobutyrate and butyramides are prepared.

EXAMPLE 56

Ethyl α -thiosulfo- γ -(2'-chloro-4-biphenyl)butyrate, sodium salt

A mixture of 0.023 moles of ethyl α -chloro- γ -(2'-chloro-4-biphenyl)butyrate and 5.7 g. of sodium thiosulfate pentahydrate in 75 ml. of 40.45 water-alcohol mixture is refluxed for 2 hours. An additional 0.8 g. of sodium thiosulfate pentahydrate is then added and refluxing continued another 1/2 hour. The reaction mixture is then evaporated to dryness in vacuo, azeotroped with ethanol and evaporated to dryness in vacuo again. The residue is triturated with ether, filtered and evaporated to dryness. The residue is then triturated with hexane and the resultant gum is dissolved in alcohol and evaporated to dryness in vacuo to obtain ethyl α -thiosulfo- γ -(2'-chloro-4-biphenyl)butyrate, sodium salt.

A. When the chlorobutyrate and chlorobutyramides of this invention are used in the above reaction, then the corresponding thiosulfobutyrate and thiosulfobutyramides are prepared.

EXAMPLE 57

α -Aminodithio- γ -(2'-chloro-4-biphenyl)butyric acid, hydrochloride

Thiourea 15.2 g. (0.2 moles) is dissolved in 150 ml. of absolute ethanol and to this is added 35.5 g. (0.11 moles) of α -chloro- γ -(2'-chloro-4-biphenyl)butyric acid. The mixture is stirred for 15 hours at 0°C. The mixture is then filtered to obtain α -aminodithio- γ -(2'-chloro-4-biphenyl)butyric acid, hydrochloride.

A. When the chlorobutyric acids, esters and amides of this invention are used in the above procedures, then the corresponding aminodibutyric acids, esters and amides are prepared.

EXAMPLE 58

α -Ethoxythiocarbamylthio- γ -(2'-chloro-4-biphenyl)butyric acid

Ethylxanthic acid, potassium salt, 3.63 g. (0.22 moles) is dissolved in 150 ml. of absolute ethanol with stirring. To this solution is added 0.11 moles of α -chloro- γ -(2'-chloro-4-biphenyl)butyric acid and the mixture stirred for 15 hours. The solid which collects is separated and washed with absolute ethanol. The solid is then treated with acetone and the insoluble material filtered off. The filtrate is concentrated to dryness to obtain α -ethoxythiocarbamylthio- γ -(2'-chloro-4-

biphenyl) butyric acid.

A. When the chlorobutyric acids, esters and amides of this invention are used in the above procedure, then the corresponding ethylxanthylbutyric acids, esters and amides are prepared.

EXAMPLE 59

α -Ethoxycarbonylthio- γ -(2'-chloro-4-biphenyl)butyric acid

A solution of α -mercapto- γ -(2'-chloro-4-biphenyl)butyric acid 0.02 moles in 25 ml. of pyridine is cooled in an ice bath. To this is added dropwise 2.1 ml. (0.022 moles) of ethyl chloroformate. The mixture is basified with 10% sodium bicarbonate solution. The alkaline mixture is worked with ether, then acidified with 10% hydrochloric acid, washed with ether, dried and filtered, the solvent is removed and the residue is triturated with hexane to obtain α -ethoxycarbonylthio- γ -(2'-chloro-4-biphenyl)butyric acid.

A. When the mercaptobutyric acids, esters and amides of this invention are used in the above procedure, then the corresponding ethoxycarbonylthiobutyric acids, esters and amides are prepared.

EXAMPLE 60

α -Diethylcarbamylthio- γ -(2'-chloro-4-biphenyl)butyric acid

A solution of α -mercapto- γ -(2'-chloro-4-biphenyl)butyric acid 0.02 moles in 25 ml. of pyridine is cooled in an ice bath. To this is added dropwise 0.022 moles of diethylcarbamyl chloride. The mixture is then stirred for 2 hours, diluted with ether and filtered. The mixture is then basified with 10% sodium bicarbonate solution. The alkaline mixture is washed with ether, acidified with 10% hydrochloric acid, extracted with ether which in turn is washed with cold water, dried and evaporated to dryness. Trituration with hexane results in α -diethylcarbamylthio- γ -(2'-chloro-4-biphenyl)butyric acid.

A. When diethylcarbamylchloride is replaced in the above procedure by carbamyl chloride (prepared in situ from potassium cyanate and anhydrous hydrogen chloride in anhydrous chloroform), ethylcarbamyl chloride or dimethylcarbamyl chloride, then the products prepared are α -carbamylthio- γ -(2'-chloro-4-biphenyl)butyric acid, α -ethylcarbamylthio- γ -(2'-chloro-4-biphenyl)butyric acid or α -dimethylcarbamylthio- γ -(2'-chloro-4-biphenyl)butyric acid.

B. When the mercaptobutyric acids, esters and amides of this invention are used in the above procedure, then the corresponding carbamylthiobutyric acids, esters and amides are prepared.

EXAMPLE 61

When the procedure of Example 49 is followed but diethylcarbonate is replaced by succinic anhydride, maleic anhydride or phthalic anhydride, then the products prepared are α -butyrylthio- γ -(2'-chloro-4-biphenyl)butyric acid, α -butenoylthio- γ -(2'-chloro-4-biphenyl)butyric acid and α -(o-carboxybenzoylthio- γ -(2'-chloro-4-biphenyl)butyric acid.

EXAMPLE 62

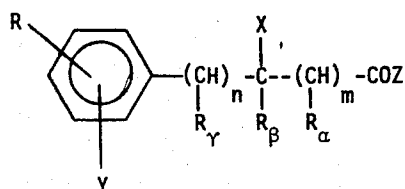
When α -methylthio- γ -(2'-chloro-4-biphenyl)butyric acid is treated with 30% hydrogen

87

peroxide, then the resultant product is α -methylsulfonyl- γ -(2'-chloro-4-biphenyl)butyric acid or α -methylsulfonyl- γ -(2'-chloro-4-biphenyl)butyric acid.

I claim:

1. A compound of the formula



where:

R is

phenyl or substituted phenyl where the substituent is Y;

Y is hydrogen, alkyl having from 1-7 carbon atoms or halo;

$n + m = 2$;

R_γ , R_β and R_α are hydrogen or loweralkyl;

X is halo

Z is hydrogen,

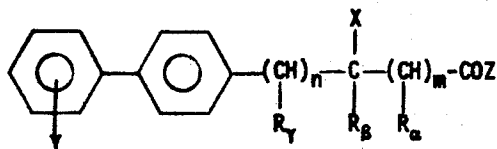
-OH,

loweralkoxy,

benzyloxy or

-OM where M is an alkali, alkaline earth or aluminum metal an ammonium salt.

2. A compound according to claim 1 of the formula



3. A compound according to claim 2, where

n is 0 and m is 2;

X is chloro;

Y is chloro;

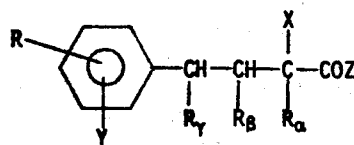
R_γ and R_β are hydrogen; and

88

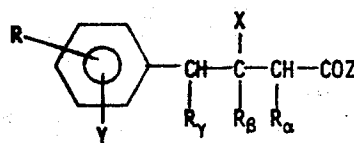
Z is selected from the group consisting of -OH and lower alkoxy,

said compound being a compound selected from the group consisting of γ -chloro- γ -(2'-chloro-4-biphenyl)butyric acid and lower alkyl ester thereof.

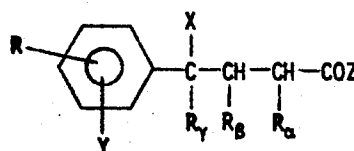
4. A compound according to claim 1 of the formula



5. A compound according to claim 1 of the formula



6. A compound according to claim 1 of the formula



7. A compound according to claim 2 where

Y is hydrogen or halo;

R_γ , R_β and R_α are hydrogen.

8. A compound according to claim 7 where

Y is 2'-chloro, X is chloro and Z is -OH.

9. A compound according to claim 8 where $n = 2$.

10. A compound according to claim 8 where $n = 1$ and $m = 1$.

11. A compound according to claim 8, where m is 2, said compound being γ -chloro- γ -(2'-chloro-4-biphenyl)butyric acid.

* * * * *

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