United States Patent [19]

Diamond et al.

[11] **3,852,323**

[45] **Dec. 3, 1974**

[54] **PHENYLACETIC ACIDS**

[75] Inventors: **Julius Diamond,** Lafayette Hill; **Norman Julian Santora,** Roslyn, both of Pa.

[73] Assignee: **William H. Rorer, Inc.,** Fort Washington, Pa.

[22] Filed: **June 11, 1971**

[21] Appl. No.: **152,387**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 34,870, May 5, 1970.

[52] **U.S. Cl.**..... **260/465 D,** 260/141, 260/239 BC, 260/482 C, 260/247.2, 260/247.7 R, 260/247.7 C, 260/247.7 H, 260/247.7 K, 260/268 R, 260/485 F, 260/485 H, 260/268 C, 260/485 J, 260/488 CD, 260/284, 260/500.5 H, 260/501.16, 260/293.72, 260/515 A, 260/515 M, 260/293.8, 260/516, 260/518 a, 260/295 R, 260/519, 260/558 R, 260/293.81, 260/558 S, 260/558 A, 260/306.7, 260/559 R, 260/559 T, 260/332.2 R, 260/559 A, 260/999, 260/332.2 A, 260/448 R, 260/455 R, 260/456 A, 260/456 P, 260/463, 260/468 R, 260/469, 260/470, 260/471 R, 260/472, 260/473 R, 260/473 A, 260/473 S, 260/475 SC, 260/496 R, 260/479 R, 260/485 F, 260/485 H, 260/485 J, 260/488 CD, 260/500.5 H, 260/501.16, 260/515 A, 260/515 M, 260/516, 260/518 A, 260/519, 260/558 R, 260/558 S, 260/558 A, 260/559 R, 260/559 T, 260/559 A, 260/999

[51] **Int. Cl. C07c 63/54,** C07c 65/14, C07c 121/64

[58] **Field of Search**..... 260/515 A, 470, 471 R, 260/472, 465 D, 501.16, 448 R, 469

Primary Examiner—James A. Patten
Attorney, Agent, or Firm—Erich M. H. Radde

[57] **ABSTRACT**

Novel α-halo-p-cycloalkylphenylacetic acids and their derivatives have been prepared. Compounds of this invention possess useful anti-inflammatory, analgestic and antipyretic antipyretic properties.

42 Claims, No Drawings

PHENYLACETIC ACIDS

CROSS REFERENCES TO RELATED APPLICATIONS

This is a continuation-in-part application of Ser. No. 34,870 filed May 5, 1970.

SUMMARY OF THE INVENTION

This invention describes certain α-halo-p-cycloalkylphenylacetic acids and their derivatives and their use in therapeutic compositions. In addition, this invention relates to the preparation of these α-halo-p-cycloalkylphenylacetic acids. When the compounds of this invention are administered to mammals, they afford significant treatment of inflammation and associated pain and fever.

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

BACKGROUND OF THE INVENTION

There has been continued efforts in research to develop drugs which would significantly inhibit the development of inflammation and relieve the pain and fever associated with it. Much of these efforts have been carried on in the field of steroids. While many of these compounds have been effective, they have had the drawback of causing many side effects.

We have unexpectedly found that α-halo-p-cycloalkylphenylacetic acid compounds and their derivatives have valuable pharmacologic properties.

We have found that α-halo-p-cycloalkylphenylacetic acid compounds and their derivatives possess useful anti-inflammatory, analgesic and antipyretic properties.

We have also found a series of anti-inflammatory compounds which are non-steroidal.

We have further found that these α-halo-p-cycloalkylphenylacetic acid compounds and their derivatives are novel.

We have also found that the compounds of this invention are useful in effectively providing a method for the inhibition of inflammation and the treatment of associated pain and fever.

We have still further found an entirely new class of antiinflammatory, analgesic and antipyretic pharmaceutical compositions containing the α-halo-p-cycloalkylphenylacetic acids and derivatives of this invention as active ingredient.

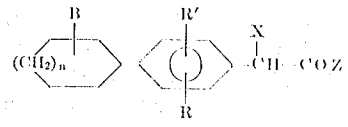
We have again found a convenient method for synthesizing these compounds.

DESCRIPTION AND PREFERRED EMBODIMENT

This invention comprises a class of novel chemical compounds which contain a cycloalkyl radical which is attached to a substituted phenyl-α-haloacetic acid in the para-position. This invention further comprises derivatives of said acids and the method of preparing the same.

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

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



I

where:

n is 0–2;

B is hydrogen or, loweralkyl;

R is halo, nitro, amino, acylamino, mono- and diloweralkylamino, mercapto, acylthio, loweralkylthio, loweralkylsulfinyl, loweralkylsulfonyl, hydroxy, loweralkoxy, acyloxy, haloloweralkyl, cyano, acetyl or loweralkyl;

R′ is hydrogen, fluoro, chloro, bromo, trifluoromethyl, cyano, nitro or loweralkylsulfonyl;

X is halo;

Z is —OH, loweralkoxy, arloweralkoxy, $—NH_2$, loweralkylamino, diloweralkylamino, cycloloweralkylamino,



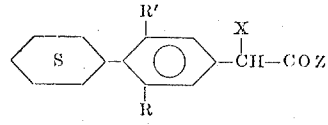
(where A is loweralkylidenyl or heteroloweralkylidenyl), —NHOH, $—NHNH_2$ or —OM (where M is an alkali, alkaline earth or aluminum metal or an ammonium salt).

The compounds of this invention contain an asymmetric carbon atom in the alpha-position of the acetic 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.

When B is loweralkyl, two racemic mixtures may exist in the case of 2′- or 3′-loweralkylcyclohexylphenyl-α-haloacetate, 2′- or 3′-loweralkylcyclopentylphenyl-α-haloacetate, 2′- or 3′- or 4′-loweralkylcycloheptylphenyl-α-haloacetate or their derivatives. It is understood that both racemic mixtures are embraced within the scope of this invention.

The preferred R and R′ substituents are in the 3 and 5 positions.

The preferred compounds of this embodiment describe the cyclohexyl class of chemical compounds which have particular usefulness as antiinflammatory, analgesic and antipyretic agents. These compounds are described in formula II



II

where:

R, R′, X and Z are as described above.

Those compounds whose properties are even more preferred are also described by formula II

where:

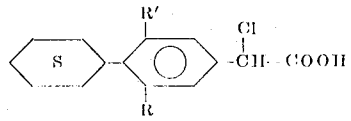
R is halo, nitro, loweralkylsulfonyl, haloloweralkyl or cyano;

R′ is hydrogen, chloro, bromo or nitro;

X is fluoro, chloro or bromo;

Z is —OH, loweralkoxy, arloweralkoxy, $—NH_2$, loweralkylamino or —OM.

The most preferred compounds of this invention describe a class of chemical compounds which have particular usefulness as anti-inflammatory, analgesic and antipyretic agents. These compounds are described in formula III



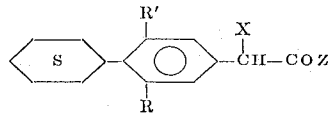
III

where:

R is halo, nitro, loweralkylsulfonyl, haloloweralkyl or cyano; and

R′ is hydrogen, chloro, bromo or nitro.

A special embodiment of this invention which describes novel compounds that are effective in 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 are described by formula IV



IV

where:

R is chloro, bromo, nitro, methylsulfonyl, triflormethyl or cyano;

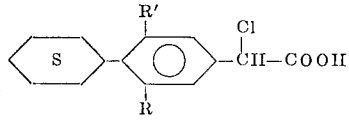
R′ is chloro, bromo or nitro;

X is fluoro, chloro or bromo; and

Z is —OH, loweralkoxy, arloweralkoxy, $—NH_2$, loweralkylamino or —OM.

Included within the scope of this further special embodiment are the racemic mixtures as well as the dextro and levorotatory isomers thereof.

The more preferred compounds of this special embodiment are those novel compounds which are effective in 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 or symptomatically related to an inflammation indication are described by formula V



V

where:

R is chloro, bromo, nitro, methylsulfonyl, trifluoromethyl or cyano;

R′ is chloro, bromo or nitro.

Included within the scope of this further special embodiment are the racemic mixtures as well as the dextro and levorotatory isomers thereof.

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

The term "loweralkyl" refers to a loweralkyl hydrocarbon group containing from 1 to about 6 carbon atoms which may be straight chained or branched.

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

Loweralkoxy signifies an alkoxy group containing from 1 to about 6 carbon atoms which may be straight chained or branched.

The term "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 salts 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-3-fluoro-4-cyclohexylphenylacetic acid

α,3-dichloro-4-cyclohexylphenylacetic acid

α-chloro-3-bromo-4-cyclohexylphenylacetic acid

α-chloro-3-iodo-4-cyclohexylphenylacetic acid

α-chloro-3-nitro-4-cyclohexylphenylacetic acid

α-chloro-3-trifluoromethyl-4-cyclohexylphenylacetic acid

α-chloro-3-mercapto-4-cyclohexylphenylacetic acid

α-chloro-3-acetylthio-4-cyclohexylphenylacetic acid

α-chloro-3-methylmercapto-4-cyclohexylphenylacetic acid

α-chloro-3-methylsulfinyl-4-cyclohexylphenylacetic acid

α-chloro-3-methylsulfonyl-4-cyclohexylphenylacetic acid

α-chloro-3-cyano-4-cyclohexylphenylacetic acid

α-chloro-3-carboxy-4-cyclohexylphenylacetic acid

α-chloro-3-carbethoxy-4-cyclohexylphenylacetic acid

α-chloro-3-amino-4-cyclohexylphenylacetic acid

α-chloro-3-acetylamino-4-cyclohexylphenylacetic acid

α-chloro-3-methylamino-4-cyclohexylphenylacetic acid

α-chloro-3-dimethylamino-4-cyclohexylphenylacetic acid

α-chloro-3-hydroxy-4-cyclohexylphenylacetic acid

α-chloro-3-acetyloxy-4-cyclohexylphenylacetic acid

α-chloro-3-methoxy-4-cyclohexylphenylacetic acid
α-chloro-3-acetoxy-4-cyclohexylphenylacetic acid
α-chloro-3-methyl-4-cyclohexylphenylacetic acid
α,3-dichloro-5-fluoro-4-cyclohexylphenylacetic acid
α,3,5-trichloro-4-cyclohexylphenylacetic acid
α,3-dichloro-5-bromo-4-cyclohexylphenylacetic acid
α,3-dichloro-5-nitro-4-cyclohexylphenylacetic acid
α,3-dichloro-5-trifluoromethyl-4-cyclohexylphenylacetic acid
α,3-dichloro-5-cyano-4-cyclohexylphenylacetic acid
α,3-dichloro-5-methylsulfonyl-4-cyclohexylphenylacetic acid
α-chloro-3-bromo-5-fluoro-4-cyclohexylphenylacetic acid
α-chloro-3,5-dibromo-4-cyclohexylphenylacetic acid
α-chloro-3-bromo-5-nitro-4-cyclohexylphenylacetic acid
α-chloro-3-bromo-5-trifluoromethyl-4-cyclohexylphenylacetic acid
α-chloro-3-bromo-5-cyano-4-cyclohexylphenylacetic acid
α-chloro-3-bromo-5-methylsulfonyl-4-cyclohexylphenylacetic acid
α-chloro-3-nitro-5-fluoro-4-cyclohexylphenylacetic acid
α-chloro-3,5-dinitro-4-cyclohexylphenylacetic acid
α-chloro-3-nitro-5-trifluoromethyl-4-cyclohexylphenylacetic acid
α-chloro-3-nitro-5cyano-4-cyclohexylphenylacetic acid
α-chloro-3-nitro-5-methylsulfonyl-4-cyclohexylphenylacetic acid
α-chloro-3-trifluoromethyl-5-fluoro-4-cyclohexylphenylacetic acid
α-chloro-3,5-ditrifluoromethyl-4-cyclohexylphenylacetic acid
α-chloro-3trifluoromethyl-5-cyano-4-cyclohexylphenylacetic acid
α-chloro-3-trifluoromethyl-5-methylsulfonyl-4-cyclohexylphenylacetic acid
α-bromo-3-fluoro-4-cyclohexylphenylacetic acid
α-bromo-3-chloro-4-cyclohexylphenylacetic acid
α,3-dibromo-4-cyclohexylphenylacetic acid
α-bromo-3-nitro-4-cyclohexylphenylacetic acid
α-bromo-3-trifluoromethyl-4-cyclohexylphenylacetic acid
α-bromo-3-cyano-4-cyclohexylphenylacetic acid
α-bromo-3-methylsulfonyl-4-cyclohexylphenylacetic acid
α-bromo-3-chloro-5-fluoro-4-cyclohexylphenylacetic acid
α-bromo-3,5-dichloro-4-cyclohexylphenylacetic acid
α-bromo-3-chloro-5-bromo-4-cyclohexylphenylacetic acid
α-bromo-3-chloro-5-nitro-4-cyclohexylphenylacetic acid
α-bromo-3-chloro-5-trifluoromethyl-4-cyclohexylphenylacetic acid
α-bromo-3-chloro-5-cyano-4-cyclohexylphenylacetic acid
α-bromo-3-chloro-5-methylsulfonyl-4-cyclohexylphenylacetic acid

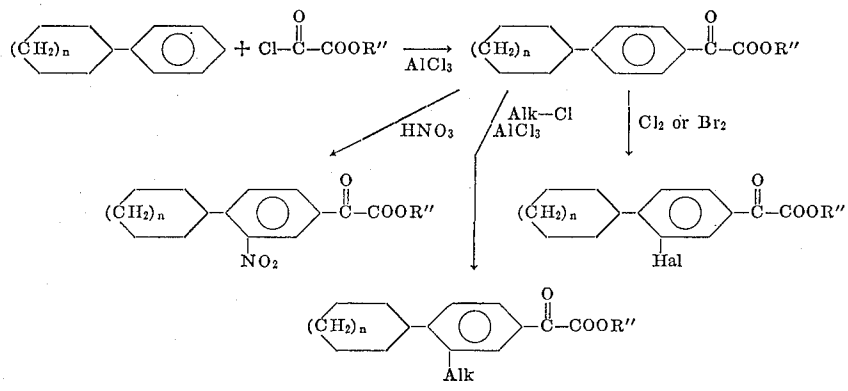
α,3-difluoro-4-cyclohexylphenylacetic acid
α-fluoro-3-chloro-4-cyclohexylphenylacetic acid
α-fluoro-3-bromo-4-cyclohexylphenylacetic acid
α-fluoro-3-nitro-4-cyclohexylphenylacetic acid
α-fluoro-3-trifluoromethyl-4-cyclohexylphenylacetic acid
α-fluoro-3-cyano-4-cyclohexylphenylacetic acid
α-fluoro-3-methylsulfonyl-4-cyclohexylphenylacetic acid
α-fluoro-3-chloro-5-fluoro-4-cyclohexylphenylacetic acid
α-fluoro-3,5-dichloro-4-cyclohexylphenylacetic acid
α-fluoro-3-chloro-5-bromo-4-cyclohexylphenylacetic acid
α-fluoro-3-chloro-5-nitro-4-cyclohexylphenylacetic acid
α-fluoro-3-chloro-5-trifluoromethyl-4-cyclohexylphenylacetic acid
α-fluoro-3-chloro-5-cyano-4-cyclohexylphenylacetic acid
α-fluoro-3-chloro-5-methylsulfonyl-4-cyclohexylphenylacetic acid
methyl α,3,5-trichloro-4-cyclohexylphenylacetate
ethyl α,3,5-trichloro-4-cyclohexylphenylacetate
benzyl α,3,5-trichloro-4-cyclohexylphenylacetate
N-methyl α,3,5-trichloro-4-cyclohexylphenylacetamide
N,N-dimethyl α,3,5-trichloro-4-cyclohexylphenylacetamide
N,N-diethyl α,3,5-trichloro-4-cyclohexylphenylacetamide
N,N-ethylmethyl α,3,5-trichloro-4-cyclohexylphenylacetamide
N-isopropyl α,3,5-trichloro-4-cyclohexylphenylacetamide
N-cyclopropyl α,3,5-trichloro-4-cyclohexylphenylacetamide
N,N-pentamethylene α,3,5-trichloro-4-cyclohexlphenylacetamide
N,N-oxydiethylene α,3,5-trichloro-4-cyclohexylphenylacetamide
N,N-methlaminoethylenetrimethylene α,3,5-trichloro-4-cyclohexylphenylacetamide
N,N-thiotrimethylene α,3,5-trichloro-4-cyclohexylphenylacetamide
α,3,5-trichloro-4-cyclohexylphenylacetic acid, sodium salt
α,3,5-trichloro-4-cyclohexylphenylacetic acid, potassium salt
α,3,5-trichloro-4-cyclohexylphenylacetic acid, calcium salt
α,3,5-trichloro-4-cyclohexylphenylacetic acid, aluminum salt
α,3,5-trichloro-4-cyclohexylphenylacetic acid, dimethylammonium salt
α,3,5-trichloro-4-cyclohexylphenylacetic acid, diethylammonium salt
α,3,5-trichloro-4-cyclohexylphenylacetic acid, β-hydroxyethylammonium salt
α,3,5-trichloro-4-cyclohexylphenylacetic acid, piperazinium salt
α,3,5-trichloro-4-cyclohexylphenylacetic acid, piperidinium salt
α,3,5-trichloro-4-cyclohexylphenylacetic acid, α-methylbenzylammonium salt
α-chloro-3-fluoro-4-cyclopentylphenylacetic acid

α,3-dichloro-4-cyclopentylphenylacetic acid
α-chloro-3-bromo-4-cyclopentylphenylacetic acid
α-chloro-3-nitro-4-cyclopentylphenylacetic acid
α-chloro-3-trifluoromethyl-4-cyclopentylphenylacetic acid
α-chloro-3-cyano-4-cyclopentylphenylacetic acid
α-chloro-3-methylsulfonyl-4-cyclopentylphenylacetic acid
α,3-dichloro-5-fluoro-4-cyclopentylphenylacetic acid
α,3,5-trichloro-5-fluoro-4-cyclopentylphenylacetic acid
α,3-dichloro-5-bromo-4-cyclopentylphenylacetic acid
α,3-dichloro-5-nitro-4-cyclopentylphenylacetic acid
α,3-dichloro-5-trifluoromethyl-4-cyclopentylphenylacetic acid
α,3-dichloro-5-cyano-4-cyclopentylphenylacetic acid
α,3-dichloro-5-methylsulfonyl-4-cyclopentylphenylacetic acid
α-bromo-3-chloro-4-cyclopentylphenylacetic acid
α-bromo-3-nitro-4-cyclopentylphenylacetic acid
α-bromo-3,5-dichloro-4-cyclopentylphenylacetic acid
α-bromo-3-chloro-5-nitro-4-cyclopentylphenylacetic acid
α-fluoro-3-chloro-4-cyclopentylphenylacetic acid
α-fluoro-3-nitro-4-cyclopentylphenylacetic acid
α-fluoro-3,5-dichloro-4-cyclopentylphenylacetic acid
α-fluoro-3-chloro-5-nitro-4-cyclopentylphenylacetic acid
methyl α,3,5-trichloro-4-cyclopentylphenylacetate
benzyl α,3,5-trichloro-4-cyclopentylphenylacetate
N-methyl α,3,5-trichloro-4-cyclopentylphenylacetamide
N,N-diethyl α,3,5-trichloro-4-cyclopentylphenylacetamide
N,N-pentamethylene α,3,5-trichloro-4-cyclopentylphenylacetamide
N,N-oxydiethylene α,3,5-trichloro-4-cyclopentylphenylacetamide
α,3,5-trichloro-4-cyclopentylphenylacetic acid, sodium salt
α,3,5-trichloro-4-cyclopentylphenylacetic acid, diethylammonium salt
α,3,5-trichloro-4-cyclopentylphenylacetic acid, piperazinium salt
α,3,5-trichloro-4-cycloheptylphenylacetic acid
α,3-dichloro-4-cycloheptylphenylacetic acid
α-chloro-3-bromo-4-cycloheptylphenylacetic acid
α-chloro-3-nitro-4-cycloheptylphenylacetic acid
α-chloro-3-trifluoromethyl-4-cycloheptylphenylacetic acid
α-chloro-3-cyano-4-cycloheptylphenylacetic acid
α-chloro-3-methylsulfonyl-4-cycloheptylphenylacetic acid
α,3-dichloro-5-fluoro-4-cycloheptylphenylacetic acid
α,3,5-trichloro-5-fluoro-4-cycloheptylphenylacetic acid
α,3-dichloro-5-bromo-4-cycloheptylphenylacetic acid
α,3-dichloro-5-nitro-4-cycloheptylphenylacetic acid
α,3-dichloro-5-trifluoromethyl-4-cycloheptylphenylacetic acid
α,3-dichloro-5-cyano-4-cycloheptylphenylacetic acid
α,3-dichloro-5-methylsulfonyl-4-cycloheptylphenylacetic acid
α-bromo-3-chloro-4-cycloheptylphenylacetic acid
α-bromo-3-nitro-4-cycloheptylphenylacetic acid
α-bromo-3,5-dichloro-4-cycloheptylphenylacetic acid
α-bromo-3-chloro-5-nitro-4-cycloheptylphenylacetic acid
α-fluoro-3-chloro-4-cycloheptylphenylacetic acid
α-fluoro-3-nitro-4-cycloheptylphenylacetic acid
α-fluoro-3,5-dichloro-4-cycloheptylphenylacetic acid
α-fluoro-3-chloro-5-nitro-4-cycloheptylphenylacetic acid
methyl α,3,5-trichloro-4-cycloheptylphenylacetate
benzyl α,3,5-trichloro-4-cycloheptylphenylacetate
N-methyl α,3,5-trichloro-4-cycloheptylphenylacetamide
N,N-diethyl α,3,5-trichloro-4-cycloheptylphenylacetamide
N,N-pentamethylene α,3,5-trichloro-4-cycloheptylphenylacetamide
N,N-oxydiethylene α,3,5-trichloro-4-cycloheptylphenylacetamide
α,3,5-trichloro-4-cycloheptylphenylacetic acid, sodium salt
α,3,5-trichloro-4-cycloheptylphenylacetic acid, diethylammonium salt
α,3,5-trichloro-4-cycloheptylphenylacetic acid, piperazinium salt
d α-chloro-3-fluoro-4-cyclohexylphenylacetic acid
l α-chloro-3-fluoro-4-cyclohexylphenylacetic acid
d α,3-dichloro-4-cyclohexylphenylacetic acid
l α,3-dichloro-4-cyclohexylphenylocetic acid
d α-chloro-3-bromo-4-cyclohexylphenylacetic acid
l α-chloro-3-bromo-4-cyclohexylphenylacetic acid
d α-chloro-3-nitro-4-cyclohexylphenylacetic acid
l α-chloro-3-nitro-4-cyclohexylphenylacetic acid
d α-chloro-3-trifluoromethyl-4-cyclohexylphenylacetic acid
l α-chloro-3-trifluoromethyl-4-cyclohexylphenylacetic acid
d α-chloro-3-cyano-4-cyclohexylphenylacetic acid
l α-chloro-3-cyano-4-cyclohexylphenylacetic acid
d α-chloro-3-methylsulfonyl-4-cyclohexylphenylacetic acid
l α-chloro-3-methylsulfonyl-4-cyclohexylphenylacetic acid
d α,3-dichloro-5-fluoro-4-cyclohexylphenylacetic acid
l α,3-dichloro-5-fluoro-4-cyclohexylphenylacetic acid
d α,3,5-trichloro-4-cyclohexylphenylacetic acid
l α,3,5-trichloro-4-cyclohexylphenylacetic acid
d α,3-dichloro-5-bromo-4-cyclohexylphenylacetic acid
l α,3-dichloro-5-bromo-4-cyclohexylphenylacetic acid
d α,3-dichloro-5-nitro-4-cyclohexylphenylacetic acid
l α,3-dichloro-5-nitro-4-cyclohexylphenylacetic acid

d α,3-dichloro-5-trifluoromethyl-4-cyclohexylphenylacetic acid
l α,3-dichloro-5-trifluoromethyl-4-cyclohexylphenylacetic acid
d α,3-dichloro-5-cyano-4-cyclohexylphenylacetic acid
l α,3-dichloro-5-cyano-4-cyclohexylphenylacetic acid
d α,3-dichloro-5-methylsulfonyl-4-cyclohexylphenylacetic acid
l α,3-dichloro-5-methylsulfonyl-4-cyclohexylphenylacetic acid
d α-bromo-3-chloro-4-cyclohexylphenylacetic acid
l α-bromo-3-chloro-4-cyclohexylphenylacetic acid
d α-bromo-3-nitro-4-cyclohexylphenylacetic acid
l α-bromo-3-nitro-4-cyclohexylphenylacetic acid
d α-bromo-3,5-dichloro-4-cyclohexylphenylacetic acid
l α-bromo-3,5-dich-oro-4-cyclohexylphenylacetic acid
d α-bromo-3-chloro-5-nitro-4-cyclohexylphenylacetic acid
l α-bromo-3-chloro-5-nitro-4-cyclohexylphenylacetic acid
d α-fluoro-3-chloro-4-cyclohexylphenylacetic acid
l α-fluoro-3-chloro-4-cyclohexylphenylacetic acid
d α-fluoro-3-nitro-4-cyclohexylphenylacetic acid
l α-fluoro-3-nitro-4-cyclohexylphenylacetic acid
d α-fluoro-3,5-dichloro-4-cyclohexylphenylacetic acid
l α-fluoro-3,5-dichloro-4-cyclohexylphenylacetic acid
d α-fluoro-3-chloro-5-nitro-4-cyclohexylphenylacetic acid
l α-fluoro-3-chloro-5-nitro-4-cyclohexylphenylacetic acid
d methyl α,3,5-trichloro-4-cyclohexylphenylacetic acid
l methyl α,3,5-trichloro-4-cyclohexylphenylacetic acid
d benzyl α,3,5-trichloro-4-cyclohexylphenylacetic acid
l benzyl α,3,5-trichloro-4-cyclohexylphenylacetic acid
d N-methyl α,3,5-trichloro-4-cyclohexylphenylacetic acid
l N-methyl α,3,5-trichloro-4-cyclohexylphenylacetic acid
d N,N-diethyl α,3,5-trichloro-4-cyclohexylphenylacetic acid
l N,N diethyl α,3,5-trichloro-4-cyclohexylphenylacetic acid
d N,N-pentamethylene α,3,5-trichloro-4-cyclohexylphenylacetic acid
l N,N-pentamethylene α,3,5trichloro-4-cyclohexylphenylacetic acid
d N,N-oxydiethylene α,3,5-trichloro-4-cyclohexylphenylacetic acid
l N,N-oxydiethylene α,3,5-trichloro-4-cyclohexylphenylacetic acid
d α,3,5-trichloro-4-cyclohexylphenylacetic acid, sodium salt
l α,3,5-trichloro-4-cyclohexylphenylacetic acid, sodium salt
d α,3,5-trichloro-4-cyclohexylphenylacetic acid, diethylammonium salt
l α,3,5-trichloro-4-cyclohexylphenylacetic acid, diethylammonium salt
d α,3,5-trichloro-4-cyclohexylphenylacetic acid, piperazinium salt
l α,3,5-trichloro-4-cyclohexylphenylacetic acid, piperazinium salt
d α,3-dichloro-4-cyclopentylphenylacetic acid
l α,3-dichloro-4-cyclopentylphenylacetic acid
d α,3,5-trichloro-4-cyclopentylphenylacetic acid
l α,3,5-trichloro-4-cyclopentylphenylacetic acid
d α-bromo-3-chloro-4-cyclopentylphenylacetic acid
l α-bromo-3-chloro-4-cyclopentylphenylacetic acid
d α-bromo-3,5-dichloro-4-cyclopentylphenylacetic acid
l α-bromo-3,5-dichloro-4-cyclopentylphenylacetic acid
d α-fluoro-3-chloro-4-cyclopentylphenylacetic acid
l α-fluoro-3-chloro-4-cyclopentylphenylacetic acid
d α-fluoro-3,5-dichloro-4-cyclopentylphenylacetic acid
l α-fluoro-3,5-dichloro-4-cyclopentylphenylacetic acid
d α,3,5-trichloro-4-cyclopentylphenylacetic acid, sodium salt
l α,3,5-trichloro-4-cyclopentylphenylacetic acid, sodium salt
d α,3-dichloro-4-cycloheptylphenylacetic acid
l α,3-dichloro-4-cycloheptylphenylacetic acid
d α,3,5-trichloro-4-cycloheptylphenylacetic acid
l α,3,5-trichloro-4-cycloheptylphenylacetic acid
d α-bromo-3-chloro-4-cycloheptylphenylacetic acid
l α-bromo-3-chloro-4-cycloheptylphenylacetic acid
d α-bromo-3,5-dichloro-4-cycloheptylphenylacetic acid
l α-bromo-3,5-dichloro-4-cycloheptylphenylacetic acid
d α-fluoro-3-chloro-4-cycloheptylphenylacetic acid
l α-fluoro-3-chloro-4-cycloheptylphenylacetic acid
d α-fluoro-3,5-dichloro-4-cycloheptylphenylacetic acid
l α-fluoro-3,5-dichloro-4-cycloheptylphenylacetic acid
d α,3,5-trichloro-4-cycloheptylphenylacetic acid, sodium salt
l α,3,5-trichloro-4-cycloheptylphenylacetic acid, sodium salt

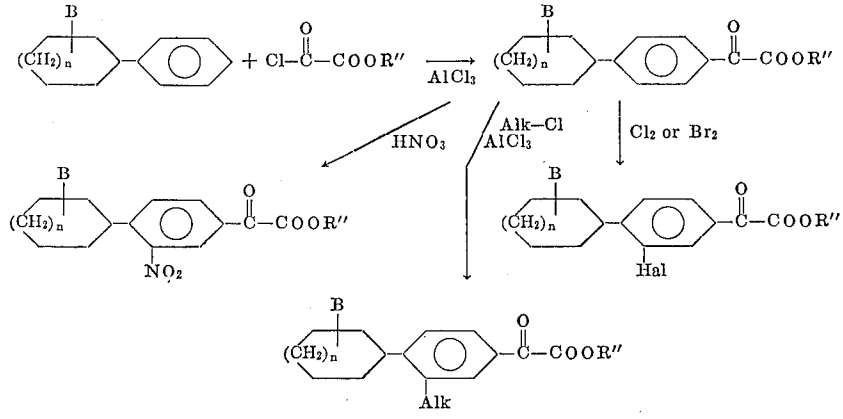
The compounds of this invention may be prepared by the following general procedures. Condensation of a cycloalkylbenzene with a loweralkyl or aralkyl oxalyl chloride in the presence of anhydrous aluminum chloride results in a p-cycloalkylphenylglyoxylate. The resulting loweralkyl or aralkyl esters of the p-cycloalkylphenylglyoxylic acid may then be a) halogenated, b) nitrated or c) alkylated to obtain the corresponding loweralkyl esters of a 3-halo-4-cycloalkylphenylglyoxylic acid, a 3-nitro-4-cycloalkylphenylglyoxylic acid or a 3-alkyl-4-cycloalkylphenyl-glyoxylic acid. Chlorination or bromination may be carried out in the presence of a small amount of iodine dissolved in an inert solvent such as carbon tetrachloride. A solution of chlorine or bromine is then added while the temperature is held near 0°C. Nitration is carried out with fuming nitric acid at about 0°C. Alkylation is carried out under Friedel Crafts conditions with an alkyl halide and alumi-

num chloride. The following reaction equations illustrate these methods.



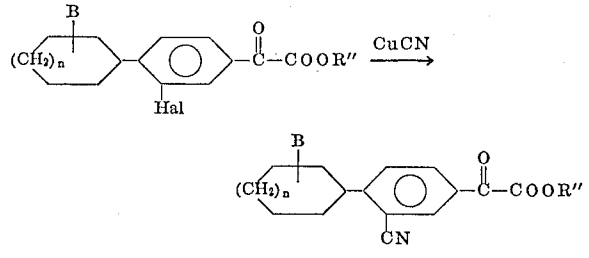
where R'' is loweralkyl or arloweralkyl and Hal is chloro or bromo.

When a loweralkyl group is desired in the cycloalkyl ring, then the condensation will take place with the appropriate loweralkyl benzene cycloalkyl followed by nitration, chlorination, bromination or alkylation as desired.

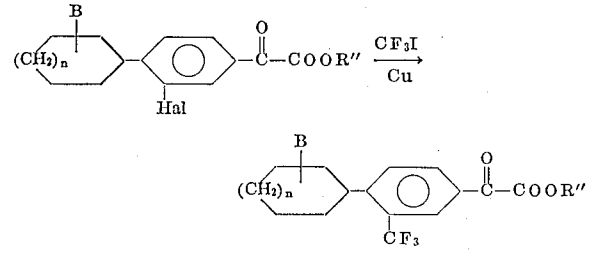


Appropriately desired end products having various R and R' substituents can be prepared by using suitable reactions in order to convert one group to another. Thus, for example, a 3-halo-4-cycloalkylphenylglyoxylate in which halo is chloro, bromo or iodo may be

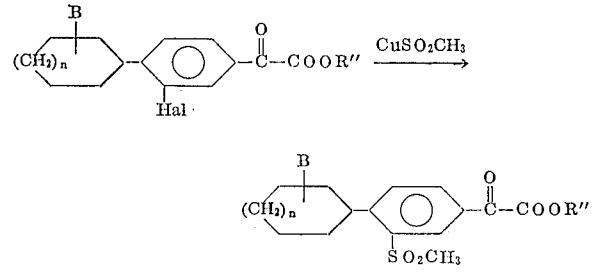
a. reacted with cuprous cyanide in quinoline at about 150°C to produce a 3-cyano-4-cycloalkylphenylglyoxylate:



b. reacted with trifluoromethyliodide and copper powder at about 150°C in dimethylformamide to obtain a 3-trifluoromethyl-4-cycloalkylphenylglyoxylate: [as described in Tetrahedron Letters: 47, 4095 (1959)]

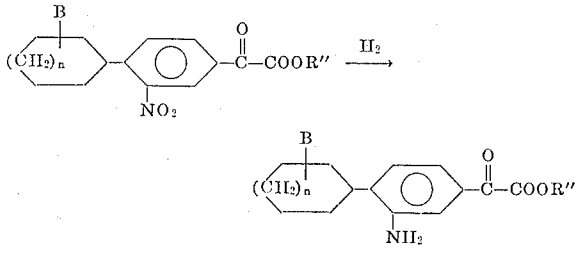


c. reacted with cuprous methanesulfinate in quinoline at about 150°C to obtain a 3-methylsulfonyl-4-cycloalkylphenylglyoxylate:

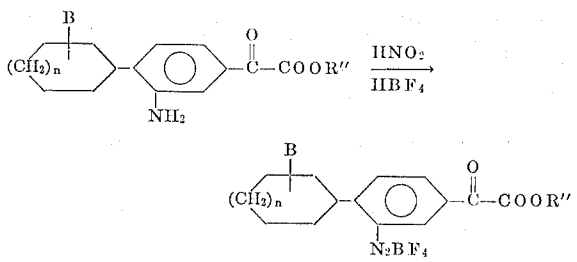


A 3-nitro-4-cycloalkylphenylglyoxylate may be selectively hydrogenated to the corresponding amine.

13

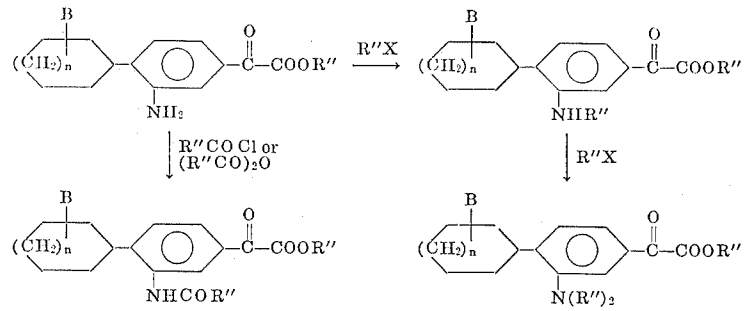


14



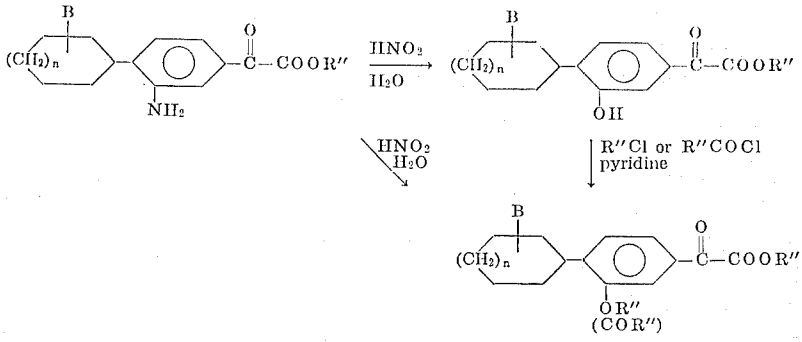
A 3-amino-4-cycloalkylphenylglyoxylate may then be

a. mono- or dialkylated with loweralkyl halides or sulfates or acylated with loweracyl chlorides or anhydrides,

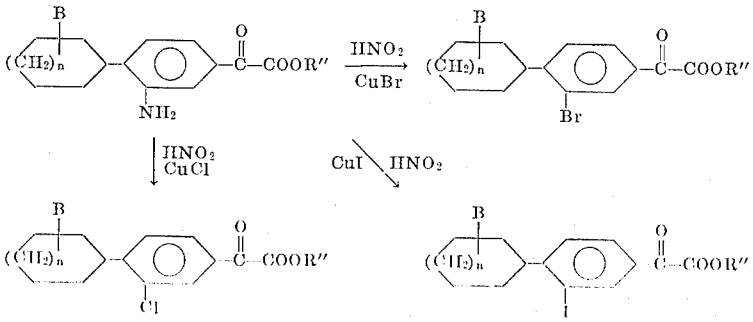


b. diazotized to the diazonium fluoroborate which is then thermally decomposed to the 3-fluoro-4-cycloalkylphenylglyoxylate,

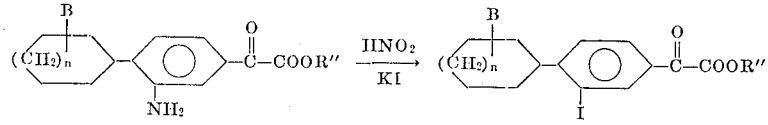
c. diazotized and heated in an aqueous medium to form the 3-hydroxy-4-cycloalkylphenylglyoxylate or heated in an alcohol to form the 3-alkoxy-4-cycloalkylphenylglyoxylate. The hydroxyl group may also be alkylated with loweralkyl halides or sulfates to the alkoxyl group or acylated with loweracyl chlorides or anhydrides to the acyloxy compound in the presence of a tertiary amine such as pyridine,



d. diazotized followed by a Sandmeyer type reaction to yield the halo group,

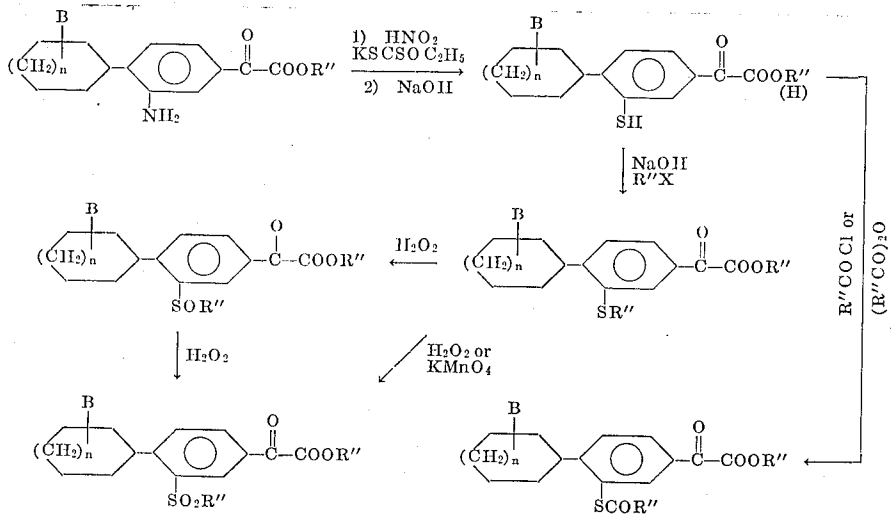


e. diazotized and heated with an aqueous solution of potassium iodide to prepare the 3-iodo-4-cycloalkylphenylglyoxylate,

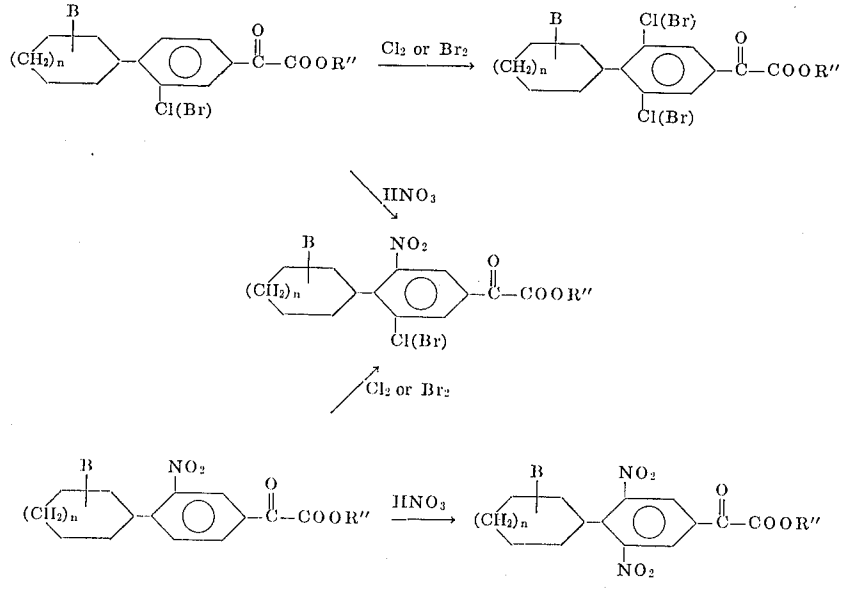


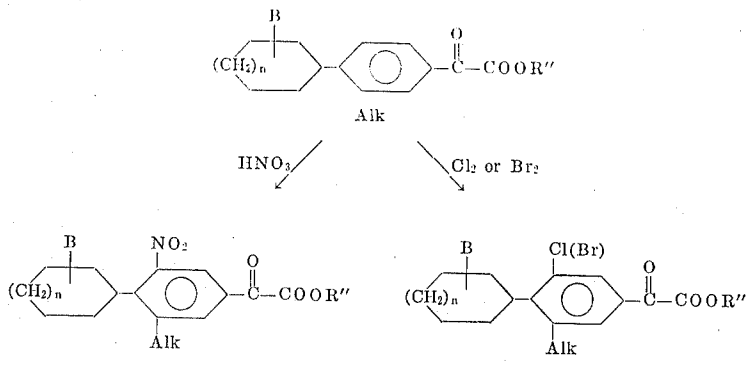
f. diazotized followed by reaction with potassium ethylxanthate followed by hydrolysis to obtain 3-mercapto-4-cycloalkylphenylglyoxylic acid which can be esterified to a 3-mercapto-4-cycloalkylphenylglyoxylate. This in turn can be lower alkylated to the lower alkylthio and oxidized to the loweralkylsulfinyl and loweralkylsulfonyl groups or acylated to the acylthio compounds.

cycloalkylphenylglyoxylate to obtain the corresponding 3,5-disubstituted-4-cycloalkylphenylglyoxylate. This may be carried out at any appropriate stage of the synthesis in order to obtain the desired substituents. Thus, for example, a 3-chloro-4-cycloalkylphenylglyoxylate may be nitrated as above to obtain a 3-chloro-5-nitro-4-cycloalkylphenylglyoxylate or chlorinated to obtain a 3,5-dichloro-4-cycloalkylphenylglyoxylate. A 3-nitro-4-cycloalkylphenylglyoxylate can be nitrated to give a 3,5-dinitro-4-cycloalkylphenylglyoxylate. A 3-alkyl compound may also be nitrated,



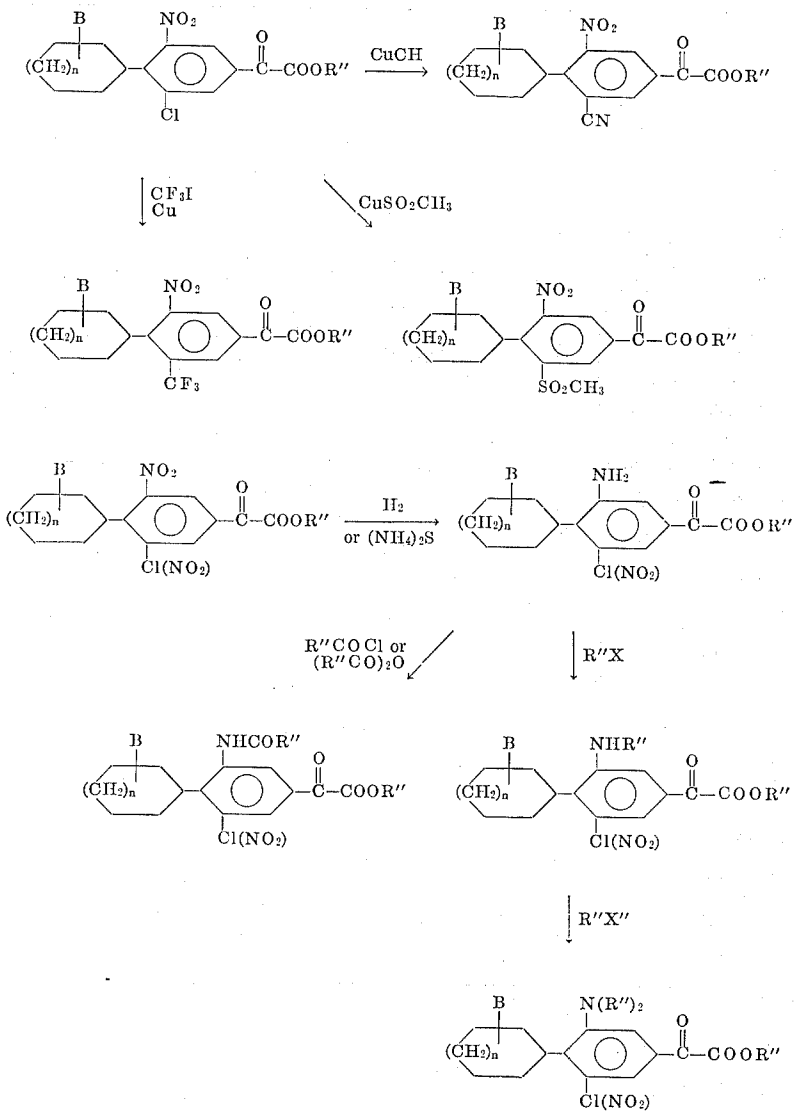
A second nitration or halogenation with chlorine or bromine may be carried out on the 3-substituted-4-chlorinated or brominated to the 3-chloro, 3-bromo or 3-nitro-5-alkyl compounds.

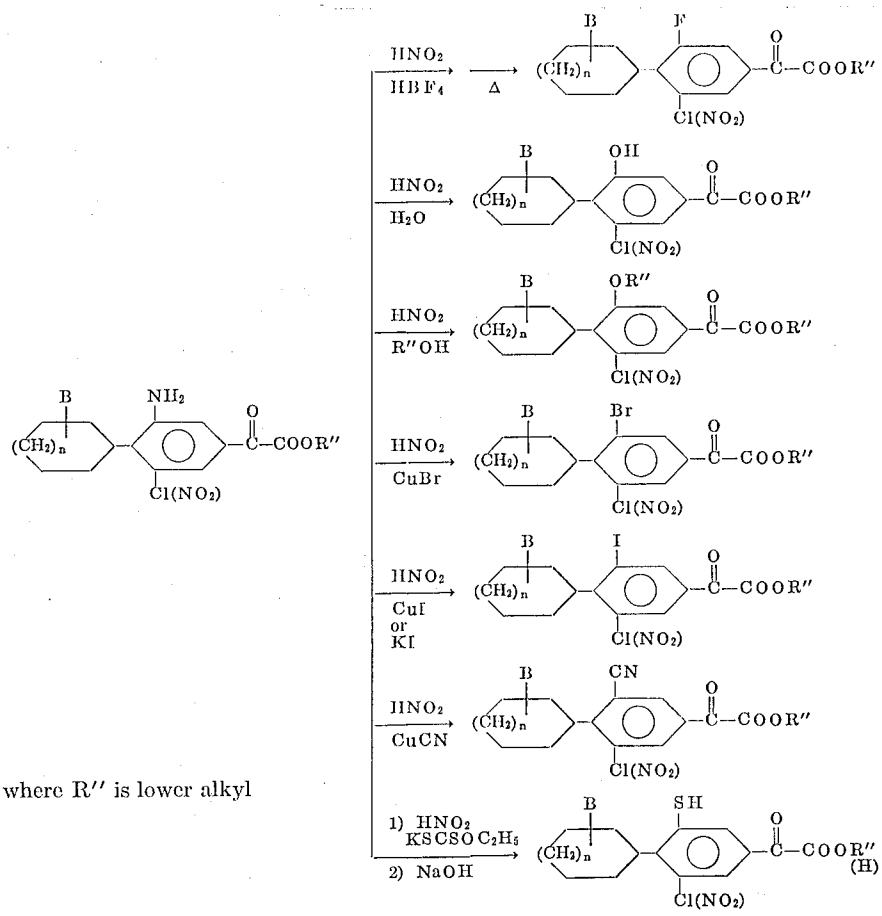




In turn, a 3-chloro-5-nitro-4-cycloalkylphenylglyoxylate can be reduced to a corresponding 3-chloro-5-amino-4-cycloalkylphenylglyoxylate. This may then be mono- or di-alkylated or acylated. The amine may also be converted via the diazonium salt to a variety of derivatives as described above.

As a further example of disubstitution, a 3-chloro-5-nitro-4-cycloalkylphenylglyoxylate can be reacted with cuprous cyanide in quinoline at 150°C to obtain a 3-cyano-5-nitro-4-cycloalkylphenylglyoxylate; or with trifluoromethyl iodide and copper powder in quinoline at 150°C to obtain a 3-trifluoromethyl-5-nitro-4-cycloalkylphenylglyoxylate; or with cuprous methanesulfinate in quinoline at 150°C to a 3-methylsulfonyl-5-nitro-4-cycloalkylphenylglyoxylate. Still another example of various disubstitution would be the selective reduction of a 3,5-dinitro-4-cycloalkylphenylglyoxylate with hydrogen or ammonium sulfide to obtain a 3-nitro-5-amino-4-cycloalkylphenylglyoxylate which in turn can be diazotized to the various derivatives.



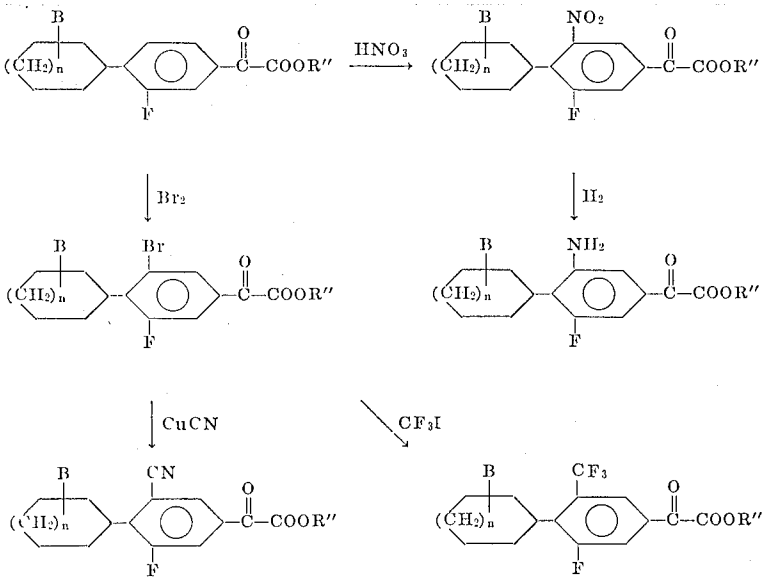


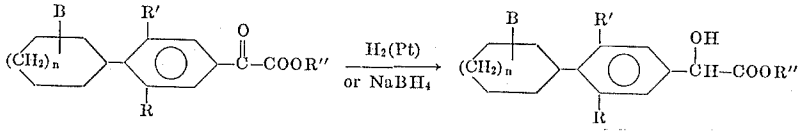
where R″ is lower alkyl

Of course, other reactions may be carried out on the above products by diazotization to obtain the desired substituents as previously described.

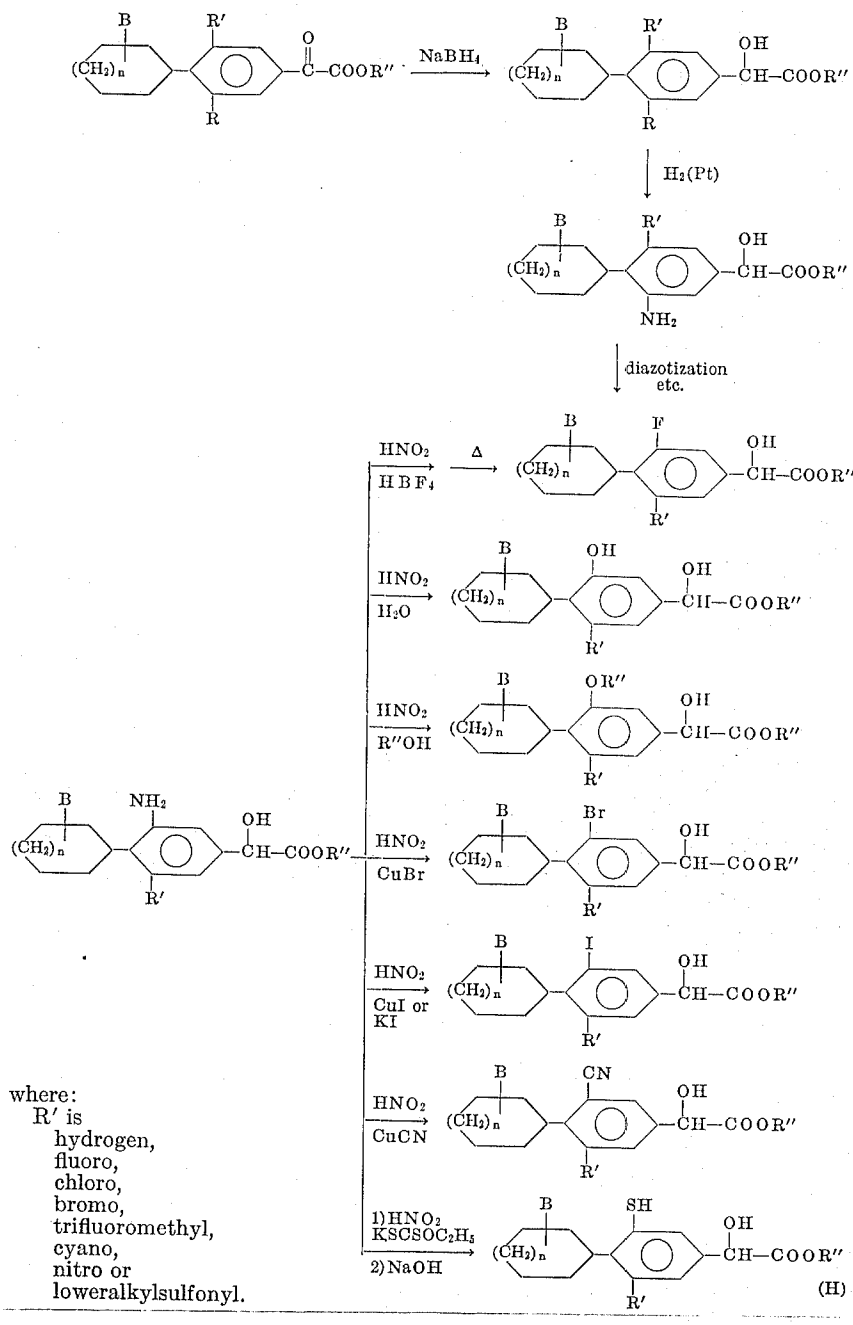
Various mono-substituted products may also be nitrated, chlorinated or brominated as above and again, in turn, converted to the various desired substituents. Thus, for example, a 3-fluoro-4-cycloalkylphenylglyoxylate may be nitrated or brominated and the nitro and bromo groups converted to various substituents.

The p-cycloalkylphenylglyoxylate ester is converted to the corresponding p-cycloalkylphenylglycolate ester by hydrogenation in the presence of platinum oxide. In the special case when R or R′ are substituents sensitive to catalytic hydrogenation, e.g., when R or R′ is NO_2, SH, SR, SOR, I, etc., a selective reduction of the keto function is effected with sodium borohydride to give the p-cycloalkylphenylglycolate ester.





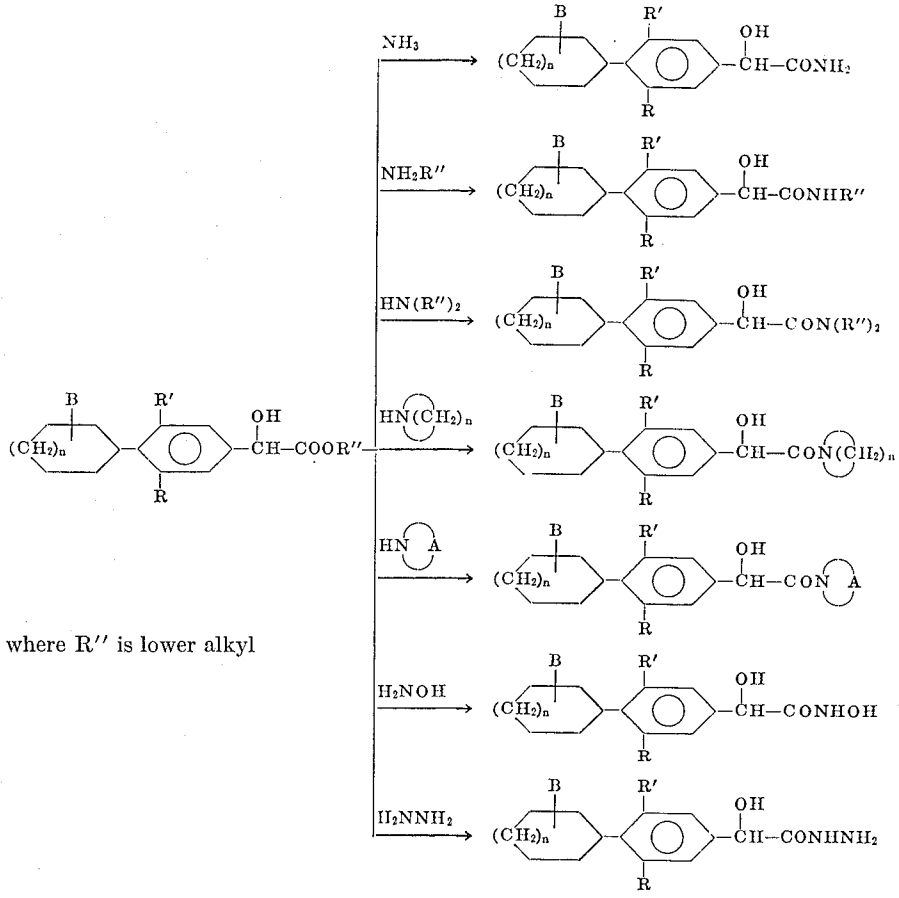
It is often more convenient to convert one substituent to another after the reduction of the glyoxylate to the glycolate. Thus, for example, a 3-nitro-4-cycloalkylphenylglyoxylate or a 3-chloro-5-nitro-4-cycloalkylphenyl-glyoxylate can be reduced under sodium borohydride conditions as above to the 3-nitro-4-cycloalkylphenylglycolate or 3-chloro-5-nitro-4-cycloalkylphenyl-glycolate. This in turn may then be catalytically reduced to the 3-amino-4-cycloalkylphenylglycolate or 3-chloro-5-amino-4-cycloalkylphenylglycolate. The amino group can then be diazotized as above to the desired substituents. This may be carried out on any of the nitro compounds as outlined. The diazotized products may then be hydrolyzed to the glycolic acid.



where:
R′ is
hydrogen,
fluoro,
chloro,
bromo,
trifluoromethyl,
cyano,
nitro or
loweralkylsulfonyl.

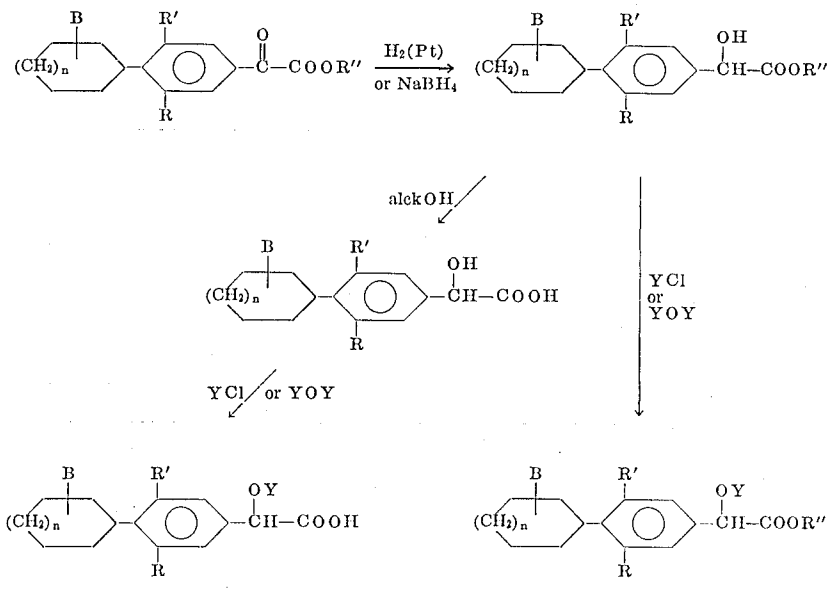
(H)

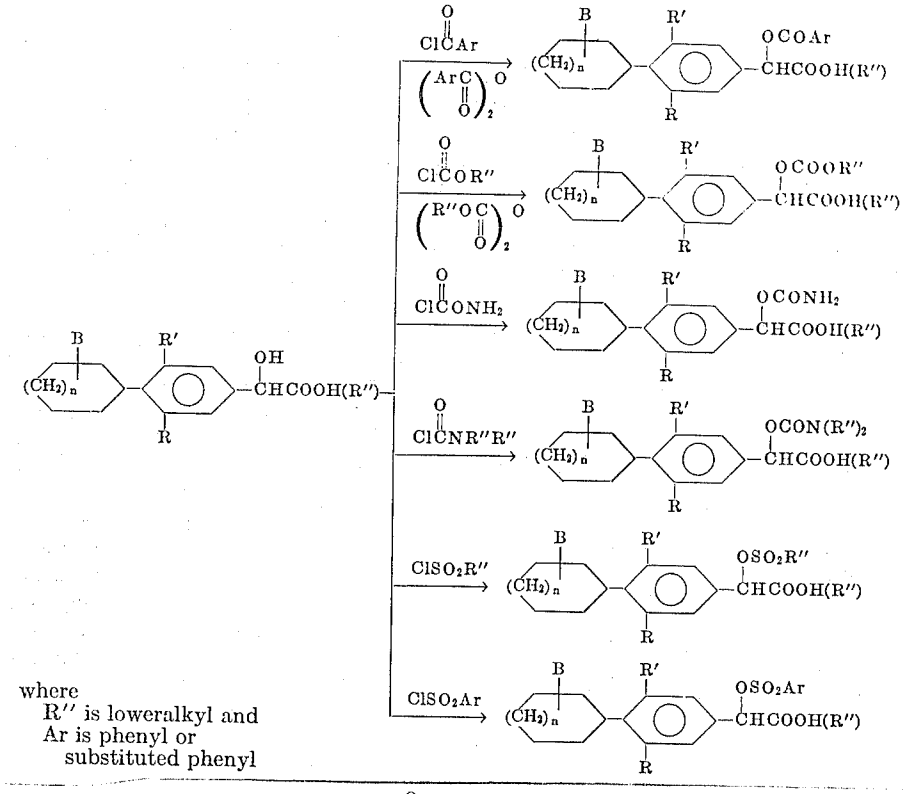
Reaction of a substituted p-cycloalkylphenylglycolate ester with a nitrogen base such as ammonia, loweralkylamine, diloweralkylamine, cycloloweralkylamine, a nitrogen containing hetero compound such as piperidine, morpholine, piperazine, hydroxylamine and hydrazine gives the corresponding amide, hydroxamic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



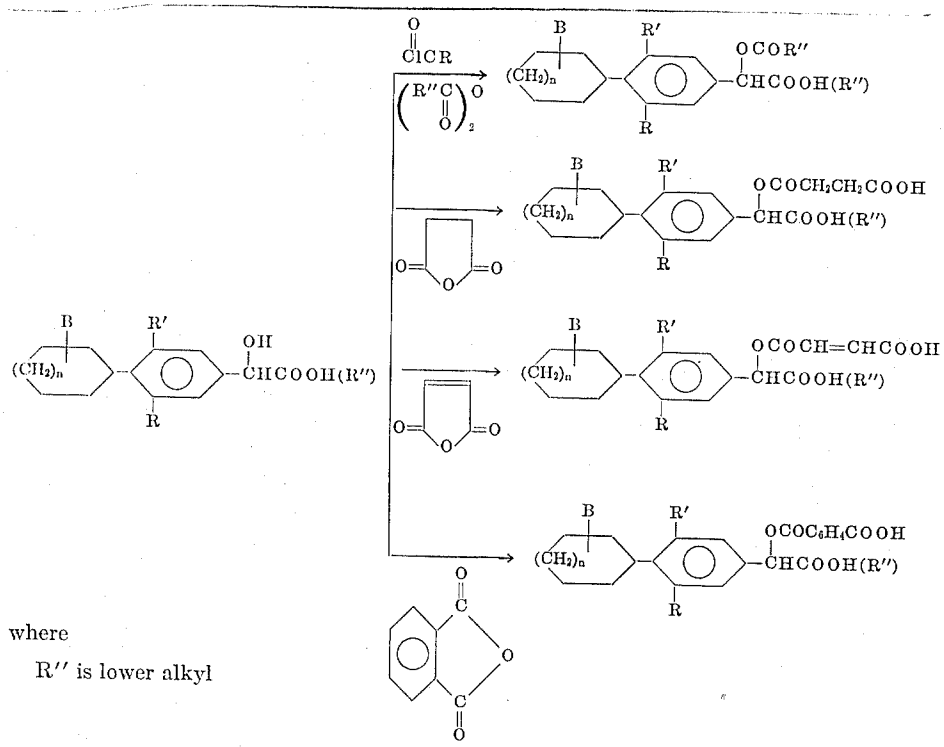
where R'' is lower alkyl

The glycolate esters may be hydrolyzed to the corresponding p-cycloalkylphenylglycolic acid. Reaction of the glycolate ester or glycolic acid with an acid chloride YCl or acid anhydride YOY in the presence of a tertiary amine such as pyridine, picoline, or quinoline results in the formation of an hydroxy derivative of the glycolate. Examples of YCl and YOY include acetyl chloride, acetic anhydride, propionyl chloride, butyryl chloride, succinic anhydride, maleic anhydride, phthalic anhydride, benzoyl chloride, benzoic anhydride, benzyl chlorocarbonate, ethyl chlorocarbonate, dimethylcarbamyl chloride, dibutylcarbamyl chloride, benzenesulfonyl chloride, methanesulfonyl chloride.



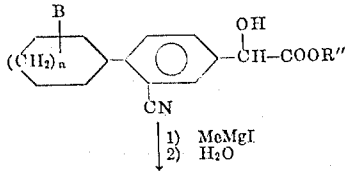


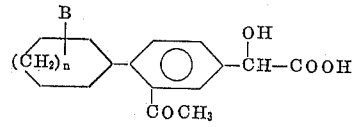
where
R'' is loweralkyl and
Ar is phenyl or
substituted phenyl



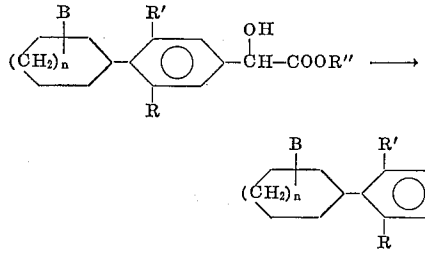
where
R'' is lower alkyl

The 3-cyanoglycolate may also be reacted with two equivalents of methylmagnesium iodide in tetrahydrofuran followed by hydrolysis to obtain the 3-acetylglycolic acid.



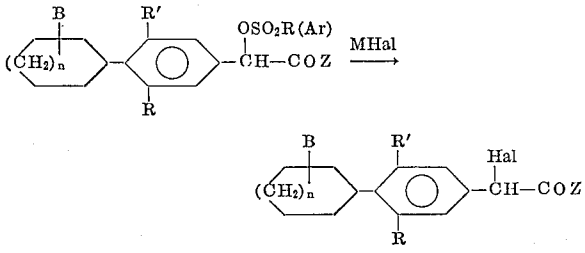


When a substituted 4-cycloalkylphenylglycolate is reacted with a phosphorus trihalide, phosphorus pentahalide, phosphorus oxyhalide, sulfurylhalide, thionyl halide, or sulfur halide the corresponding substituted α-halo-4-cycloalkylphenylacetate is prepared.



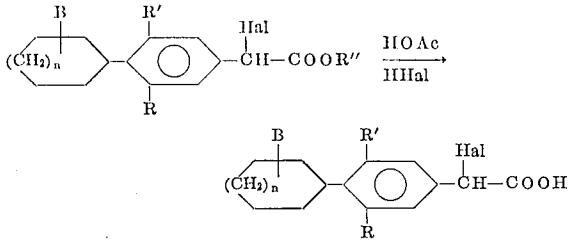
where R'' is lower alkyl;
where Hal is fluoro, chloro, bromo or iodo.

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



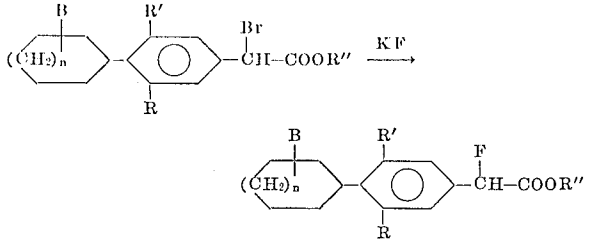
where Z is as described on page 4.

The corresponding α-haloacetic acid may be prepared by heating the ester with acetic acid containing the corresponding hydrogen halide.

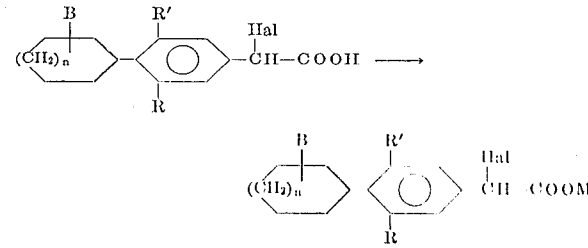


where R'' is lower alkyl.

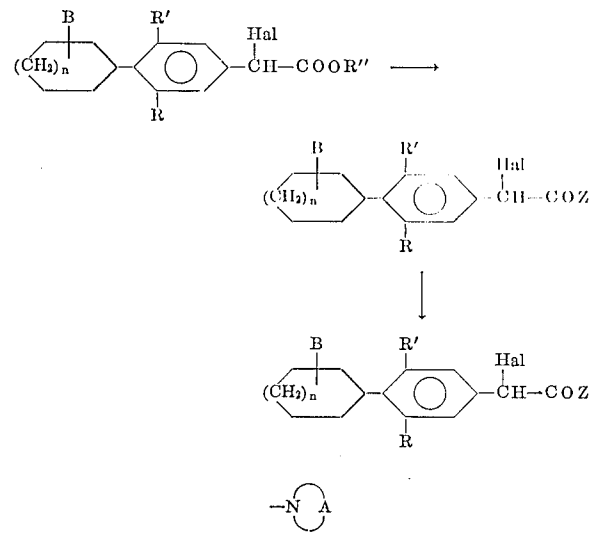
The substituted α-fluoro-4-cycloalkylphenylacetic acid derivatives may also be obtained from the corresponding α-iodo, α-bromo or α-chloro-4-cycloalkylphenylacetic acid derivatives by reaction with potassium fluoride at about 130°–200°C.

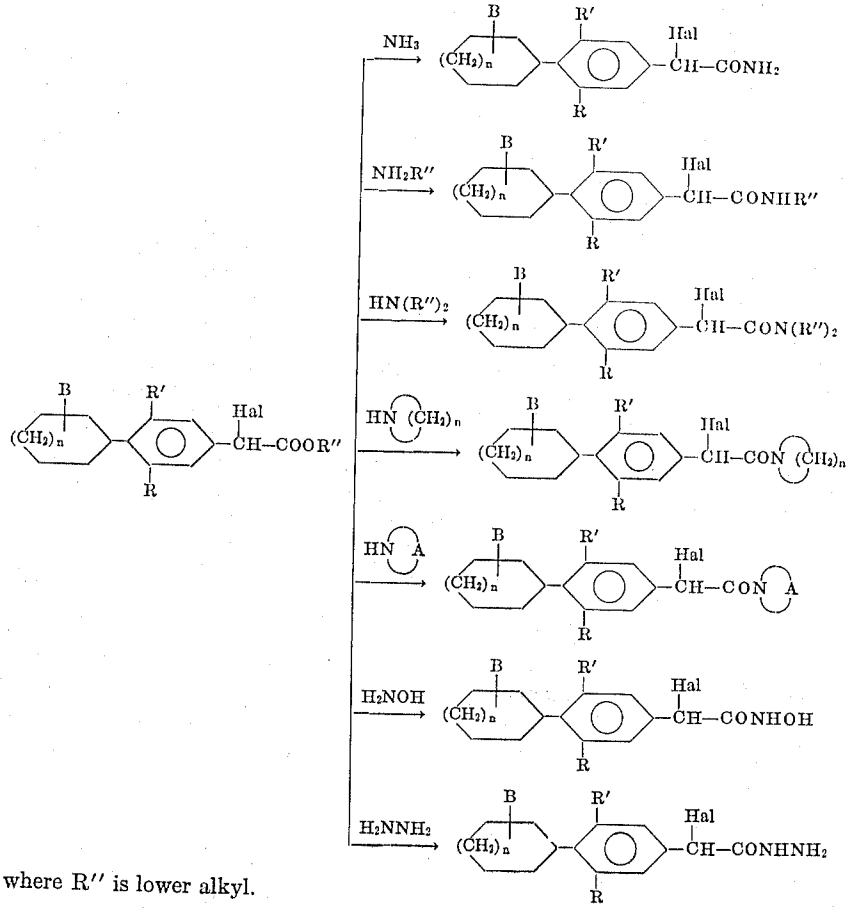


This invention further relates to the acid addition salts formed by the action of one equivalent of a suitable base with the substituted α-halo-4-cycloalkylphenylacetic acid. Suitable bases thus include for example the alkali metal alkoxides such as sodium methoxide, etc., and the alkali metal and alkaline earth metal hydroxides, carbonates, bicarbonates, etc. (such as sodium hydroxide, potassium hydroxide, calcium hydroxide, 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 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. The acid addition salts thus obtained are the functional equivalent of the corresponding substituted α-halo-P-cycloalkylphenylacetic acid products and one skilled in the art will appreciate that to the extent that the instant acids are useful in therapy, the variety of acid addition salts embraced by this invention are limited only by the criterion that the bases employed in forming the therapeutically useful salts be both non-toxic and physiologically acceptable. The alkaloidal salts are useful for effecting optical resolutions.



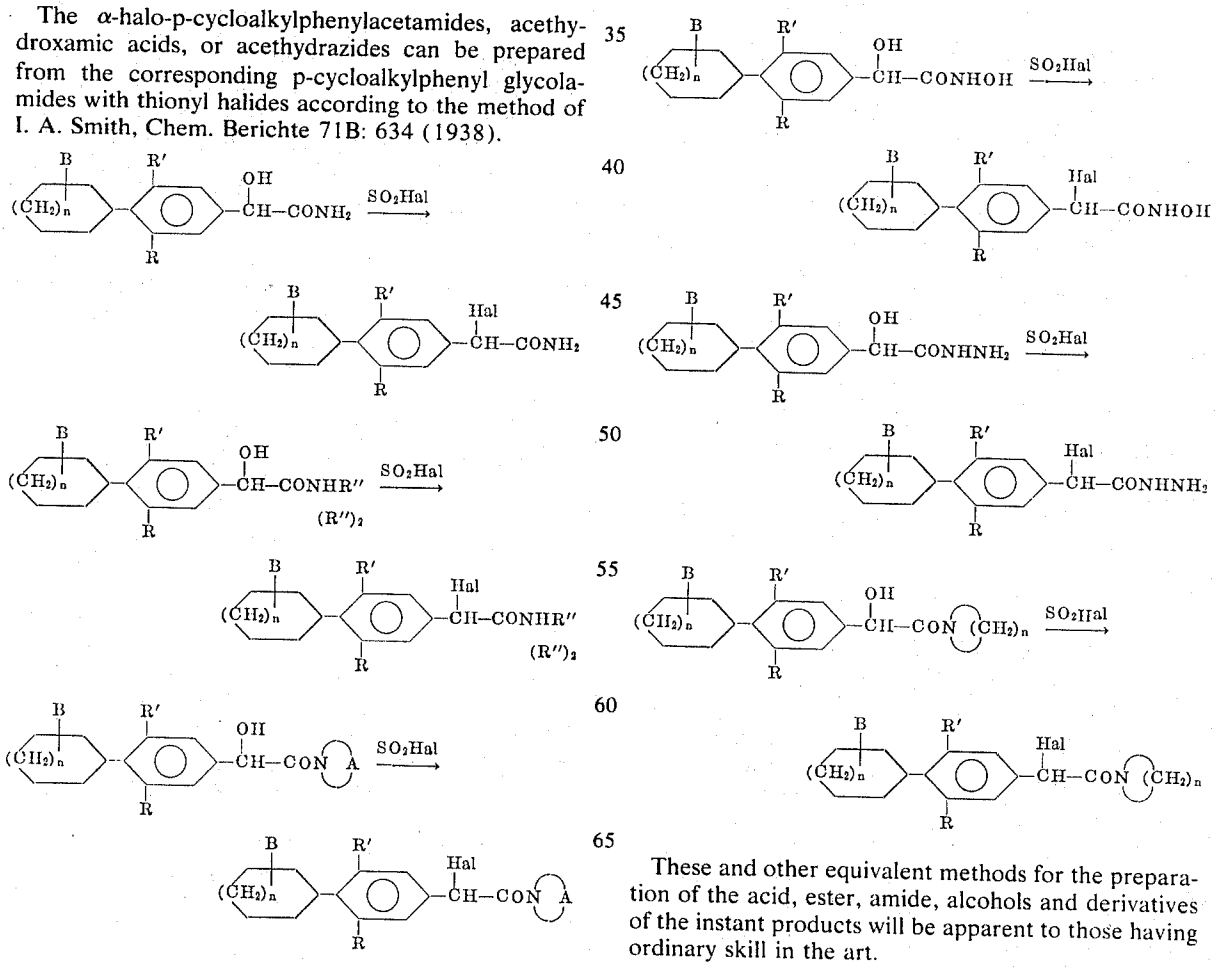
Reaction of a substituted α-halo-p-cycloalkylphenylacetate ester with a nitrogen base such as ammonia, loweralkylamine, diloweralkylamine, cycloloweralkylamine, a nitrogen containing hetero compound such as piperidine, morpholine, piperazine results in the corresponding amide. The acetate ester with hydroxylamine gives the corresponding hydroxamic acid, and with hydrazine gives the corresponding hydrazide.





where R'' is lower alkyl.

The α-halo-p-cycloalkylphenylacetamides, acethydroxamic acids, or acethydrazides can be prepared from the corresponding p-cycloalkylphenyl glycolamides with thionyl halides according to the method of I. A. Smith, Chem. Berichte 71B: 634 (1938).



These and other equivalent methods for the preparation of the acid, ester, amide, alcohols and derivatives of the instant products will be apparent to those having ordinary skill in the art.

The products of this invention may be obtained as racemic mixtures of their dextro and levorotatory isomers. These may be separated by any of the various methods of resolution. One method that may be employed is combining the racemic compound with an optically active compound by salt formtion, 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* and *l* acids are obtained. Preferably, a cycloalkylphenylglycolic 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 p-cycloalkylphenylglycolic acid. Alternatively, a p-cycloalkylphenylglycolate 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 p-cycloalkylphenylglycolamides which may be separated by fractional crystallization. Each optically active amide may be hydrolyzed with mineral acid to its respective optically active acid.

Still alternatively, a p-cycloalkylphenylglycolate may be reacted with an optically active alcohol such as l-menthol or d-borneol, or l-α-methylbenzylalcohol, to produce a mixture of diastereomeric p-cyclo- alkylphenylglycolate 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.

The optically active glycolate may then be reacted with a phosphorus trihalide, phosphorus pentahalide, phosphorus oxyhalide, sulfurylhalide, thionylhalide or sulfur halide to give an optically active α-halo p-cycloalkylphenylacetic acid, ester or amide thereof.

The racemic chloroacetic acids, esters and amides may also be resolved into their optical isomers by the processes described for the glycolic acids, esters and amides.

We 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 muscluar 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 anti-inflammatory, analgesic and-/or 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 preferred 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 α-halo-p-cycloalkyphenylacetic 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 maize starch, alginic acid, etc., lubricating 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 α-halo-p-cycloalkylphenylacetic 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-inflammed 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 α-halo-p-cycloalkylphenylacetic acids and derivatives can be considered to be active anti-inflammatory agents.

One method for measuring the pain threshold of the α-halo-p-cycloalkylphenylacetic acids and derivatives is the Randall-Selitto test. Analgesic activity is shown by antinocieceptive testing of the inflammed 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 meas-

urement of rectal temperatures is carried out to determine the response by the test compounds.

In view of the results of the above tests, the α-halo-p-cyclo-alkylphenylacetic 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 1

Ethyl p-cyclohexylphenylglyoxylate

Cyclohexylbenzene 53 g. (0.33 mole) and 50.5 g. (0.37 mole) of ethyl oxalyl chloride are dissolved in 200 ml. of dry 1,1,2,2-tetrachloro-ethane. 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 15°–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 × 100 ml. portions of a 1:1 mixture of saturated sodium chloride solution and 10 percent HCl solution, and 5 × 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 p-cyclohexylphenylglyoxylate. (b.p. 165°–7°C/1.1 mm.)

When cyclohexylbenzene in the above example is replaced with cyclopentylbenzene, cycloheptylbenzene, 2'-methylcyclohexybenzene, 3'-methylcyclohexylbenzene, 4'-methylcyclohexylbenzene, 2'-methylcyclopentylbenzene or 2'-methylcycloheptylbenzene then the product obtained is ethyl p-cyclopentylphenylglyoxylate, ethyl p-cycloheptylphenylglyoxylate, ethyl 4-(2'-methylcyclohexyl)phenylglyoxylate, ethyl 4-(3'-methycyclohexyl)phenyl-glyoxylate, ethyl 4-4'-methylcyclohexyl)phenylglyoxylate, ethyl 4(2'-methylcyclopentyl)phenylglyoxylate or ethyl 4-(2'-methylcycloheptyl)phenyl-glyoxylate.

When ethyl oxalyl chloride in the above example is replaced with methyl oxalyl chloride, propyl oxalyl chloride, i-propyl oxalyl chloride, t-butyl oxalyl chloride, or benzyl oxalyl chloride then the product obtained is methyl p-cyclohexylphenylglyoxylate, propyl p-cyclohexylphenylglyoxylate, i-propyl p-cyclohexylphenylglyoxylate, t-butyl p-cyclohexylphenylglyoxylate, or benzyl p-cyclohexylphenylglyoxylate.

EXAMPLE 2

Ethyl 3-chloro-4-cyclohexylphenylglyoxylate

Ethyl p-cyclohexylphenylglyoxylate 98.9 g. (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 3-chloro-4-cyclohexylphenylglyoxylate. (b.p. 190°C/2.7 mm.)

When ethyl p-cyclohexylphenylglyoxylate in the above example is replaced with the esters of Example 1 then the corresponding product of Table I below is prepared.

Table I

ethyl 3-chloro-4-cyclopentylphenylglyoxylate
ethyl 3-chloro-4-(2'-methylcyclopentyl)phenyl-glyoxylate
ethyl 3-chloro-4-cycloheptylphenylglyoxylate
ethyl 3-chloro-4-(2'-methylcycloheptyl)phenyl-glyoxylate
ethyl 3-chloro-4-(2'-methylcyclohexyl)phenyl-glyoxylate
ethyl 3-chloro-4-(3'-methylcyclohexyl)phenyl-glyoxylate
ethyl 3-chloro-4-(4'-methylcyclohexyl)phenyl-glyoxylate
methyl 3-chloro-4-cyclohexylphenylglyoxylate
propyl 3-chloro-4-cyclohexylphenylglyoxylate
i-propyl 3-chloro-4-cyclohexylphenylglyoxylate
t-butyl 3-chloro-4-cyclohexylphenylglyoxylate
benzyl 3-chloro-4-cyclohexylphenylglyoxylate

EXAMPLE 3

Ethyl 3,5-dichloro-4-cyclohexylphenylglyoxylate

Ethyl p-cyclohexylphenylglyoxylate, 49.5 g (0.19 mole) and 6.1 g. of iodine are dissolved in 100 ml. of carbon tetrachloride. to this solution is added a solution of 56.7 g (0.8 mole) of chlorine dissolved in 500 ml. of carbon tetrachloride over a period of 3 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 30 hours. The solvent is removed in vacuo. The residue is fractionally distilled to obtain ethyl 3,5-dichloro-four-cyclohexylphenylglyoxylate.

When ethyl p-cyclohexylphenylglyoxylate in the above example is replaced by the esters of Example 1, then the corresponding product of Table I below is prepared.

TABLE I

ethyl 3,5-dichloro-4-cyclopentylphenylglyoxylate
ethyl 3,5-dichloro-4-(2'-methylcyclopentyl)phenyl-glyoxylate
ethyl 3,5-dichloro-4-cycloheptylphenylglyoxylate
ethyl 3,5-dichloro-4-(2'-methylcycloheptyl)phenyl-glyoxylate
ethyl 3,5-dichloro-4-(2'-methylcyclohexyl)phenyl-glyoxylate
ethyl 3,5-dichloro-4-(3'-methylcyclohexyl)phenyl-glyoxylate
ethyl 3,5-dichloro-4-(4'-methylcyclohexyl)phenyl-glyoxylate
methyl 3,5-dichloro-4-cyclohexylphenylglyoxylate
propyl 3,5-dichloro-4-cyclohexylphenylglyoxylate
i-propyl 3,5-dichloro-4-cyclohexylphenylglyoxylate

t-butyl 3,5-dichloro-4-cyclohexylphenylglyoxylate
benzyl 3,5-dichloro-4-cyclohexylphenylyoxylate

When the esters of Table I, Example 2 are used then the same products are obtained.

EXAMPLE 4

When bromine is used in place of chlorine in Examples 2 and 3, the products obtained are shown in Tables I and II below.

TABLE I

ethyl 3-bromo-4-cyclopentylphenylglyoxylate
ethyl 3-bromo-4-(2'-methylcyclopentyl)phenylglyoxylate
ethyl 3-bromo-4-cycloheptylphenylglyoxylate
ethyl 3-bromo-4-(2'-methylcycloheptyl)phenylglyoxylate
ethyl 3-bromo-4-cyclohexylphenylglyoxylate
ethyl 3-bromo-4-(2'-cyclohexyl)phenylglyoxylate
ethyl 3-bromo-4-(3'-cyclohexyl)phenylglyoxylate
ethyl 3-bromo-4-(4'-cyclohexyl)phenylglyoxylate
methyl 3-bromo-4-cyclohexylphenylglyoxylate
propyl 3-bromo-4-cyclohexylphenylglyoxylate
i-propyl 3-bromo-4-cyclohexylphenylglyoxylate
t-butyl 3-bromo-4-cyclohexylphenylglyoxylate
benzyl 3-bromo-4-cyclohexylphenylglyoxylate

TABLE II

ethyl 3,5-dibromo-4-cyclopentylphenylglyoxylate
ethyl 3,5-dibromo-4-(2'-methylcyclopentyl)phenylglyoxylate
ethyl 3,5-dibromo-4-cycloheptylphenylglyoxylate
ethyl 3,5-dibromo-4-(2'-methylcycloheptyl)phenylglyoxylate
ethyl 3,5-dibromo-4-cyclohexylphenylglyoxylate
ethyl 3,5-dibromo-4-(2'-methylcyclohexyl)phenylglyoxylate
ethyl 3,5-dibromo-4-(3'-methylcyclohexyl)phenylglyoxylate
ethyl 3,5-dibromo-4-(4'-methylcyclohexyl)phenylglyoxylate
methyl 3,5-dibromo-4-cyclohexylphenylglyoxylate
propyl 3,5-dibromo-4-cyclohexylphenylglyoxylate
i-propyl 3,5-dibromo-4-cyclohexylphenylglyoxylate
t-butyl 3,5-dibromo-4-cyclohexylphenylglyoxylate
benzyl 3,5-dibromo-4-cyclohexylphenylglyoxylate

EXAMPLE 5

Ethyl 3-nitro-4-cyclohexylphenylglyoxylate

Ethyl p-cyclohexylphenylglyoxylate 17.2 g. (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 ½hour, 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 3-nitro-4-cyclohexylphenyl-glyoxylate.

When ethyl p-cyclohexylphenylglyoxylate in the above example is replaced by the esters of Example I, then the corresponding product of Table I below is prepared.

Table I

ethyl 3-nitro-4-cyclopentylphenylglyoxylate
ethyl 3-nitro-4-(2'methylcyclopentyl)phenylglyoxylate
ethyl 3-nitro-4-cycloheptylphenylglyoxylate
ethyl 3-nitro-4-(2'-methylcycloheptyl)phenylglyoxylate
ethyl 3-nitro-4-(2'-methylcyclohexyl)phenylglyoxylate
ethyl 3-nitro-4-(3'-methylcyclohexyl)phenylglyoxylate
ethyl 3-nitro-4-(4'-methylcyclohexyl)phenylglyoxylate
methyl 3-nitro-4-cyclohexylphenylglyoxylate
propyl 3-nitro- 4-cyclohexylphenylglyoxylate
i-propyl 3-nitro-4-cyclohexylphenylglyoxylate
t-butyl 3-nitro-4-cyclohexylphenylglyoxylate benzyl 3-nitro-4-cyclohexylphenylglyoxylate

When ethyl p-cyclohexylphenylglyoxylate in the above example is replaced by the esters of Example 2 and Table I of Example 4, then the corresponding product of Table II below is prepared.

TABLE II

ethyl 3-chloro-5-nitro-4-cyclopentylphenylglyoxylate
ethyl 3-chloro-5-nitro-4-(2'-methylcyclopentyl)-phenylglyoxylate
ethyl 3-chloro-5-nitro-4-cycloheptylphenylglyoxylate
ethyl 3-chloro-5-nitro-4-(2'-methylcycloheptyl)-phenylglyoxylate
ethyl 3-chloro-5-nitro-4-(2'-methylcyclohexyl)-phenylglyoxylate
ethyl 3-chloro-5-nitro-4-(3'-methylcyclohexyl)-phenyl-glyoxylate
ethyl 3-chloro-5-nitro-4-(4'-methylcyclohexyl)-phenylglyoxylate
methyl 3-chloro-5-nitro-4-cyclohexylphenylglyoxylate
ethyl 3-chloro-5nitro-4-cyclohexylphenylglyoxylate
propyl 3-chloro-5-nitro-4-cyclohexylphenylglyoxylate
i-propyl 3-chloro-5-nitro-4-cyclohexylphenylglyoxylate t-butyl 3-chloro-5-nitro-4-cyclohexylphenylglyoxylate
benzyl 3-chloro-5-nitro-4-cyclohexylphenylglyoxylate
ethyl 3-bromo-5-nitro-4-cyclopentylphenylglyoxylate
ethyl 3-bromo-5-nitro-4-(2'-methylcyclopentyl)-phenylglyoxylate
ethyl 3-bromo-5-nitro-4-cycloheptylphenylglyoxylate
ethyl 3-bromo-5-nitro-4-(2'-methylcycloheptyl)-phenylglyoxylate
ethyl 3-bromo-5-nitro-4-cyclohexylphenylglyoxylate
ethyl 3-bromo-5nitro-4-(2'-methylcyclohexyl)-phenylglyoxylate
ethyl 3-bromo-5-nitro-4-(3'-methylcyclohexyl)-phenylglyoxylate
ethyl 3-bromo-5-nitro-4-(4'-methylcyclohexyl)-phenylglyoxylate
methyl 3-bromo-5-nitro-4-cyclohexylphenylglyoxylate
ethyl 3-bromo-5-nitro-4-cyclohexylphenylglyoxylate
propyl 3-bromo-5-nitro-4-cyclohexylphenylglyoxylate
i-propyl 3-bromo-5-nitro-4-cyclohexylphenylglyoxylate
t-butyl 3-bromo-5-nitro-4-cyclohexylphenylglyoxylate

benzyl 3-bromo-5-nitro-4-cyclohexylphenylglyoxylate

EXAMPLE 6

Ethyl 3,5-dinitro-4-cyclohexylphenylglyoxylate

Ethyl p-cyclohexylphenylglyoxylate 17.2 g. (0.066 mole) is added to ice-cold concentrated sulfuric acid (54 ml.) and stirred with cooling for 5 minutes. Concentrated nitric acid (Sp. G. 1.51) (7.5 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 3 hours, then poured into water. The mixture is made alkaline with sodium hydroxide, then extracted with ether. The ether extract is washed, dried over sodium sulfite, evaporated and the residue is fractionally distilled to obtain ethyl 3,5-dinitro-4-cyclohexylphenylglyoxylate.

When ethyl p-cyclohexylphenylglyoxylate in the above example is replaced by the esters of Example 1, then the corresponding product of Table I below is prepared.

TABLE I

ethyl 3,5-dinitro-4-cyclopentylphenylglyoxylate
ethyl 3,5-dinitro-4-(2'-methylcyclopentyl)phenylglyoxylate
ethyl 3,5-dinitro-4-cycloheptylphenylglyoxylate
ethyl 3,5-dinitro-4-(2'-methylcycloheptyl)phenylglyoxylate
ethyl 3,5-dinitro-4-(2'-methylcyclohexyl)phenylglyoxylate
ethyl 3,5-dinitro-4-(3'-methylcyclohexyl)phenylglyoxylate
ethyl 3,5-dinitro-4-(4'-methylcyclohexyl)phenylglyoxylate
methyl 3,5-dinitro-4-cyclohexylphenylglyoxylate
propyl 3,5-dinitro-4-cyclohexylphenylglyoxylate
i-propyl 3,5-dinitro-4-cyclohexylphenylglyoxylate
t-butyl 3,5-dinitro-4-cyclohexylphenylglyoxylate
benzyl 3,5-dinitro-4-cyclohexylphenylglyoxylate

When the esters of Table I, Example 4 are used then the same products are prepared.

EXAMPLE 7

Ethyl 3-trifluoromethyl-4-cyclohexylphenylglyoxylate

To a solution of 0.01 moles of ethyl 3-bromo-4-cyclohexylphenylglyoxylate in 50 ml. of dimethylformamide is added 0.15 moles of trifluoromethyl iodide and 0.02 g. of copper power. 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 3-trifluoromethyl-4-cyclohexylphenylglyoxylate.

When ethyl 3-bromo-4-cyclohexylphenylglyoxylate in the above example is replaced by equimolar amounts of the compounds of Tables I and II of Example 4 and Table II, Example 5, then the corresponding product is obtained.

EXAMPLE 8

Ethyl 3-amino-4-cyclohexylphenylglyoxylate

A mixture of 15.3 g. (0.05 moles) of ethyl 3-nitro-4-cyclohexylphenylglyoxylate in 100 ml. methanol containing 0.05 mole citric acid and 1.5 g. of 5 percent palladium-on-carbon is shaken with hydrogen at 3 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 3-amino-4-cyclohexylphenylglyoxylate, isolated as the citrate salt.

When ethyl 3-nitro-4-cyclohexylphenylglyoxylate in the above example is replaced by equimolar amounts of the compounds of Tables I and II, Example 5 and Table I, Example 6, then the corresponding products are obtained.

EXAMPLE 9

Ethyl 3-methylamino-4-cyclohexylphenylglyoxylate

To a solution of 0.01 moles of ethyl 3-amino-4-cyclohexylphenylglyoxylate 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 3-methylamino-4-cyclohexylphenylglyoxylate.

When ethyl 3-amino-4-cyclohexylphenylglyoxylate in the above example is replaced by equimolar amounts of the compounds of Example 8, then the corresponding products are obtained.

When 0.01 moles of acetyl chloride is used in place of methyl iodide in the above example, then the product prepared is ethyl-3-acetylamino-4-cyclohexylphenylglyoxylate.

EXAMPLE 10

Ethyl 3-dimethylamino-4-cyclohexylphenylglyoxylate

A solution of 0.005 moles of ethyl 3-nitro-4-cyclohexylphenylglyoxylate and 1.6 ml. of 37 percent formaldehyde in 50 ml. of methanol is shaken with hydrogen over 0.5 g. of 5 percent palladium-on-charcoal at 42 lbs. and 27°C until five 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 3-dimethylamino-4-cyclohexylphenylglyoxylate.

When ethyl 3-nitro-4-cyclohexylphenylglyoxylate in the above example is replaced by equimolar amounts of the compounds of Tables I and II, Example 5 and Table 1, Example 6, then the corresponding products are obtained.

EXAMPLE 11

Ethyl 3-cyano-4-cyclohexylphenylglyoxylate

To 29.4 g. (0.1 moles) of ethyl 3-amino-4-cyclohexylphenylglyoxylate in 35 ml. of 28 percent 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 nitride 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 g. 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 separate, dried over sodium sulfate and evaporated to dryness to obtain ethyl 3-cyano-4-cyclohexylphenylglyoxylate.

When ethyl 3-amino-4-cyclohexylphenylglyoxylate in the above example is replaced by equimolar amounts

of the compounds of Example 8, then the corresponding products are obtained.

EXAMPLE 12

Ethyl 3-fluoro-4-cyclohexylphenylglyoxylate

To 44.2 g. (0.15 moles) of ethyl 3-amino-4-cyclohexylphenylglyoxylate 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 percent 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 percent hydrofluoric acid. The reaction mixture is then stirred for ½ 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 3-fluoro-4-cyclohexylphenylglyoxylate.

When ethyl 3-amino-4-cyclohexylphenylglyoxylate in the above example is replaced by the compounds of Example 8, then the corresponding products are obtained.

EXAMPLE 13

3-Hydroxy-4-cyclohexylphenylglyoxylic acid

To 4.5 g. of ethyl 3-amino-4-cyclohexylphenylglyoxylate suspension in 125 ml. of 80 percent 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 percent 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 3-hydroxy-4-cyclohexylphenylglyoxylic acid.

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

When ethyl 3-amino-4-cyclohexylphenylglyoxylate in the above example is replaced by equimolar amounts of the compounds of Example 8, then the corresponding products are obtained.

EXAMPLE 14

Ethyl 3-methoxy-4-cyclohexylphenylglyoxylate

To a stirred suspension 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 3-hydroxy-4-cyclohexylphenylglyoxylate in 10 ml. of dimethylformamide. The reaction mixture is stirred for 15 minutes and 0.015 moles of methyliodide 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 3-methoxy-4-cyclohexylphenylglyoxylate.

When ethyl 3-hydroxy-4-cyclohexylphenylglyoxylate in the above example is replaced by equimolar amounts of the compounds of Example 13, then the corresponding products are obtained.

When 0.01 moles of acetyl chloride is used in place of methyliodide in the above reaction, then the product prepared is ethyl 3-acetyloxy-4-cyclohexylphenylglyoxylate.

EXAMPLE 15

3-Bromo-4-cyclohexylphenylglyoxylic acid

To 11.1 g. (0.044 moles) of ethyl 3-amino-4-cyclohexylphenylglyoxylate suspension in 225 ml. of 40 percent 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 percent 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 3-bromo-4-cyclohexylphenylglyoxylic acid.

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

When ethyl 3-amino-4-cyclohexylphenylglyoxylate in the above example is replaced by the compounds of Example 8, then the corresponding products are obtained.

EXAMPLE 16

3-Iodo-4-cyclohexylphenylglyoxylic acid

To .05 moles of ethyl 3-amino-4-cyclohexylphenylglyoxylate 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 percent 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 .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 3-iodo-4-cyclohexylphenylglyoxylic acid.

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

When ethyl 3-amino-4-cyclohexylphenylglyoxylate in the above example is replaced by equimolar amounts of the compounds of Example 8, then the corresponding products are obtained.

EXAMPLE 17

3-Mercapto-4-cyclohexylphenylglyoxylic acid

To 17.3 g. of ethyl 3-amino-4-cyclohexylphenylglyoxylate 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 minutes 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 3-mercapto-4-cyclohexylphenylglyoxylic acid.

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

When ethyl 3-amino-4-cyclohexylphenylglyoxylate in the above example is replaced by equimolar amounts of the compounds of Example 8, then the corresponding products are prepared.

EXAMPLE 18

Ethyl 3-methylthio-4-cyclohexylphenylglyoxylate

To 3.85 g. of ethyl 3-mercapto-4-cyclohexylphenylglyoxylate 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 3-methylthio-4-cyclohexylphenylglyoxylate.

When the above 3-methylthio-4-cyclohexylphenylglyoxylate is treated with 30 percent H_2O_2, then the resultant product is ethyl 3-methylsulfinyl-4-cyclohexylphenylglyoxylate or ethyl 3-methylsulfonyl-4-cyclohexylphenylglyoxylate.

When 3-mercapto-4-cyclohexylphenylglyoxylate in the above example is replaced by the compounds of Example 17, then the corresponding products are prepared.

When an equimolar amount of acetyl chloride is used in place of dimethyl sulfate in the above reaction, then the product prepared is ethyl 3-acetylthio-4-cyclohexylphenylglyoxylate.

EXAMPLE 19

Ethyl 3-nitro-5-trifluoromethyl-4-cyclohexylphenylglyoxylate

To a solution of 0.01 moles of ethyl 3-bromo-5-nitro-4-cyclohexylphenylglyoxylate 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, 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 3-nitro-5-trifluoromethyl-4-cyclohexylphenylglyoxylate.

When ethyl 3-bromo-5-nitro-4-cyclohexylphenylglyoxylate in the above reaction is replaced by ethyl 3-bromo-5-fluoro-4-cyclohexylphenylglyoxylate or ethyl 3-bromo-5-chloro-4-cyclohexylphenylglyoxylate, then the products obtained are ethyl 3-fluoro-5-trifluoromethyl-4-cyclohexylphenylglyoxylate and ethyl 3-chloro-5-trifluoromethyl-4-cyclohexylphenylglyoxylate.

EXAMPLE 20

Ethyl 3-amino-5-nitro-4-cyclohexylphenylglyoxylate

A mixture of 17.6 g. (0.05 moles) of ethyl 3,5-dinitro-4-cyclohexylphenylglyoxylate in 100 ml. of methanol containing 0.05 moles of citric acid and 1.5 g. of 5 percent palladium-on-carbon is shaken with hydrogen at 3 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 3-amino-5-nitro-4-cyclohexylphenylglyoxylate isolated as the citrate salt.

When ethyl 3.5-dinitro-4-cyclohexylphenylglyoxylate in the above example is replaced by ethyl 3-chloro-5-nitro-4-cyclohexylphenylglyoxylate, ethyl 3-bromo-5-nitro-4-cyclohexylphenylglyoxylate, ethyl 3-fluoro-5-nitro-4-cyclohexylphenylglyoxylate or ethyl 3-trifluoromethyl-5-nitro-4-cyclohexylphenylglyoxylate, then the products obtained are ethyl 3-amino-5-chloro-4-cyclohexylphenylglyoxylate, ethyl 3-amino-5-bromo-4-cyclohexylphenylglyoxylate, ethyl 3-amino-5-fluoro-4-cyclohexylphenylglyoxylate and ethyl 3-amino-5-trifluoromethyl-4-cyclohexylphenylglyoxylate.

EXAMPLE 21

When the procedures of Examples 2–18 are followed using the appropriate starting material, then the corresponding product is obtained.

STARTING MATERIAL	PRODUCT	EXAMPLE
ethyl 3-amino-5-bromo-4-cyclohexylphenylglyoxylate	ethyl 3-cyano-5-bromo-4-cyclohexylphenylglyoxylate	11
ethyl 3-trifluoromethyl-4-cyclohexylphenylglyoxylate	ethyl 3-trifluoromethyl-5-chloro-4-cyclohexylphenylglyoxylate	2
ethyl 3-amino-5-nitro-4-cyclohexylphenylglyoxylate	ethyl 3-methylthio-5-nitro-4-cyclohexylphenylglyoxylate	18
ethyl 3-amino-5-fluoro-4-cyclohexylphenylglyoxylate	ethyl 3-iodo-5-fluoro-4-cyclohexylphenylglyoxylate	16
ethyl 3-amino-5-chloro-4-cyclohexylphenylglyoxylate	ethyl 3-methoxy-5-chloro-4-cyclohexylphenylglyoxylate	14
ethyl 3-amino-5-trifluoromethyl-4-cyclohexylphenylglyoxylate	ethyl 3-hydroxy-5-trifluoromethyl-4-cyclohexylphenylglyoxylate	13
ethyl 3-amino-5-fluoro-4-cyclohexylphenylglyoxylate	ethyl 3,5-difluoro-4-cyclohexylphenylglyoxylate	12
ethyl 3-nitro-5-fluoro-4-cyclohexylphenylglyoxylate	ethyl 3-dimethylamino-5-fluoro-4-cyclohexylphenylglyoxylate	10
ethyl 3-amino-5-chloro-4-cyclohexylphenylglyoxylate	ethyl 3-methylamino-5-chloro-4-cyclohexylphenylglyoxylate	9
ethyl 3-amino-5-nitro-4-cyclohexylphenylglyoxylate	ethyl 3-mercapto-5-nitro-4-cyclohexylphenylglyoxylate	17
ethyl 3-amino-5-nitro-4-cyclohexylphenylglyoxylate	ethyl methylsulfonyl-5-nitro-4-cyclohexylphenylglyoxylate	17,18
ethyl 3-nitro-5-trifluoromethyl-4-cyclohexylphenylglyoxylate	ethyl 3-amino-5-trifluoromethyl-4-cyclohexylphenylglyoxylate	8
ethyl 3-amino-5-trifluoromethyl-4-cyclohexylphenylglyoxylate	ethyl 3-trifluoromethyl-5-methylsulfonyl-4-cyclohexylphenylglyoxylate	17,18
ethyl 3-amino-5-trifluoromethyl-4-cyclohexylphenylglyoxylate	ethyl 3-fluoro-5-trifluoromethyl-4-cyclohexylphenylglyoxylate	12
ethyl 3,5-diamino-4-cyclohexylphenylglyoxylate	ethyl 3,5-diiodo-4-cyclohexylphenylglyoxylate	16
ethyl 3-amino-5-nitro-4-cyclohexylphenylglyoxylate	ethyl 3-carbamyl-5-nitro-4-cyclohexylphenylglyoxylate	11
ethyl 3-amino-5-nitro-4-cyclohexylphenylglyoxylate	ethyl 3-carbethoxy-5-nitro-4-cyclohexylphenylglyoxylate	11
ethyl 3-amino-5-nitro-4-cyclohexylphenylglyoxylate	ethyl 3-carboxy-5-nitro-4-cyclohexylphenylglyoxylate	11
ethyl 3-mercapto-5-nitro-4-cyclohexylphenylglyoxylate	ethyl 3-methylsulfinyl-5-nitro-4-cyclohexylphenylglyoxylate	18
ethyl 3-amino-5-bromo-4-cyclohexylphenylglyoxylate	ethyl 3-methylsulfonyl-5-bromo-4-cyclohexylphenylglyoxylate	17,18
ethyl 3-fluoro-4-cyclohexylphenylglyoxylate	ethyl 3-nitro-5-fluoro-4-cyclohexylphenylglyoxylate	5
ethyl 3-fluoro-4-cyclohexylphenylglyoxylate	ethyl 3-bromo-5-fluoro-4-cyclohexylphenylglyoxylate	4

Continued –

STARTING MATERIAL	PRODUCT	EXAMPLE
ethyl 3-methylsulfonyl-4-cyclohexylphenylglyoxylate	ethyl 3-chloro-5-methylsulfonyl-4-cyclohexylphenylglyoxylate	2
ethyl 3-amino-5-nitro-4-cyclohexylphenylglyoxylate	ethyl 3-cyano-5-nitro-4-cyclohexylphenylglyoxylate	11
ethyl 3-amino-5-trifluoromethyl-4-cyclohexylphenylglyoxylate	ethyl 3-trifluoromethyl-5-iodo-4-cyclohexylphenylglyoxylate	16
ethyl 3-ido-4-cyclohexylphenylglyoxylate	ethyl 3-amino-5-iodo-4-cyclohexylphenylglyoxylate	5,8
ethyl 3-fluoro-4-cyclohexylphenylglyoxylate	ethyl 3-chloro-5-fluoro-4-cyclohexylphenylglyoxylate	2
ethyl 3,5-dinitro-4-cyclohexylphenylglyoxylate	ethyl 3-acetylamino-5-nitro-4-cylcohexylphenylglyoxylate	20,9
ethyl 3-amino-5-chloro-4-cyclohexylphenylglyoxylate	ethyl 3-acetyloxy-5-chloro-4-cyclohexylphenylglyoxylate	13,14
ethyl 3-amino-5-nitro-4-cyclohexylphenylglyoxylate	ethyl 3-acetylthio-5-nitro-4-cyclohexylphenylglyoxylate	17,18
ethyl 3-nitro-5-bromo-4-cyclohexylphenylglyoxylate	ethyl 3,5-ditrifluoromethyl-4-cyclohexylphenylglyoxylate	19,8,15,7
ethyl 3-fluoro-4-(2'-methylcyclohexyl)phenylglyoxylate	ethyl 3-nitro-5-fluoro-4-(2'-methylcyclohexyl)phenylglyoxylate	5
ethyl 3-bromo-5-nitro-4-(2'-methylcyclohexyl)phenylglyoxylate	ethyl 3-nitro-5-trifluoromethyl-4-(2'-methylcyclohexyl)phenylglyoxylate	7
ethyl 3-fluoro-4-(2'-methylcyclohexyl)phenylglyoxylate	ethyl 3-chloro-5-fluoro-4-(2'-methylcyclohexyl)phenylglyoxylate	2
ethyl 3-amino-5-fluoro-4-(2'-methylcyclohexyl)phenylglyoxylate	ethyl 3-fluoro-5-bromo-4-(2'-methylcyclohexyl)phenylglyoxylate	15
ethyl 3-cyano-4-(2'-methylcyclohexyl)phenylglyoxylate	ethyl 3-cyano-5-chloro-4-(2'-methylcyclohexyl)phenylglyoxylate	2
ethyl 3,5-dinitro-4-(2'-methylcyclohexyl)phenylglyoxylate	ethyl 3-amino-5-nitro-4-(2'-methylcyclohexyl)phenylglyoxylate	20
ethyl 3,5-dinitro-4-(3'-methylcyclohexyl)phenylglyoxylate	ethyl 3-amino-t-nitro-4-(3'-methylcyclohexyl)phenylglyoxylate	20
ethyl 3,5-dinitro-4-(4'-methylcyclohexyl)phenylglyoxylate	ethyl 3-amino-5-nitro-4-(4'-methylcyclohexyl)phenylglyoxylate	20
ethyl 3-chloro-5-bromo-4-(4'-methylcyclohexyl)phenylglyoxylate	ethyl 3-chloro-5-trifluoromethyl-4-(4'-methylcyclohexyl)phenylglyoxylate	7
ethyl 3-chloro-4-(4'-methylcyclohexyl)phenylglyoxylate	ethyl 3-bromo-5-chloro-4-(4'-methylcyclohexyl)phenylglyoxylate	4
ethyl 3-amino-5-trifluoromethyl-4-(4'-methylcyclohexyl)phenylglyoxylate	ethyl 3-trifluoromethyl-5-fluoro-4-(4'-methylcyclohexyl)phenylglyoxylate	12
p-(4'-methylcyclohexyl)phenylglyoxylate	ethyl 3,5-dichloro-4-(4'-methylcyclohexyl)phenylglyoxylate	3
ethyl 3-chloro-4-(4'-methylcyclohexyl)phenylglyoxylate	ethyl 3-nitro-5-chloro-4-(4'-methylcyclohexyl)phenylglyoxylate	5
ethyl 3-chloro-4-(2'-methylcyclohexyl)phenylglyoxylate	ethyl 3-nitro-5-chloro-4-(2'-methylcyclohexyl)phenylglyoxylate	5
p-(4'-methylcyclohexyl)phenylglyoxylate	ethyl 3,5-dinitro-4-(4'-methylcyclohexyl)phenylglyoxylate	6
ethyl 3-chloro-4-(4'-methylcyclohexyl)phenylglyoxylate	ethyl 3,5-dichloro-4-(4'-methylcyclohexyl)phenylglyoxylate	2
ethyl p-cyclohexylphenylglyoxylate	ethyl 3-methyl-4-cyclohexylphenylglyoxylate	1
ethyl 3-methyl-4-cyclohexylphenylglyoxylate	ethyl 3-chloro-5-methyl-4-cyclohexylphenylglyoxylate	2
ethyl 3-methyl-4-cyclohexylphenylglyoxylate	ethyl 3-nitro-5-methyl-4-cyclohexylphenylglyoxylate	3
ethyl 3-methyl-5-nitro-4-cyclohexylphenylglyoxylate	ethyl 3-amino-5-methyl-4-cyclohexylphenylglyoxylate	8
ethyl 3-methyl-4-cyclohexylphenylglyoxylate	ethyl 3-bromo-5-methyl-4-cyclohexylphenylglyoxylate	4
ethyl 3-bromo-5-methyl-4-cyclohexylphenylglyoxylate	ethyl 3-methyl-5-trifluoromethyl-4-cyclohexylphenylglyoxylate	7
ethyl 3-amino-5-methyl-4-cyclohexylphenylglyoxylate	ethyl 3-fluoro-5-methyl-4-cyclohexylphenylglyoxylate	12
ethyl p-(2'-methylcyclohexyl)phenylglyoxylate	ethyl 3,2'-dimethyl-4-cyclohexylphenylglyoxylate	1
ethyl 3,2'-dimethyl-4-cyclohexylphenylglyoxylate	ethyl 3,2'-dimethyl-5-nitro-4-cyclohexylphenylglyoxylate	3

EXAMPLE 22

Ethyl 3-cyano-5-fluoro-4-cyclohexylphenylglycolate

A mixture of 0.32 mole of ethyl 3-bromo-5-fluoro-4-cyclohexylphenylglycolate, 0.39 mole of dry powdered cuprous cyanide and 30 ml. of quinoline are combined and heated at 150°C for 15 hours. The resultant solution is poured while still hot into a solution of 150 ml. of aqueous ammonia and 150 ml. of water. To this mixture is added 140 ml. of benzene with stirring. The mixture is then extracted with ether and the organic portion is washed 4 × 100 ml. of dilute aqueous ammonia, 2 × 100 ml. 6 N HCl, 2 × 100 ml. water and 2 × 100 ml. of saturated sodium chloride solution, and evaporated to dryness in vacuo. The residue is fractionally distilled to obtain ethyl 3-cyano-5-fluoro-4-cyclohexylphenylglycolate.

EXAMPLE 23

Ethyl 3-chloro-4-cyclohexylphenylglycolate

Into a Paar hydrogenation bottle is added 42.4 g. (0.144 mole) of ethyl 3-chloro-4-cyclohexylphenylglyoxylate, 2 ml. of 0.1 M - ferrous sulfate solution; 220 ml. of isopropanol, and 1.0 g. of 84.1 percent platinum oxide. The mixture is shaken for 2 hours at room temperature with hydrogen gas until 0.144 mole of hydrogen is absorbed. The catalyst is then filtered off and the solution is evaporated in vacuo and the residue fractionally distilled to obtain ethyl 3-chloro-4-cyclohexylphenylglycolate.

EXAMPLE 24

Ethyl 3,5-dichloro-4-cyclohexylphenylglycolate

To a solution of 24.5 g. (.074 moles) of ethyl 3,5-dichloro-4-cyclohexylphenylglyoxylate in 125 ml. of 95 percent ethanol is added 1.2 ml. of 0.1 M ferrous sulfate solution and 0.6 g. of 83 percent platinum oxide. The mixture is shaken with hydrogen gas at 8 p.s.i. for 1-¾ hours. The catalyst is filtered off and the filtrate treated with charcoal and filtered. The reaction mixture is evaporated in vacuo to obtain ethyl 3,5-dichloro-4-cyclohexylphenylglycolate.

EXAMPLE 25

When ethyl 3-chloro-4-cyclohexylphenylglyoxylate or ethyl 3,5-dichloro-4-cyclohexylphenylglyoxylate in Examples 23 and 24 is replaced by an equimolar amount of the glyoxylate esters of Examples 1–22, then the corresponding glycolate product is prepared. A representative list of the compounds prepared is shown in Table I, below.

TABLE 1

ethyl 3-methoxy-5-chloro-4-cyclohexylphenylglycolate

ethyl 3-methyl-5-chloro-4-cyclohexylphenylglycolate

ethyl 3-bromo-5-chloro-4-cyclohexylphenylglycolate

ethyl 3-methyl-5-fluoro-4-cyclohexylphenylglycolate

ethyl 3-methyl-5-bromo-4-cyclohexylphenylglycolate

ethyl 3-methyl-5-trifluoromethyl-4-cyclohexylphenylglycolate

ethyl 3-acetyl-5-chloro-4-cyclohexylphenylglycolate

ethyl 3-methyl-5-nitro-4-cyclohexylphenylglycolate

ethyl 3,5-difluoro-4-cyclohexylphenylglycolate

ethyl 3-cyano-5-fluoro-4-cyclohexylphenylglycolate

benzyl 3-cyano-5-fluoro-4-cyclohexylphenylglycolate

ethyl 3-bromo-5-fluoro-4-cyclohexylphenylglycolate

ethyl 3-acetyl-5-fluoro-4-cyclohexylphenylglycolate

ethyl 3-cyano-5-bromo-4-cyclohexylphenylglycolate

benzyl 3-cyano-5-bromo-4-cyclohexylphenylglycolate

ethyl 3,5-dibromo-4-cyclohexylphenylglycolate

ethyl 3-acetyl-5-bromo-4-cyclohexylphenylglycolate

ethyl 3-fluoro-5-trifluoromethyl-4-cyclohexylphenylglycolate

ethyl 3-cyano-5-trifluoromethyl-4-cyclohexylphenylglycolate

ethyl 3-dimethylamino-5-trifluoromethyl-4-cyclohexylphenylglycolate

ethyl 3-bromo-5-trifluoromethyl-4-cyclohexylphenylglycolate

ethyl 3-hydroxy-5-trifluoromethyl-4-cyclohexylphenylglycolate

ethyl 3-acetyl-5-trifluoromethyl-4-cyclohexylphenylglycolate

ethyl 3,5-ditrifluoromethyl-4-cyclohexylphenylglycolate

ethyl 3-chloro-4-cyclopentylphenylglycolate

ethyl 3-bromo-4-cyclopentylphenylglycolate

ethyl 3-chloro-4-cycloheptylphenylglycolate

ethyl 3-bromo-4-cycloheptylphenylglycolate

ethyl 3-cyano-4-cyclohexylphenylglycolate

benzyl 3-cyano-4-cyclohexylphenylglycolate

ethyl 3-trifluoromethyl-4-cyclohexylphenylglycolate

ethyl 3-amino-4-cyclohexylphenylglycolate

ethyl 3-methylamino-4-cyclohexylphenylglycolate

ethyl 3-dimethylamino-4-cyclohexylphenylglycolate

ethyl 3-fluoro-4-cyclohexylphenylglycolate

ethyl 3-hydroxy-4-cyclohexylphenylglycolate

ethyl 3-methoxy-4-cyclohexylphenylglycolate

ethyl 3-bromo-4-cyclohexylphenylglycolate

ethyl 3-acetyl-4-cyclohexylphenylglycolate

ethyl 3,2'-dimethyl-4-cyclohexylphenylglycolate

ethyl 3-methyl-4-cyclohexylphenylglycolate

ethyl 3-amino-5-methyl-4-cyclohexylphenylglycolate

ethyl 3-amino-5-fluoro-4-cyclohexylphenylglycolate

ethyl 3-amino-5-chloro-4-cyclohexylphenylglycolate

ethyl 3-amino-5-bromo-4-cyclohexylphenylglycolate

ethyl 3-amino-5-trifluoromethyl-4-cyclohexylphenylglycolate

ethyl 3-amino-5-cyano-4-cyclohexylphenylglycolate

ethyl 3-methylamino-5-chloro-4-cyclohexylphenylglycolate

ethyl 3-dimethylamino-5-chloro-4-cyclohexylphenylglycolate

ethyl 3-cyano-5-chloro-4-cyclohexylphenylglycolate

benzyl 3-cyano-5-chloro-4-cyclohexylphenylglycolate

ethyl 3-fluoro-5-chloro-4-cyclohexylphenylglycolate

ethyl 3-trifluoro-5-chloro-4-cyclohexylphenylglycolate

ethyl 3-hydroxy-5-chloro-4-cyclohexylphenylglycolate

ethyl 3,5-dichloro-4-cyclopentylphenylglycolate

ethyl 3,5-dichloro-4-cycloheptylphenylglycolate

methyl 3-chloro-4-cyclohexylphenylglycolate

methyl 3,5-dichloro-4-cyclohexylphenylglycolate

propyl 3,5-dichloro-4-cyclohexylphenylglycolate

i-propyl 3-chloro-4-cyclohexylphenylglycolate

i-propyl 3,5-dichloro-4-cyclohexylphenylglycolate

t-butyl 3-chloro-4-cyclohexylphenylglycolate

t-butyl 3,5-dichloro-4-cyclohexylphenylglycolate

ethyl 3-chloro-4-(2'-methylcyclopentyl)phenylglycolate

ethyl 3,5-dichloro-4-(2'-methylcyclopentyl)phenylglycolate

ethyl 3-chloro-4-(2'-methylcyclohexyl)phenylglycolate

ethyl 3,5-dichloro-4-(2'-methylcyclohexyl)phenylglycolate

ethyl 3-chloro-4-(2'-methylcycloheptyl)phenylglycolate

ethyl 3,5-dichloro-4-(2'-methylcycloheptyl)phenylglycolate

ethyl 3-chloro-4-(3'-methylcyclohexyl)phenylglycolate

ethyl 3,5-dichloro-4-(3'-methylcyclohexyl)phenylglycolate

ethyl 3-chloro-4-(4'-methylcyclohexyl)phenylglycolate

ethyl 3,5-dichloro-4-(4'-methylcyclohexyl)phenylglycolate

ethyl 3-chloro-5-fluoro-(2'-methylcyclohexyl)-phenylglycolate

ethyl 3-fluoro-5-bromo-(2'-methylcyclohexyl)-phenylglycolate

ethyl 3-cyano-5-chloro-(2'-methylcyclohexyl)-phenylglycolate

ethyl 3-chloro-5-trifluoromethyl-(4'-methylcyclohexyl)phenylglycolate

ethyl 3-bromo-5-chloro-(4'-methylcyclohexyl)-phenylglycolate

ethyl 3-fluoro-5-trifluoromethyl-(4'-methylcyclohexyl)phenylglycolate

ethyl 3,5-dichloro-(4'-methylcyclohexyl)phenylglycolate

EXAMPLE 26

Ethyl 3-nitro-4-cyclohexylphenylglycolate

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 17.9 g. (0.0587 mole) of ethyl 3-nitro-4-cyclohexylphenylglycolate, 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 then is adjusted to acidic by addition of 18 N sulfuric acid (2.8 ml.). The gum product is extracted with ether. The ether extract is washed with 2 × 25 ml. of saturated sodium bisulfite to remove the traces of initial carbonyl compound and then dried over anhydrous sodium sulfite for 2 hours. The drying agent is removed and the solvent is then removed to obtain ethyl 3-nitro-4-cyclohexylphenylglycolate.

When ethyl 3-nitro-4-cyclohexylphenylglyoxylate in the above example is replaced by an equimolar amount of the glyoxylate esters of Examples 1–25, then the corresponding glycolate product is prepared. A representative list of the compounds prepared is shown in Table 1, below.

TABLE 1

ethyl 3-nitro-4-cyclopentylphenylglycolate
ethyl 3-nitro-4-cycloheptylphenylglycolate
ethyl 3,5-dinitro-4-cyclohexylphenylglycolate
ethyl 3,5-dinitro-4-cyclopentylphenylglycolate
ethyl 3,5-dinitro-4-cycloheptylphenylglycolate
ethyl 3-nitro-5-chloro-4-cyclohexylphenylglycolate
ethyl 3-cyano-5-nitro-4-cyclohexylphenylglycolate
benzyl 3-cyano-5-nitro-4-cyclohexylphenylglycolate
ethyl 3-amino-5-nitro-4-cyclohexylphenylglycolate
ethyl 3-dimethylamino-5-nitro-4-cyclohexylphenylglycolate
ethyl 3-fluoro-5-nitro-4-cyclohexylphenylglycolate
ethyl 3-hydroxy-5-nitro-4-cyclohexylphenylglycolate
ethyl 3-methoxy-5-nitro-4-cyclohexylphenylglycolate
ethyl 3-bromo-5-nitro-4-cyclohexylphenylglycolate
ethyl 3-trifluoromethyl-5-nitro-4-cyclohexylphenylglycolate
ethyl 3-iodo-5-nitro-4-cyclohexylphenylglycolate
ethyl 3-mercapto-5-nitro-4cyclohexylphenylglycolate
ethyl 3-methylthio-5-nitro-4-cyclohexylphenylglycolate
ethyl 3-acetylthio-5-nitro-4-cyclohexylphenylglycolate
ethyl 3-acetyloxy-5-nitro-4-cyclohexylphenylglycolate
ethyl 3-acetylamino-5-nitro-4-cyclohexylphenylglycolate
ethyl 3-methylsulfonyl-5-nitro-4-cyclohexylphenylglycolate
ethyl 3-amino-5-iodo-4-cyclohexylphenylglycolate
ethyl 3-amino-5-methylsulfonyl-4-cyclohexylphenylglycolate
ethyl 3-trifluoromethyl-5-methylsulfonyl-4-cyclohexylphenylglycolate
ethyl 3-nitro-5-methylsulfinyl-4-cyclohexylphenylglycolate
ethyl 3-bromo-5-methylsulfinyl-4-cyclohexylphenylglycolate
ethyl 3-chloro-5-methylsulfinyl-4-cyclohexylphenylglycolate
ethyl 3-methylsulfinyl-4-cyclohexylphenylglycolate
ethyl 3-methylsulfonyl-4-cyclohexylphenylglycolate
ethyl 3-iodo-4-cyclohexylphenylglycolate
ethyl 3-mercapto-4-cyclohexylphenylglycolate
ethyl 3-iodo-5-chloro-4-cyclohexylphenylglycolate
ethyl 3-mercapto-5-chloro-4-cyclohexylphenylglycolate
ethyl 3-iodo-5-fluoro-4-cyclohexylphenylglycolate
ethyl 3-mercapto-5-fluoro-4-cyclohexylphenylglycolate
ethyl 3-iodo-5-bromo-4-cyclohexylphenylglycolate
ethyl 3-iodo-5-acetyl-4-cyclohexylphenylglycolate
ethyl 3-iodo-5-methylsulfonyl-4-cyclohexylphenylglycolate
ethyl 3-nitro-4-(2′-methylcyclopentyl)phenylglycolate
ethyl 3-nitro-4-(2′-methylcyclohexyl)phenylglycolate
ethyl 3-nitro-4-(2′-methylcycloheptyl)phenylglycolate
ethyl 3-nitro-4-(3′-methylcyclohexyl)phenylglycolate
ethyl 3-nitro-4-(4′-methylcyclohexyl)phenylglycolate
ethyl 3-amino-5-nitro-4-(2′-methylcyclohexyl)-phenylglycolate
ethyl 3-amino-5-nitro-4-(3′-methylcyclohexyl)-phenylglycolate
ethyl 3-amino-5-nitro-4-(4′-methylcyclohexyl)-phenylglycolate
ethyl 3,5-dinitro-4-(4′-methylcyclohexyl)phenylglycolate

EXAMPLE 27

3-Chloro-4-cyclohexylphenylglycolic acid

To a solution of 0.144 moles of ethyl 3-chloro-4-cyclohexylphenylglycolate 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 percent HCl and the precipitate is taken up in ehter. The ether layer is dried, filtered and the filtrate concentrated to dryness. Recrystallization of residue from benzenecyclohexane 1:1 gives 3-chloro-4-cyclohexylphenylglycolic acid.

EXAMPLE 28

3,5-dichloro-4-cyclohexylphenylglycolic acid

To a solution of 0.15 moles of ethyl 3,5-dichloro-4-cyclohexylphenylglycolate dissolved in 225 ml. of isopropanol is added 40 g. of potassium hydroxide. This mixture is then heated to reflux temperature in a nitrogen atmosphere. The solution is concentrated in vacuo and the residue is dissolved in 500 ml. of water and acidified with 10 percent HCl. The mixture is extracted with ether, dried and evaporated to dryness. The residue is recrystallized from benzene-cyclohexane to give 3,5-dichloro-4-cyclohexylphenylglycolic acid.

EXAMPLE 29

When a equimolar amount of the glycolate compounds of Examples 23–26 are used in Examples 27–28, then the corresponding glycolic acid of Table I below is prepared.

TABLE I

3-chloro-4-cyclopentylphenylglycolic acid
3-bromo-4-cyclopentylphenylglycolic acid
3-chloro-4-cycloheptylphenylglycolic acid
3-bromo-4-cycloheptylphenylglycolic acid

3-trifluoromethyl-4-cyclohexylphenylglycolic acid
3-amino-4-cyclohexylphenylglycolic acid
3-methylamino-4-cyclohexylphenylglycolic acid
3-dimethylamino-4-cyclohexylphenylglycolic acid
3-fluoro-4-cyclohexylphenylglycolic acid
3-hydroxy-4-cyclohexylphenylglycolic acid
3-methoxy-4-cyclohexylphenylglycolic acid
3-bromo-4-cyclohexylphenylglycolic acid
3-acetyl-4-cyclohexylphenylglycolic acid
3,2'-dimethyl-4-cyclohexylphenylglycolic acid
3-methyl-4-cyclohexylphenylglycolic acid
3-amino-5-methyl-4-cyclohexylphenylglycolic acid
3-amino-5-fluoro-4-cyclohexylphenylglycolic acid
3-amino-5-chloro-4-cyclohexylphenylglycolic acid
3-amino-5-bromo-4-cyclohexylphenylglycolic acid
3-amino-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
3-amino-5-cyano-4-cyclohexylphenylglycolic acid
3-methylamino-5-chloro-4-cyclohexylphenylglycolic acid
3-dimethylamino-5-chloro-4-cyclohexylphenylglycolic acid
3-fluoro-5-chloro-4-cyclohexylphenylglycolic acid
3-trifluoromethyl-5-chloro-4-cyclohexylphenylglycolic acid
3-hydroxy-5-chloro-4-cyclohexylphenylglycolic acid
3-methoxy-5-chloro-4-cyclohexylphenylglycolic acid
3-methyl-5-chloro-4-cyclohexylphenylglycolic acid
3-bromo-5-chloro-4-cyclohexylphenylglycolic acid
3-methyl-5-fluoro-4-cyclohexylphenylglycolic acid
3-methyl-5-bromo-4-cyclohexylphenylglycolic acid
3-methyl-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
3-acetyl-5-chloro-4-cyclohexylphenylglycolic acid
3-methyl-5-nitro-4-cyclohexylphenylglycolic acid
3,5-difluoro-4-cyclohexylphenylglycolic acid
3-bromo-5-fluoro-4-cyclohexylphenylglycolic acid
3-acetyl-5-fluoro-4-cyclohexylphenylglycolic acid
3,5-dibromo-4-cyclohexylphenylglycolic acid
3-acetyl-5-bromo-4-cyclohexylphenylglycolic acid
3-fluoro-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
3-carboxy-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
3-dimethylamino-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
3-bromo-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
3-hydroxy-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
3-acetyl-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
3,5-ditrifluoromethyl-4-cyclohexylphenylglycolic acid
3-acetyl-5-carboxy-4-cyclohexylphenylglycolic acid
3-chloro-4-cyclohexylphenylglycolic acid
3-chloro-4-(2'-methylcyclopentyl)phenylglycolic acid (2 racemates)
3-chloro-4-(2'-methylcyclohexyl)phenylglycolic acid (2 racemates)
3-chloro-4-(2'-methylcycloheptyl)phenylglycolic acid (2 racemates)
3-chloro-4-(3'-methylcyclohexyl)phenylglycolic acid (2 racemates)
3-chloro-4-(4'-methylcyclohexyl)phenylglycolic acid
3-chloro-5-fluoro-(2'-methylcyclohexyl)phenylglycolic acid (2 racemates)
3-fluoro-5-bromo-(2'-methylcyclohexyl)phenylglycolic acid (2 racemates)
3-chloro-5-fluoro-(2'-methylcyclohexyl)phenylglycolic acid (2 racemates)
3-carboxy-5-chloro-(2'-methylcyclohexyl)phenylglycolic acid (2 racemates)
3-chloro-5-trifluoromethyl-(4'-methylcyclohexyl)-phenylglycolic acid
3-bromo-5-chloro-(4'-methylcyclohexyl)phenylglycolic acid
3-fluoro-5-trifluoromethyl-(4'-methylcyclohexyl)-phenylglycolic acid
3,5-dichloro-(4'-methylcyclohexyl)phenylglycolic acid
3-nitro-4-cyclopentylphenylglycolic acid
3-nitro-4-cycloheptylphenylglycolic acid
3,5-dinitro-4-cyclohexylphenylglycolic acid
3,5-dinitro-4-cyclopentylphenylglycolic acid
3,5-dinitro-4-cycloheptylphenylglycolic acid
3-nitro-5-chloro-4-cyclohexylphenylglycolic acid
3-amino-5-nitro-4-cyclohexylphenylglycolic acid
3-dimethylamino-5-nitro-4-cyclohexylphenylglycolic acid
3-fluoro-5-nitro-4-cyclohexylphenylglycolic acid
3-hydroxy-5-nitro-4-cyclohexylphenylglycolic acid
3-methoxy-5-nitro-4-cyclohexylphenylglycolic acid
3-bromo-5-nitro-4-cyclohexylphenylglycolic acid
3-trifluoromethyl-5-nitro-4-cyclohexylphenylglycolic acid
3-iodo-5-nitro-4-cyclohexylphenylglycolic acid
3-mercapto-5-nitro-4-cyclohexylphenylglycolic acid
3-methylthio-5-nitro-4-cyclohexylphenylglycolic acid
3-methyl-5-nitro-4-cyclohexylphenylglycolic acid
3-carboxy-5-nitro-4-cyclohexylphenylglycolic acid
3,2'-dimethyl-5-nitro-4-cyclohexylphenylglycolic acid
3-methylsulfonyl-5-nitro-4-cyclohexylphenylglycolic acid
3-amino-5-iodo-4-cyclohexylphenylglycolic acid
3-amino-5-methylsulfonyl-4-cyclohexylphenylglycolic acid
3-trifluoromethyl-5-methylsulfonyl-4-cyclohexylphenylglycolic acid
3-nitro-5-methylsulfinyl-4-cyclohexylphenylglycolic acid
3-bromo-5-methylsulfinyl-4-cyclohexylphenylglycolic acid
3-chloro-5-methylsulfinyl-4-cyclohexylphenylglycolic acid
3-methylsulfinyl-4-cyclohexylphenylglycolic acid
3-methylsulfonyl-4-cyclohexylphenylglycolic acid
3-iodo-4-cyclohexylphenylglycolic acid
3-mercapto-4-cyclohexylphenylglycolic acid
3-iodo-5-chloro-4-cyclohexylphenylglycolic acid
3-mercapto-5-chloro-4-cyclohexylphenylglycolic acid
3-iodo-5-fluoro-4-cyclohexylphenylglycolic acid
3-mercapto-5-fluoro-4-cyclohexylphenylglycolic acid
3-iodo-5-bromo-4-cyclohexylphenylglycolic acid
3-iodo-5-acetyl-4-cyclohexylphenylglycolic acid

3-iodo-5-methylsulfonyl-4-cyclohexylphenylglycolic acid
3-nitro-4-(2'-methylcyclopentyl)phenylglycolic acid (2 racemates)
3-nitro-4-(2'-methylcycloheptyl)phenylglycolic acid (2racemates)
3-nitro-4-(2'-methylcyclohexyl)phenylglycolic acid (2 racemates)
3-nitro-4-(3'-methylcyclohexyl)phenylglycolic acid (2 racemates)
3-nitro-4-(4'-methylcyclohexyl)phenylglycolic acid
3-amino-5-nitro-4-(2'-methylcyclohexyl)phenylglycolic acid (2 racemates)
3-amino-5-nitro-4-(3'-methylcyclohexyl)phenylglycolic acid (2 racemates)
3-amino-5-nitro-4-(4'-methylcyclohexyl)phenylglycolic acid
3,5-dinitro-4-(4'-methylcyclohexyl)phenylglycolic acid

EXAMPLE 30

3-Cyano-4-cyclohexylphenylglycolic acid

A solution of 0.01 moles of benzyl 3-cyano-4-cyclohexylphenylglycolate dissolved in 100 ml. of acetic acid and containing 0.01 mole of hydrogen chloride is shaken with hydrogen over a 5 percent 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 3-cyano-4-cyclohexylphenylglycolic acid.

When the benzyl ester used is
benzyl 3-cyano-4-cyclohexylphenylglycolate
benzyl 3-cyano-5-chloro-4-cyclohexylphenylglycolate
benzyl 3-cyano-5-fluoro-4-cyclohexylphenylglycolate
benzyl 3-cyano-5-bromo-4-cyclohexylphenylglycolate
benzyl 3,5-dicyano-4-cyclohexylphenylglycolate
benzyl 3-cyano-5-nitro-4-cyclohexylphenylglycolate
benzyl 3-acetylamino-4-cyclohexylphenylglycolate
benzyl 3-acetylthio-4-cyclohexylphenylglycolate
benzyl 3-acetyloxy-4-cyclohexylphenylglycolate

then the products obtained are
3-cyano-4-cyclohexylphenylglycolic acid
3-cyano-5-chloro-4-cyclohexylphenylglycolic acid
3-cyano-5-fluoro-4-cyclohexylphenylglycolic acid
3-cyano-5-bromo-4-cyclohexylphenylglycolic acid
3,5-dicyano-4-cyclohexylphenylglycolic acid
3-cyano-5-nitro-4-cyclohexylphenylglycolic acid
3-acetylamino-4-cyclohexylphenylglycolic acid
3-acetylthio-4-cyclohexylphenylglycolic acid
3-acetyloxy-4-cyclohexylphenylglycolic acid

EXAMPLE 31

l 3-Chloro-4-cyclohexylphenylglycolic acid

To a boiling solution of 29.4 g. (0.10 mole) of cinchonidine in 1 liter of absolute ethanol is added a boiling solution of 26.9 g. (0.10 mole) of dl 3-chloro-4-cyclohexylphenylglycolic 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 × 25 ml. of ethanol and air dried. Recrystallization from isopropanol gives white needle crystals. This material is hydrolyzed with 200 ml. of 1.2 HCl. The white solid is collected, washed with 3 × 50 ml. water and dried at 55°C overnight. Recrystallization from benzene = cyclohexane 3:2 gives l 3-chloro-4-cyclophexylphenylglycolic acid. (m.p. 158°–60°C) $[\alpha]_D$–86.5° (C=1 percent, EtOH).

When modifications of the above resolution procedure is followed but dl 3-chloro-4-cyclohexylphenylglycolic acid is replaced by an equimolar amount of the dl glycolic acids of Examples 27–30, then the corresponding l-isomer of Table I below is prepared.

TABLE I

l 3,5-dichloro-4-cyclohexylphenylglycolic acid
l 3-chloro-4-cyclopentylphenylglycolic acid
l 3-bromo-4-cyclopentylphenylglycolic acid
l 3-chloro-4-cycloheptylphenylglycolic acid
l 3-bromo-4-cycloheptylphenylglycolic acid
l 3-trifluoromethyl-4-cyclohexylphenylglycolic acid
l 3-amino-4-cyclohexylphenylglycolic acid
l 3-methylamino-4-cyclohexylphenylglycolic acid
l 3-dimethylamino-4-cyclohexylphenylglycolic acid
l 3-fluoro-4-cyclohexylphenyglycolic acid
l 3-hydroxy-4-cyclohexylphenylglycolic acid
l 3-methoxy-4-cyclohexylphenylglycolic acid
l 3-bromo-4-cyclohexylphenylglycolic acid
l 3-acetyl-4-cyclohexylphenylglycolic acid
l 3,2'-dimethyl-4-cyclohexylphenylglycolic acid
l 3-methyl-4-cyclohexylphenylglycolic acid
l 3-amino-5-methyl-4-cyclohexylphenylglycolic acid
l 3-amino-5-fluoro-4-cyclohexylphenylglycolic acid
l 3-amino-5-chloro-4-cyclohexylphenylglycolic acid
l 3-amino-5-bromo-4-cyclohexylphenylglycolic acid
l 3-amino-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
l 3-amino-5-cyano-4-cyclohexylphenylglycolic acid
l 3-methylamino-5-chloro-4-cyclohexylphenylglycolic acid
l 3-dimethylamino-5-chloro-4-cyclohexylphenylglycolic acid
l 3-fluoro-5-chloro-4-cyclohexylphenylglycolic acid
l 3-trifluoromethyl-5-chloro-4-cyclohexylphenylglycolic acid
l 3-hydroxy-5-chloro-4-cyclohexylphenylglycolic acid
l 3-methoxy-5-chloro-4-cyclohexylphenylglycolic acid
l methyl-5-chloro-4-cyclohexylphenylglycolic acid
l 3-bromo-5-chloro-4-cyclohexylphenylglycolic acid
l 3-methyl-5-fluoro-4-cyclohexylphenylglycolic acid
l 3-methyl-5-bromo-4-cyclohexylphenylglycolic acid
l 3-methyl-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
l 3-acetyl-5chloro-4-cyclohexylphenylglycolic acid
l 3-methyl-5-nitro-4-cyclohexylphenylglycolic acid
l 3,5-difluoro-4-cyclohexylphenylglycolic acid
l 3-bromo-5-fluoro-4-cyclohexylphenylglycolic acid
l 3-acetyl-5-fluoro-4-cyclohexylphenylglycolic acid
l 3,5-dibromo-4-cyclohexylphenylglycolic acid
l 3-acetyl-5-bromo-4-cyclohexylphenylglycolic acid
l 3-fluoro-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
l 3-carboxy-b 5-trifluoromethyl-4-cyclohexylphenylglycolic acid

l 3-dimethylamino-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
l 3-bromo-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
l 3-hydroxy-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
l 3-acetyl-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
l 3,5-ditrifluromethyl-4-cyclohexylphenylglycolic acid
l 3,5-dichloro-4-cyclopentylphenylglycolic acid
l 3,5-dichloro-4-cycloheptylphenylglycolic acid
l 3-chloro-4-cyclohexylphenylglycolic acid
l 3-chloro-4-(2'-methylcyclopentyl)phenylglycolic acid
l 3,5-dichloro-4-(2'-methylcyclopentyl)phenylglycolic acid
l 3-chloro-4-(2'-methylcyclohexyl)phenylglycolic acid
l 3,5-dichloro-4-(2'-methylcyclohexyl)phenylglycolic acid
l 3-chloro-4-(2'-methylcycloheptyl)phenylglycolic acid
l 3,5-dichloro-4-(2'-methylcycloheptyl)phenylglycolic acid
l 3-chloro-4-(3'-methylcyclohexyl)phenylglycolic acid
l 3,5-dichloro-4-(3'-methylcyclohexyl)phenylglycolic acid
l 3-chloro-4-(4'-methylcyclohexyl)phenylglycolic acid
l 3,5-dichloro-4-(4'-methylcyclohexyl)phenylglycolic acid
l 3-chloro-5-fluoro-(2'-methylcyclohexyl)phenylglycolic acid
l 3-fluoro-5-bromo-(2'-methylcyclohexyl)phenylglycolic acid
l 3-chloro-5-fluoro-(2'-methylcyclohexyl)phenylglycolic acid
l 3-chloro-5-trifluoromethyl-(4'-methylcyclohexyl)-phenylglycolic acid
l 3-bromo-5-chloro-(4'-methylcyclohexyl)phenylglycolic acid
l 3-fluoro-5-trifluoromethyl-4'-methylcyclohexyl)-pheneylglycolic acid
l 3,5-dichloro-(4'-methylcyclohexyl)phenylglycolic acid
l 3-nitro-4-cyclopentylphenylglycolic acid
l 3-nitro-4-cycloheptylpheneylglycolic acid
l 3,5-dinitro-4-cyclohexylphenylglycolic acid
l 3,5-dinitro-4-cyclopentylphenylglycolic acid
l 3,5-dinitro-4-cycloheptylphenylglycolic acid
l 3-nitro-5-chloro-4-cyclohexylphenylglycolic acid
l 3-amino-5-nitro-4-cyclohexylphenylglycolic acid
l 3-dimethylamino-5-nitro-4-cyclohexylphenylglycolic acid
l 3-fluoro-5-nitro-4-cyclohexylphenylglycolic acid
l 3-hydroxy-5-nitro-4-cyclohexylphenylglycolic acid
l 3-methoxy-5-nitro-4-cyclohexylphenylglycolic acid
l 3-bromo-5-nitro-4-cyclohexylphenylglycolic acid
l 3-trifluoromethyl-5-nitro-4-cyclohexylphenylglycolic acid
l 3-iodo-5-nitro-4-cyclohexylphenylglycolic acid
l 3-mercapto-5-nitro-4-cyclohexylphenylglycolic acid
l 3-methylthio-5-nitro-4-cyclohexylphenylglycolic acid
l 3-methyl-5-nitro-4-cyclohexylphenylglycolic acid
l 3-carboxy-5-nitro-4-cyclohexylphenylglycolic acid
l 3,2'-dimethyl-5-nitro-4-cyclohexylphenylglycolic acid
l 3-methylsulfonyl-5-nitro-4-cyclohexylphenylglycolic acid
l 3-amino-5-iodo-4-cyclohexylphenylglycolic acid
l 3-amino-5-methylsulfonyl-4-cyclohexylphenylglycolic acid
l 3-trifluoromethyl-5-methylsulfonyl-4-cyclohexylphenylglycolic acid
l 3-nitro-5-methylsulfinyl-4-cyclohexylphenylglycolic acid
l 3-bromo-5-methylsulfinyl-4-cyclohexylphenylglycolic acid
l 3-chloro-5-methylsulfinyl-4-cyclohexylphenylglycolic acid
l 3-methylsulfinyl-4-cyclohexylphenyglycolic acid
l 3-methylsulfonyl-4-cyclohexylphenylglycolic acid
l 3-iodo-4-cyclohexylphenylglycolic acid
l 3-mercapto-4-cyclohexylphenylglycolic acid
l 3-iodo-5-chloro-4-cyclohexylphenylglycolic acid
l 3-mercapto-5-chloro-4-cyclohexylphenylglycolic acid
l 3-iodo-5-fluoro-4-cyclohexylphenylglycolic acid
l 3-mercapto-5-fluoro-4-cyclohexylphenylglycolic acid
l 3-iodo-5-bromo-4-cyclohexylphenylglycolic acid
l 3-iodo-5-acetly-4-cyclohexylphenylglycolic acid
l 3-iodo-5-methylsulfonyl-4-cyclohexylphenylglycolic acid
l 3-nitro-4-(2'-methylcyclopentyl)phenylglycolic acid
l 3-nitro-4-(2'-methylcycloheptyl)phenylglycolic acid
l 3-nitro-4-(2'-methylcyclohexyl)phenylglycolic acid
l 3-nitro-4-(3'-methylcyclohexyl)phenylglycolic acid
l 3-nitro-4-(4'-methylcyclohexyl)phenylglycolic acid
l 3-amino-5-nitro-4-(2'-methylcyclohexyl)phenyglycolic acid
l 3-amino-5-nitro-4-(3'-methylcyclohexyl)phenylglycolic acid
l 3-amino-5-nitro-4-(4'-methylcyclohexyl)phenylglycolic acid
l 3,5-dinitro-4-(4'-methylcyclohexyl)phenylglycolic acid
l 3-cyano-4-cyclohexylphenylglycolic acid
l 3-cyano-5-chloro-4-cyclohexylphenylglycolic acid
l 3-cyano-5-fluoro-4-cyclohexylphenylglycolic acid
l 3-cyano-5-bromo-4-cyclohexylphenylglycolic acid
l 3,5-dicyano-4-cyclohexylphenyglycolic acid
l 3-cyano-5-nitro-4-cyclohexylphenylglycolic acid

EXAMPLE 32

d 3-Chloro-4-cyclohexylphenylglycolic acid

The combined ethanol and isopropanol filtrates from Example 27 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 × 25 ml. of water, and dried at 55°C. Recrystalli-

zation from benzene-cyclohexane 3:2 gives d 3-chloro-4-cyclohexylphenylglycolic acid. (m.p. 158°–60°C) $[\alpha]_D$+86.5° (C=1 percent, CH_3OH)

When modifications of the above resolution procedure is followed but dl 3-chloro-4-cyclohexylphenylglycolic acid is replaced by an equimolar amount of the dl glycolic acids of Examples 27–30, then the corresponding d-isomer of Table I below is prepared.

TABLE I

d 3-chloro-4-cyclopentylphenylglycolic acid
d 3-bromo-4-cyclopentylphenylglycolic acid
d 3-chloro-4-cycloheptylphenylglycolic acid
d 3-bromo-4-cycloheptylphenylglycolic acid
d 3-trifluoromethyl-4-cyclohexylphenylglycolic acid
d 3-amino-4-cyclohexylphenylglycolic acid
d 3-methylamino-4-cyclohexylphenylglycolic acid
d 3-dimethylamino-4-cyclohexylphenylglycolic acid
d 3-fluoro-4-cyclohexylphenylglycolic acid
d 3-hydroxy-4-cyclohexylphenyglycolic acid
d 3-methoxy-4-cyclohexylphenylglycolic acid
d 3-bromo-4-cyclohexylphenylglycolic acid
d 3-acetyl-4-cyclohexylphenylglycolic acid
d 3,2′-dimethyl-4-cyclohexylphenylglycolic acid
d 3-methyl-4-cyclohexylphenylglycolic acid
d 3-amino-5-methyl-4-cyclohexylphenylglycolic acid
d 3-amino-5-fluoro-4-cyclohexylphenylglycolic acid
d 3-amino 5-chloro-4-cyclohexylphenylglycolic acid
d 3-amino-5-bromo-4-cyclohexylphenylglycolic acid
d 3-amino-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
d 3-amino-5-cyano-4-cyclohexylphenylglycolic acid
d 3-methylamino-5-chloro-4-cyclohexylphenylglycolic acid
d 3-dimethylamino-5-chloro-4-cyclohexylphenylglycolic acid
d 3-fluoro-5-chloro-4-cyclohexylphenylglycolic acid
d 3-trifluoromethyl-5-chloro-4-cyclohexylphenylglycolic acid
d 3-hydroxy-5-chloro-4-cyclohexylphenylglycolic acid
d 3-methoxy-5-chloro-4-cyclohexylphenyglycolic acid
d 3-methtyl-5-chloro-4-cyclohexylphenylglycolic acid
d 3-bromo-5-chloro-4-cyclohexylphenyglycolic acid
d 3,5-dichloro-4-cyclohexylphenylglycolic acid
d 3-methyl-5-fluoro-4-cyclohexylphenylglycolic acid
d 3-methyl-5-bromo-4-cyclohexylphenylglycolic acid
d 3-methyl-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
d 3acetyl-5-chloro-4-cyclohexylphe-ylglycolic acid
d 3-methyl-5-nitro-4-cyclohexylphenylglycolic acid
d 3,5-difluoro-4-cyclohexylphenylglycolic acid
d 3-bromo-5-fluoro-4-cyclohexylphenylglycolic acid
d 3-acetyl-5-fluoro-4-cyclohexylphenylglycolic acid
d 3,5-dibromo-4-cyclohexylphenylglycolic acid
d 3-acetyl-5-bromo-4-cyclohexylphenylglycolic acid
d 3-fluoro-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
d 3-carboxy-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
d 3-dimethylamino-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
d 3-bromo-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
d 3-hydroxy-5-trifluoromethyl-4-cyclohexylphenylglycolic acid
d 3-acetyl-5-trifluoromethyl-4-cyclohexylphenyglycolic acid
d 3,5-ditrifluoromethyl-4-cyclohexylphenylglycolic acid
d 3,5-dichloro-4-cyclopentylphenylglycolic acid
d 3,5-dichloro-4-cycloheptylphenylglycolic acid
d 3-chloro-4-cyclohexylphenylglycolic acid
d 3-chloro-4-(2′-methylcyclopentyl)phenylglycolic acid
d 3,5-dichloro-4-(2′-methylcyclopentyl)phenylglycolic acid
d 3-chloro-4-(2′-methylcyclohexyl)phenylglycolic acid
d 3,5-dichloro-4-(2′-methylcyclohexy)phenylglycolic acid
d 3-chloro-4-(2′-methylcycloheptyl)phenylglycolic acid
d 3,5-dichloro-4-(2′-methylcyclheptyl)phenylglycolic acid
d 3-chloro-4-(3′-methylcyclohexyl)phenylglycolic acid
d 3,5-dichloro-4-(3′-methylcyclohexyl)phenylglycolic acid
d 3-chloro-4-(4′-methylcyclohexyl)phenylglycolic acid
d 3,5-dichloro-4-(4′-methylcyclohexyl)phenylglycolic acid
d 3-chloro-5-fluoro-(2′-methylcyclohexyl)phenylglycolic acid
d 3-fluoro-5-bromo-(2′-methylcyclohexyl)phenylglycolic acid
d 3-chloro-5-fluoro-(2′-methylcyclohexyl)phenylglycolic acid
d 3-chloro-5-trifluoromethyl-(4′-methylcyclohexyl)-phenyglycolic acid
d 3-bromo-5-chloro-(4′-methylcyclohexyl)phenylglycolic acid
d 3-fluoro-5-trifluoromethyl-(4′-methylcyclohexyl)-phenylglycolic acid
d 3,5-dichloro-(4′-methylcyclohexyl)phenyglycolic acid
d 3-nitro-4-cyclopentylphenylglycolic acid
d 3-nitro-4-cycloheptylphenylglycolic acid
d 3,5-dinitro-4-cyclohexylphenylglycolic acid
d 3,5-dinitro-4-cyclopentylphenylglycolic acid
d 3,5-dinitro-4-cycloheptylphenylglycolic acid
d 3-nitro-5-chloro-4-cyclohexylphenylglycolic acid
d 3-amino-5-nitro-4-cyclohexylphenylglycolic acid
d 3-dimethylamino-5-nitro-4-cyclohexylphenylcolic acid
d 3-fluoro-5-nitro-4-cyclohexylphenylglycolic acid
d 3-hydroxy-5-nitro-4-cyclohexylphenylglycolic acid
d 3-methoxy-5-nitro-4-cyclohexylphenyglycolic acid

d 3-bromo-5-nitro-4-cyclohexylphenylglycolic acid
d 3-trifluoromethyl-5-nitro-4-cyclohexylphenylglycolic acid
d 3-iodo-5-nitro-4-cyclohexylphenylglycolic acid
d 3-mercapto-5-nitro-4-cyclohexylphenylglycolic acid
d 3-methyl-5-nitro-4-cyclohexylphenylglycolic acid
d 3-carboxy-5-nitro-4-cyclohexylphenylglycolic acid
d 3,2'-dimethyl-5-nitro-4-cyclohexylphenylglycolic acid
d 3-acetylamino-5-nitro-4-cyclohexylphenylglycolic acid
d 3-methylsulfonyl-5-nitro-4-cyclohexylphenylglycolic acid
d 3-amino-5-iodo-4-cyclohexylphenylglycolic acid
d 3-amino-5-methylsulfonyl-4-cyclohexylphenylglycolic acid
d 3-trifluoromethyl-5-methysulfonyl-4-cyclohexylphenylglycolic acid
d 3-nitro-5-methylsulfinyl-4-cyclohexylphenylglycolic acid
d 3-bromo-5-methylsulfinyl-4-cyclohexylphenylglycolic acid
d 3-chloro-5-methylsulfinyl-4-cyclohexylphenylglycolic acid
d 3-methylsulfinyl-4-cyclohexylphenylglycolic acid
d 3-methylsulfonyl-4-cyclohexylphenylglycolic acid
d 3-iodo-5-cyclohexylphenylglycolic acid
d 3-mercapto-4-cyclohexylphenylglycolic acid
d 3-iodo-5-chloro-4-cyclohexylphenylglycolic acid
d 3-mercapto-5-chloro-4-cyclohexylphenylglycolic acid
d 3-iodo-5-fluoro-4-cyclohexylphenylglycolic acid
d 3-mercapto-5-fluoro-4-cyclohexylphenylglycolic acid
d 3-iodo-5-bromo-4-cyclohexylphenylglycolic acid
d 3-iodo-5-acetyl-4-cyclohexylphenylglycolic acid
d 3-iodo-5-methylsulfonyl-4-cyclohexylphenylglycolic acid
d 3-iodo-5-methylsulfonyl-4-cyclohexylphenylglycolic acid
d 3-nitro-4-(2'-methylcyclopentyl)phenylglycolic acid
d 3-nitro-4-(2'-methylcycloheptyl)phenylglycolic acid
d 3-nitro14-(2'-methylcyclohexyl)phenylglycolic acid
d 3-nitro-4-(3'-methylcyclohexyl)phenylglycolic acid
d 3-nitro-4-(4'-methylcyclohexyl)phenylglycolic acid
d 3-amino-5-nitro-4-(2'-methylcyclohexyl)phenylglycolic acid
d 3-amino-5-nitro-4-(3'-methylcyclohexyl)phenylglycolic acid
d 3-amino-5-nitro-4-(4'-methylcyclohexyl)phenylglycolic acid
d 3,5-dinitro-4-(4'-methylcyclohexyl)phenylglycolic acid
3-cyano-4-cyclohexylphenylglycolic acid
d 3-cyano-5-chloro-4-cyclohexylphenylglycolic acid
d 3-cyano-5-fluoro-4-cyclohexylphenylglycolic acid
d 3-cyano-5-bromo-4-cyclohexylphenylglycolic acid
d 3,5-dicyano-4-cyclohexylphenylglycolic acid
d 3-cyano-5-nitro-4-cyclohexylphenylglycolic acid

EXAMPLE 33

3-Chloro-4-cyclohexylphenylglycolic 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 44.1 g. (0.164 moles) of 3-chloro-4-cyclohexylphenylglycolic 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 disiccator to obtain 3-chloro-4-cyclohexylphenylglycolic acid, sodium salt.

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

TABLE I

sodium hydroxide
potassium hydroxide
calcium hydroxide
potassium carbonate
magnesium bicarbonate

TABLE II

3-chloro-4-cyclohexylphenylglycolic acid, sodium salt
3-chloro-4-cyclohexylphenylglycolic acid, potassium salt
3-chloro-4-cyclohexylphenylglycolic acid, calcium salt
3-chloro-4-cyclohexylphenylglycolic acid, magnesium salt

When 3,5-dichloro-4-cyclohexylphenylglycolic acid is used in place of 3-chloro-4-cyclohexylphenylglycolic acid in the above procedure, then the products obtained are:

3,5-dichloro-4-cyclohexylphenylglycolic acid, sodium salt
3,5-dichloro-4-cyclohexylphenylglycolic acid, potassium salt
3,5-dichloro-4-cyclohexylphenylglycolic acid, calcium salt
3,5-dichloro-4-cyclohexylphenylglycolic acid, magnesium salt

When the dl, *d* and *l* glycolic acid compounds of this invention are used in the above reaction, the corresponding salt is prepared.

EXAMPLE 34

3-Chloro-4-cyclohexylphenylglycolic acid, diethylammonium salt

Anhydrous diethylamine (0.11 moles) is added dropwise to a stirred solution of 3-chloro-4-cyclohexylphenylglycolic 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 3-chloro-4-cyclohexylphenylglycolic acid, diethylammonium salt.

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

Table I

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

Table I

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

TABLE II

3-chloro-4-cyclohexylphenylglycolic acid, dimethylammonium salt
3-chloro-4-cyclohexylphenylglycolic acid, β-hydroxyethylammonium salt
3-chloro-4-cyclohexylphenylglycolic acid, piperazinium salt
3-chloro-4-cyclohexylphenylglycolic acid, piperidinium salt
3-chloro-4-cyclohexylphenylglycolic acid, α-methylbenzylammonium salt
3-chloro-4-cyclohexylphenylglycolic acid, cyclohexylammonium salt
3-chloro-4-cyclohexylphenylglycolic acid, triethylammonium salt
3-chloro-4-cyclohexylphenylglycolic acid, phenethylammonium salt

When 3,5-dichloro-4-cyclohexylphenylglycolic acid is used in place of 3-chloro-4-cyclohexylphenylglycolic acid in the above procedure, then the products obtained are:

3,5-dichloro-4-cyclohexylphenylglycolic acid, diethylammonium salt
3,5-dichloro-4-cyclohexylphenylglycolic acid, dimethylammonium salt
3,5-dichloro-4-cyclohexylphenylglycolic acid, β-hydroxyethylammonium salt
3,5-dichloro-4-cyclohexylphenylglycolic acid, piperazinium salt
3,5-dichloro-4-cyclohexylphenylglycolic acid, piperidinium salt
3,5-dichloro-4-cyclohexylphenylglycolic acid, α-methylbenzylammonium salt
3,5-dichloro-4-cyclohexylphenylglycolic acid, cyclohexylammonium salt
3,5-dichloro-4-cyclohexylphenylglycolic acid, triethylammonium salt
3,5-dichloro-4-cyclohexylphenylglycolic acid, phenethylammonium salt

When the dl, *d* and *l* glycolic acids of this invention are used in the above reaction, then the corresponding salt is prepared.

EXAMPLE 35

N-isopropyl-3-chloro-4-cyclohexylphenylglycolamide

Ethyl 3-chloro-4-cyclohexylphenylglycolate 29.48 g. (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 3-chloro-4-cyclohexylphenylglycolamide.

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

TABLE II

N,N-diethyl-3-chloro-4-cyclohexylphenylglycolamide
N-methyl-N-ethyl-3-chloro-4-cyclohexylphenylglycolamide
N-t-butyl-3-chloro-4-cyclohexylphenylglycolamide
N-cyclopropyl-3-chloro-4-cyclohexylphenylglycolamide
N,N-pentamethylene-3-chloro-4-cyclohexylphenylglycolamide
N,N-oxydiethylene-3-chloro-4-cyclohexylphenylglycolamide
N,N-methylaminodiethylene-3-chloro-4-cyclohexylphenylglycolamide
N,N-methylaminoethylenetrimethylene-3-chloro-4-cyclohexylphenylglycolamide
N,N-thiotrimethylene-3-chloro-4-cyclohexylphenylglycolamide

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 3-chloro-4-cyclohexylphenylglycolamide, N-methyl-3-chloro-4-cyclohexylphenylglycolamide or N,N-dimethyl-3-chloro-4-cyclohexylphenylglycolamide.

When ethyl 3,5-dichloro-4-cyclohexylphenylglycolate is used in the above procedure in place of ethyl 3-chloro-4-cyclohexylphenylglycolate, then the products obtained are:

N-isopropyl 3,5-dichloro-4-cyclohexylphenylglycolamide
N,N-diethyl 3,5-dichloro-4-cyclohexylphenylglycolamide
N-methyl-N-ethyl 3,5-dichloro-4-cyclohexylphenylglycolamide
N-t-butyl 3,5-dichloro-4-cyclohexylphenylglycolamide
N-cyclopropyl 3,5-dichloro-4-cyclohexylphenylglycolamide
N,N-pentamethylene 3,5-dichloro-4-cyclohexylphenylglycolamide
N,N-oxydiethylene 3,5-dichloro-4-cyclohexylphenylglycolamide
N-methyl 3,5-dichloro-4-cyclohexylphenylglycolamide
N,N-dimethyl 3,5-dichloro-4-cyclohexylphenylglycolamide

When the dl, *d* or *l* glycolic acids of this invention are used in the above reaction, then the corresponding amide is prepared.

EXAMPLE 36

Ethyl α,3-dichloro-4-cyclohexylphenylactate

A mixture of 221.75 g. (0.747 mole) of ethyl 3-chloro-4-cyclohexylphenylglycolate 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,3-dichloro-4-cyclohexylphenylacetate.

EXAMPLE 37

Ethyl α,3,5-trichloro-4-cyclohexylphenylacetate

To a mixture of 24.7 g. (0.077 moles) of ethyl 3,5-dichloro-4-cyclohexylphenylglycolate in 35 ml. of benzene is added 19.2 g. (0.092 moles) of phosphorous pentachloride in small portions over 1-½ hours. The mixture is stirred for 20 hours and then poured into an ice-water mixture. The reaction mixture is extracted with petroleum ether which is then washed with cold 10 percent sodium bicarbonate solution followed by water. On drying, the mixture is evaporated in vacuo to ethyl α,3,5-trichloro-4-cyclohexylphenylacetate.

EXAMPLE 38

When the procedures of Examples 36 and 37 are followed but ethyl 3-chloro-4-cyclohexylphenylglycolate and ethyl 3,5-dichloro-4-cyclohexylphenylglycolate are replaced by the dl, *d* and *l* glycolates of this invention, then the corresponding dl, *d* and *l*α-chloroacetate products are prepared. A representative list of the compounds obtained are shown in Table I, below.

TABLE I

ethyl α-chloro-3,5-ditrifluoromethyl-4-cyclohexylphenylacetate
ethyl α,3-dichloro-4-cyclopentylphenylacetate
ethyl α-chloro-3-bromo-4-cyclopentylphenylacetate
ethyl α,3-dichloro-4-cycloheptylphenylacetate
ethyl α-chloro-3-bromo-4-cycloheptylphenylacetate
ethyl α-chloro-3-cyano-4-cyclohexylphenylacetate
benzyl α-chloro-3-cyano-4-cyclohexylphenylacetate
ethyl α-chloro-3-trifluoromethyl 4-cyclohexylphenylacetate
ethyl α-chloro-3-dimethylamino-4-cyclohexylphenylacetate
ethyl α-chloro-3-fluoro-4-cyclohexylphenylacetate
ethyl α-chloro-3-hydroxy-4-cyclohexylphenylacetate
ethyl α-chloro-3-methoxy-4-cyclohexylphenylacetate
ethyl α-chloro-3-bromo-4-cyclohexylphenylacetate
ethyl α-chloro-3-acetyl-4-cyclohexylphenylacetate
ethyl α-chloro-3,2′-dimethyl-4-cyclohexylphenylacetate
ethyl α-chloro-3-methyl-4-cyclohexylphenylacetate
ethyl α-chloro-3-nitro-5-methyl-4-cyclohexylphenylacetate
ethyl α-chloro-3-nitro-5-fluoro-4-cyclohexylphenylacetate
ethyl α,3-dichloro-5-nitro-4-cyclohexylphenylacetate
ethyl α-chloro-3-nitro-5-bromo-4-cyclohexylphenylacetate
ethyl α-chloro-3-nitro-5-trifluoromethyl-4-cyclohexylphenylacetate
ethyl α-chloro-3-nitro-3-amino-5-cyano-4-cyclohexylphenylacetate
ethyl α,3-dichloro-5-dimethylamino-4-cyclohexylphenylacetate
ethyl α,3-dichloro-5-cyano-4-cyclohexylphenylacetate
benzyl α,3-dichloro-5-cyano-4-cyclohexylphenylacetate
ethyl α,3-dichloro-5-fluoro-4-cyclohexylphenylacetate
ethyl α,3-dichloro-5-trifluoromethyl-4-cyclohexylphenylacetate
ethyl α,3-dichloro-5-methyl-4-cyclohexylphenylacetate
ethyl α,3-dichloro-5-methylsulfonyl-4-cyclohexylphenylacetate
ethyl α,3-dichloro-5-iodo-4-cyclohexylphenylacetate
ethyl α,3-dichloro-5-fluoro-4-cyclohexylphenylacetate
ethyl α,3-dichloro-5-methoxy-4-cyclohexylphenylacetate
ethyl α,3-dichloro-5-methyl-4-cyclohexylphenylacetate
ethyl α,3-dichloro-5-bromo-4-cyclohexylphenylacetate
ethyl α-chloro-3-methyl-5-fluoro-4-cyclohexylphenylacetate
ethyl α-chloro-3-methyl-5-bromo-4-cyclohexylphenylacetate
ethyl α-chloro-3-methyl-5-trifluoromethyl-4-cyclohexylphenylacetate
ethyl α,3-dichloro-5-acetyl-4-cyclohexylphenylacetate
ethyl α-chloro-3-methyl-5-nitro-4-cyclohexylphenylacetate
ethyl α-chloro-3,5-difluoro-4-cyclohexylphenylacetate
ethyl α-chloro-3-cyano-5-fluoro-4-cyclohexylphenylacetate
benzyl α-chloro-3-cyano-5-fluoro-4-cyclohexylphenylacetate
ethyl α-chloro-3-bromo-5-fluoro-4-cyclohexylphenylacetate
ethyl α-chloro-3-acetyl-5-fluoro-4-cyclohexylphenylacetate
ethyl α-chloro-3-cyano-5-bromo-4-cyclohexylphenylacetate
benzyl α-chloro-3-cyano-5-bromo-4-cyclohexylphenylacetate
ethyl α-chloro-3,5-dibromo-4-cyclohexylphenylacetate
ethyl α-chloro-3-acetyl-5-bromo-4-cyclohexylphenylacetate
ethyl α-chloro-3-fluoro-5-trifluoromethyl-4-cyclohexylphenylacetate
ethyl α-chloro-3-cyano-5-trifluoromethyl-4-cyclohexylphenylacetate
ethyl α-chloro-3-dimethylamino-5-trifluoromethyl-4-cyclohexylphenylacetate
ethyl α-chloro-3-bromo-5-trifluoromethyl-4-cyclohexylphenylacetate
ethyl α-chloro-3-hydroxy-5-trifluoromethyl-4-cyclohexylphenylacetate
ethyl α-chloro-3-acetyl-5-trifluoromethyl-4-cyclohexylphenylacetate

ethyl α-chloro-3,5-ditrifluoromethyl-4-cyclohexylphenylacetate
ethyl α,3,5-trichloro-4-cyclopentylphenylacetate
ethyl α,3,5-trichloro-4-cycloheptylphenylacetate
methyl α,3-dichloro-4-cyclohexylphenylacetate
methyl α,3,5-trichloro-4-cyclohexylphenylacetate
propyl α,3-dichloro-4-cyclohexylphenylacetate
propyl α,3,5-trichloro-4-cyclohexylphenylacetate
i-propyl α,3-dichloro-4-cyclohexylphenylacetate
i-propyl α,3,5-trichloro-**-cyclohexylphenylacetate**
t-butyl α,3-dichloro-4-cyclohexylphenylacetate
t-butyl α,3,5-trichloro-4-cyclohexylphenylacetate
ethyl α,3-dichloro-4-(2′-methylcyclopentyl)phenylacetate
ethyl α,3,5-trichloro-4-(2′-methylcyclopentyl)phenylacetate
ethyl α,3-dichloro-4-(2′-methylcyclohexyl)phenylacetate
ethyl α,3,5-trichloro-4-(2′-methylcyclohexyl)phenylacetate
ethyl α,3-dichloro-4-(2′-methylcycloheptyl)phenylacetate
ethyl α,3,5-trichloro-4-(2′-methylcycloheptyl)phenylacetate
ethyl α,3-dichloro-4-(3′-methylcyclohexyl)phenylacetate
ethyl α,3,5-trichloro-4-(3′-methylcyclohexyl)phenylacetate
ethyl α, 3-dichloro-4-(4′-methylcyclohexyl)phenylacetate
ethyl α,3,5-trichloro-4-(4′-methylcyclohexyl)phenylacetate
ethyl α,3-dichloro-5-fluoro-(2′-methylcyclohexyl)-phenylacetate
ethyl α-chloro-3-fluoro-5-bromo-(2′-methylcyclohexyl)phenylacetate
ethyl α,3-dichloro-5-cyano-(2′-methylcyclohexyl)-phenylacetate
ethyl α,3-dichloro-5-trifluoromethyl-(4′-methylcyclohexyl)phenylacetate
ethyl α,3-dichloro-5-bromo-(4′-methylcyclohexyl)-phenylacetate
ethyl α-chloro-3-fluoro-5-trifluoromethyl-(4′-methylcyclcohexyl)phenylacetate
ethyl α,3,5-trichloro-(4′-methylcyclohexyl)phenylacetate
ethyl α-chloro-3-nitro-4-cyclopentylphenylacetate
ethyl α-chloro-3-nitro-4-cycloheptylphenylacetate
ethyl α-chloro-3,5-dinitro-4-cyclohexylphenylacetate
ethyl α-chloro-3,5-dinitro-4-cyclopentylphenylacetate
ethyl α-chloro-3,5-dinitro-4-cycloheptylphenylacetate
ethyl α,3-dichloro-5-nitro-4-cyclopentylphenylacetate
ethyl α-chloro-3-dimethylamino-5-nitro-4-cyclohexylphenylacetate
ethyl α-chloro-3-methoxy-5-nitro-4-cyclohexylphenylacetate
ethyl α-chloro-3-iodo-5-nitro-4-cyclohexylphenylacetate
ethyl α-chloro-3-mercapto-5-nitro-4-cyclohexylphenylacetate
ethyl α-chloro-3-methylthio-5-nitro-4-cyclohexylphenylacetate
ethyl α-chloro-3-acetylthio-5-nitro-4-cyclohexylphenylacetate
ethyl α-chloro-3-acetyloxy-5-nitro-4-cyclohexylphenylacetate
ethyl α-chloro-3-acetylamino-5-nitro-4-cyclohexylphenylacetate
ethyl α-chloro-3-methylsulfonyl-5-nitro-4-cyclohexylphenylacetate
ethyl α-chloro-3-trifluoromethyl-5-methylsulfonyl-4-cyclohexylphenylacetate
ethyl α-chloro-3-nitro-5-methylsulfonyl-4-cyclohexylphenylacetate
ethyl α-chloro-3-bromo-5-methylsulfonyl-4-cyclohexylphenylacetate
ethyl α,3-dichloro-5-methylsulfonyl-4-cyclohexylphenylacetate
ethyl α-chloro-3-methylsulfinyl-4-cyclohexylphenylacetate
ethyl α-chloro-3-methylsulfonyl-4-cyclohexylphenylacetate
ethyl α-chloro-3-iodo-4-cyclohexylphenylacetate
ethyl α-chloro-3-mercapto-4-cyclohexylphenylacetate
ethyl α,3-dichloro-5-iodo-4-cyclohexylphenylacetate
ethyl α,3-dichloro-5-mercapto-4-cyclohexylphenylacetate
ethyl α-chloro-3-iodo-5-fluoro-4-cyclohexylphenylacetate
ethyl α-chloro-3-mercapto-5-fluoro-4-cyclohexylphenylacetate
ethyl α-chloro-3-iodo-5-bromo-4-cyclohexylphenylacetate
ethyl α-chloro-3-iodo-5-acetyl-4-cyclohexylphenylacetate
ethyl α-chloro-3-iodo-5-methylsulfonyl-4-cyclohexylphenylacetate
ethyl α-chloro-3-nitro-4-(2′-methylcyclopentyl)phenylacetate
ethyl α-chloro-3-nitro-4-(2′-methylcycloheptyl)phenylacetate
ethyl α-chloro-3-nitro-4-(2′-methylcyclohexyl)phenylacetate
ethyl α-chloro-3-nitro-4-(3′-methylcyclohexyl)phenylacetate
ethyl α-chloro-3-nitro-4-(4′-methylcyclohexyl)phenylacetate
ethyl α-chloro-3,5-dinitro-4-(4′-methylcyclohexyl)-phenylacetate

EXAMPLE 39

When the procedures of Examples 36–37 are followed but ethyl 3-chloro-4-cyclohexylphenylglycolate and ethyl 3,5-dichloro-4-cyclohexylphenylglycolate are replaced by amides of Table II, Example 35 then the products obtained are shown in Table I, below.

N-methyl-3-chloro-4-cyclohexylphenylacetamide
N,N-dimethyl-3-chloro-4-cyclohexylphenylacetamide
N-isoprop-α,3-dichloro-4-cyclohexylphenylacetamide
N,N-diethyl-α,3-dichloro-4-cyclohexylphenylacetamide
N-methyl-N-ethyl-α,3-dichloro-4-cyclohexylphenylacetamide
N-t-butyl-α,3-dichloro-4-cyclohexylphenylacetamide

N-cyclopropyl-α,3-dichloro-4-cyclohexylphenylacetamide
N,N-pentamethylene-α,3-dichloro-4-cyclohexylphenylacetamide
N,N-oxydiethylene-α,3-dichloro-4-cyclohexylphenylacetamide
N,N-methylaminodiethylene-α,3-dichloro-4-cyclohexylphenylacetamide
N,N-methylaminoethylenetrimethylene-α,3-dichloro-4-cyclohexylphenylacetamide
N,N-thiotrimethylene-α,3-dichloro-4-cyclohexylphenylacetamide

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

EXAMPLE 40

α,3-Dichloro-4-cyclohexylphenylacetic acid

A mixture of 52.5 g. (0.167 moles) of the ethyl ,3-dichloro-4-cyclohexylphenylacetate and 160 ml. of glacial acetic acid containing 40 ml. of 37 percent 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 icecold water (100 ml. total), dried over sodium sulfate and filtered. The hexane is removed to give α,3-dichloro-4-cyclohexylphenylacetic acid.

EXAMPLE 41

α,3,5-Trichloro-4-cyclohexylphenylacetic acid

A solution of 24.6 g. of ethyl α,3,5-trichloro-4-cyclohexylphenylacetate dissolved in 50 ml. of glacial acetic acid is heated for 24 hours with 75 ml. of concentrated hydrochloric acid. The solvent is then removed and the residue dissolved in 180 ml. of n-hexane. The hexane solution is then washed with cold water, dried over sodium sulfate and evaporated in vacuo to dryness. The residue is then triturated with n-hexane and filtered. The filtrate is then concentrated in vacuo to obtain α,3,5-trichloro-4-cyclohexylphenylacetic acid.

EXAMPLE 42

When the procedures of Examples 40 – 41 are followed but ethyl α,3-dichloro-4-cyclohexylphenylacetate and α,3,5-trichloro-4-cyclohexylphenylacetate are replaced by the dl, *d* and *l* α-chloroacetates of this invention, then the corresponding dl, *d* and *l* α-chloroacetic acids are prepared. A representative list of the products obtained are shown in Table I, below.

Table I

α-chloro-3,5-ditrifluoromethyl-4-cyclohexylphenylacetic acid
α-,3-dichloro-4-cyclopentylphenylacetic acid
α-chloro-3-bromo-4-cyclopentylphenylacetic acid
α,3-dichloro-4-cycloheptylphenylacetic acid
α-chloro-3-bromo-4-cycloheptylphenylacetic acid
α-chloro-3-cyano-4-cyclohexylphenylacetic acid
α-chloro-3-cyano-4-cyclohexylphenylacetic acid
α-chloro-3-trifluoromethyl-4-cyclohexylphenylacetic acid
α-chloro-3-dimethylamino-4-cyclohexylphenylacetic acid
α-chloro-3-fluoro-4-cyclohexylphenylacetic acid
α-chloro-3-hydroxy-4-cyclohexylphenylacetic acid
α-chloro-3-methoxy-4-cyclohexylphenylacetic acid
α-chloro-4-bromo-4-cyclohexylphenylacetic acid
α-chloro-3-acetyl-4-cyclohexylphenylacetic acid
α-chloro-3,2′-dimethyl-4-cyclohexylphenylacetic acid
α-chloro-3-methyl-4-cyclohexylphenylacetic acid
α-chloro-3-nitro-5-methyl-4-cyclohexylphenylacetic acid
α-chloro-3-nitro-5-fluoro-4-cyclohexylphenylacetic acid
α,3-dichloro-5-nitro-4-cyclohexylphenylacetic acid
α-chloro-3-nitro-5-bromo-4-cyclohexylphenylacetic acid
α-chloro-3-nitro-5-trifluoromethyl-4-cyclohexylphenylacetic acid
α-chloro-3-nitro-3-amino-5-cyano-4-cyclohexylphenylacetic acid
α,3-dichloro-5-dimethylamino-4-cyclohexylphenylacetic acid
α,3-dichloro-5-cyano-4-cyclohexylphenylacetic acid
α,3-dichloro-5-cyano-4-cyclohexylphenylacetic acid
α,3-dichloro-5-fluoro-4-cyclohexylphenylacetic acid
α,3-dichloro-5-trifluoromethyl-4-cyclohexylphenylacetic acid
α,3-dichloro-5-methyl-4-cyclohexylphenylacetic acid
α,3-dichloro-5-methylsulfonyl-4-cyclohexylphenylacetic acid
α,3-dichloro-5-iodo-4-cyclohexylphenylacetic acid
α,3-dichloro-5-fluoro-4-cyclohexylphenylacetic acid
α,3-dichloro-5-methoxy-4-cyclohexylphenylacetic acid
α,3-dichloro-5-methyl-4-cyclohexylphenylacetic acid
α,3-dichloro-5-bromo-4-cyclohexylphenylacetic acid
α-chloro-3-methyl-5-fluoro-4-cyclohexylphenylacetic acid
α-chloro-3-methyl-5-bromo-4-cyclohexylphenylacetic acid
α-chloro-3-methyl-5-trifluoromethyl-4-cyclohexylphenylacetic acid
α,3-dichloro-5-acetyl-4-cyclohexylphenylacetic acid
α-chloro-3-methyl-5-nitro-4-cyclohexylphenylacetic acid
α-chloro-3,5-difluoro-4-cyclohexylphenylacetic acid
α-chloro-3-cyano-5-fluoro-4-cyclohexylphenylacetic acid
α-chloro-3-cyano-5-fluoro-4-cyclohexylphenylacetic acid
α-chloro-3-bromo-5-fluoro-4-cyclohexylphenylacetic acid
α-chloro-3-acetyl-5-fluoro-4-cyclohexylphenylacetic acid
α-chloro-3-cyano-5-bromo-4-cyclohexylphenylacetic acid
α-chloro-3-cyano-5-bromo-4-cyclohexylphenylacetic acid
α-chloro-3,5-dibromo-4-cyclohexylphenylacetic acid
α-chloro-3-acetyl-5-bromo-4-cyclohexylphenylacetic acid

α-chloro-3-fluoro-5-trifluoromethyl-4-cyclohexylphenylacetic acid
α-chloro-3-cyano-5-trifluoromethyl-4-cyclohexylphenylacetic acid
α-chloro-3-dimethylamino-5-trifluormethyl-4-cyclohexylphenylacetic acid
α-chloro-3-bromo-5-trifluoromethyl-4-cyclohexylphenylacetic acid
α-chloro-3-hydroxy-5-trifluoromethyl-4-cyclohexylphenylacetic acid
α-chloro-3-acetyl-5-trifluoromethyl-4-cyclohexylphenylacetic acid
α-chloro-3,5-ditrifluoromethyl-4-cyclohexylphenylacetic acid
α,3,5-trichloro-4-cyclopentylphenylacetic acid
α,3-dichloro-4-cyclohexylphenylacetic acid
α3,5-trichloro-4-cyclohexylphenylacetic acid
α,3-dichloro-4-(2′-methylcyclopentyl)phenylacetic acid
α,3,5-trichloro-4-(2′-methylcyclopentyl)phenylacetic acid
α,3-dichloro-4-(2′-methylcyclohexyl)phenylacetic acid
α,3,5-trichloro-4-(2′-methylcyclohexyl)phenylacetic acid
α,3-dichloro-4-(2′-methylcycloheptyl)phenylacetic acid
α,3,5-trichloro-4-(2′-methylcycloheptyl)phenylacetic acid
α,3-dichloro-4-(3′-methylcyclohexyl)phenylacetic acid
α,3,5-trichloro-4-(3′-methylcyclohexyl)phenylacetic acid
α,3-dichloro-4-(4′-methylcyclohexyl)phenylacetic acid
α,3,5-trichloro-4-(4′-methylcyclohexyl)phenylacetic acid
α,3-dichloro-5-fluoro-(2′-methylcyclohexyl)-phenylacetic acid
α-chloro-3-fluoro-5-bromo-(2′-methycyclohexyl)-phenylacetic acid
α,3-dichloro-5-cyano-(2′-methylcyclohexyl)-phenylacetic acid
α,3-dichloro-5-trifluoromethyl-(4′-methylcyclohexyl)phenylacetic acid
α,3-dichloro-5-bromo-(4′-methylcyclohexyl)-phenylacetic acid
α-chloro-3-fluoro-5-trifluoromethyl-(4′-methylcyclohexyl)phenylacetic acid
α,3,5-trichloro-(4′-methylcyclohexyl)phenylacetic acid
α-chloro-3-nitro-4-cyclopentylphenylacetic acid
α-chloro-3-nitro-4-cycloheptylphenylacetic acid
α-chloro-3,5-dinitro-4-cyclohexylphenylacetic acid
α-chloro-3,5-dinitro-4-cyclopentylphenylacetic acid
α-chloro-3,5-dinitro-4-cycloheptylphenylacetic acid
α,3-dichloro-5-nitro-4-cyclopentylphenylacetic acid
α-chloro-3-dimethylamino-5-nitro-4-cyclohexylphenylacetic acid
α-chloro-3-methoxy-5-nitro-4-cyclohexylphenylacetic acid
α-chloro-3-iodo-5-nitro-4-cyclohexylphenylacetic acid
α-chloro-3-mercapto-5-nitro-4-cyclohexylphenylacetic acid
α-chloro-3-methylthio-5-nitro-4-cyclohexylphenylacetic acid
α-chloro-3-acetylthio-5-nitro-4-cyclohexylphenylacetic acid
α-chloro-3-acetyloxy-5-nitro-4-cyclohexylphenylacetic acid
α-chloro-3-acetylamino-5-nitro-4-cyclohexylphenylacetic acid
α-chloro-3-methylsulfonyl-5-nitro-4-cyclohexylphenylacetic acid
α-chloro-3-trifluoromethyl-5-methylsulfonyl-4-cyclohexylphenylacetic acid
α-chloro-3-nitro-5-methylsulfonyl-4-cyclohexylphenylacetic acid
α-chloro-3-bromo-5-methylsulfonyl-4-cyclohexylphenylacetic acid
α,3-dichloro-5-methylsulfonyl-4-cyclohexylphenylacetic acid
α-chloro-3-methylsulfinyl-4-cyclohexylphenylacetic acid
α-chloro-3-methylsulfonyl-4-cyclohexylphenylacetic acid
α-chloro-3-iodo-4-cyclohexylphenylacetic acid
α-chloro-3-mercapto-4-cyclohexylphenylacetic acid
α,3-dichloro-5-iodo-4-cyclohexylphenylacetic acid
α,3-dichloro-5-mercapto-4-cyclohexylphenylacetic acid
α-chloro-3-iodo-5-fluoro-4-cyclohexylphenylacetic acid
α-chloro-3-mercapto-5-fluoro-4-cyclohexylphenylacetic acid
α-chloro-3-iodo-5-bromo-4-cyclohexylphenylacetic acid
α-chloro-3-iodo-5-acetyl-4-cyclohexylphenylacetic acid
α-chloro-3-iodo-5-methylsulfonyl-4-cyclohexylphenylacetic acid
α-chloro-3-nitro-4-(2′-methylcyclopentyl)phenylacetic acid
α-chloro-3-nitro-4-(2′-methylcycloheptyl)phenylacetic acid
α-chloro-3-nitro-4-(2′-methylcyclohexyl)phenylacetic acid
α-chloro-3-nitro-4-(3′-methylcyclohexyl)phenylacetic acid
α-chloro-3-nitro-4-(4′-methylcyclohexyl)phenylacetic acid
α-chloro-3,5-dinitro-4-(4′-methylcyclohexyl)-phenylacetic acid

EXAMPLE 43

α,3-Dichloro-4-cyclohexylphenylacetic acid, sodium salt

A solution of 12.4 g. of sodium bicarbonate in 135 ml. water is added dropwise to a stirred solution of 47.1 g. (0.164 moles) of α,3-dichloro-4-cyclohexylphenylacetic 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,3-dichloro-4-cyclohexylphenylacetic acid, sodium salt.

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

TABLE I

sodium hydroxide
potassium hydroxide
calcium hydroxide
potassium carbonate
magnesium bicarbonate

TABLE II

α,3-dichloro-4-cyclohexylphenylacetic acid, sodium salt
α,3-dichloro-4-cyclohexylphenylacetic acid, potassium salt
α,3-dichloro-4-cyclohexylphenylacetic acid, calcium salt
α,3-dichloro-4-cyclohexylphenylacetic acid, magnesium salt

When α,3-dichloro-4-cyclohexylphenylacetic acid is replaced by *d* α,3-dichloro-4-cyclohexylphenylacetic acid and *l* α,3-dichloro-4-cyclohexylphenylacetic acid then the products prepared are:

d α,3-dichloro-4-cyclohexylphenylacetic acid, sodium salt
d α,3-dichloro-4-cyclohexylphenylacetic acid, potassium salt
d α,3-dichloro-4-cyclohexylphenylacetic acid, calcium salt
d α,3-dichloro-4-cyclohexylphenylacetic acid, magnesium salt
l α,3-dichloro-4-cyclohexylphenylacetic acid, sodium salt
l α,3-dichloro-4-cyclohexylphenylacetic acid, potassium salt
l α,3-dichloro-4-cyclohexylphenylacetic acid, calcium salt
l α,3-dichloro-4-cyclohexylphenylacetic acid, magnesium salt

When the dl, *d* and *l* α-chloroacetic acid compounds of this invention are used in the above reaction, the corresponding salt is prepared.

EXAMPLE 44

α,3-Dichloro-4-cyclohexylphenylacetic acid, diethylammonium salt

Anhydrous diethylamine (0.11 moles) is added dropwise to a stirred solution of α,3-dichloro-4-cyclohexylphenylacetic 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,3-dichloro-4-cyclohexylphenylacetic acid, diethylammonium salt.

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

TABLE I

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

TABLE II

α,3-dichloro-4-cyclohexylphenylacetic acid, dimethylammonium salt
α,3-dichloro-4-cyclohexylphenylacetic acid, β-hydroxyethylammonium salt
α,3-dichloro-4-cyclohexylphenylacetic acid, piperazinium salt
α,3acid, piperidinium salt
α,3-dichloro-4-cyclohexylphenylacetic acid, α-methylbenzylammonium salt
α,3-dichloro-4-cyclohexylphenylacetic acid, cyclohexylammonium salt
α,3-dichloro-4-cyclohexylphenylacetic acid, triethylammonium salt
α,3-dichloro-4-cyclohexylphenylacetic acid, phenethylammonium salt

EXAMPLE 45

N-isopropyl α,3-Dichloro-4-cyclohexylphenylacetamide

A mixture of 5 g. (0.016 moles) of ethyl α,3-dichloro-4-cyclohexylphenylacetate and 5.5 ml. of anhydrous isopropylamine are stirred over Linde 4A molecular sieve for 16 hours at room temperature. The reaction mixture is filtered and excess isopropylamine is removed in vacuo. The residue is taken up in ether and washed three times with 15 ml. of 10 percent 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,3-dichloro-4-cyclohexylphenylacetamide.

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

Table I

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

Table II

N,N-diethyl-α,3-dichloro-4-cyclohexylphenylacetamide
N-methyl-N-ethyl-α,3-dichloro-4-cyclohexylphenylacetamide
N-t-butyl-α,3-dichloro-4-cyclohexylphenylacetamide
N-cyclopropyl-α,3-dichloro-4-cyclohexylphenylacetamide N,N-pentamethylene-α,3-dichloro-4-cyclohexylphenylacetamide
N,N-oxydiethylene-α,3-dichloro-4-cyclohexylphenylacetamide
N,N-methylaminodiethylene-α,3-dichloro-4-cyclohexylphenylacetamide
N,N-methylaminoethylenetrimethylene-α,3-dichloro-4-cyclohexylphenylacetamide
N,N-thiotrimethylene-α,3-dichloro-4-cyclohexylphenylacetamide

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,3-dichloro-4-cyclohexylphenylacetamide, N-methyl-α,3-dichloro-4-cyclohexylphenylacetamide or N,N-dimethyl-α,3-dichloro-4-cyclohexylphenylacetamide.

When the dl, *d* or *l* α-chloroacetates of this invention are used in the above reaction, then the corresponding amide is prepared.

EXAMPLE 46

Ethyl α-bromo-3-chloro-4-cyclohexylphenylacetate

To 15.0 g. (0.0476 moles) of ethyl 3-chloro-4-cyclohexylphenylglycolate 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-3-chloro-4-cyclohexylphenylacetate.

When ethyl 3-chloro-4-cyclohexylphenylglycolate in the above procedure is replaced by *d* ethyl 3-chloro-4-cyclohexylphenylglycolate, *l* ethyl 3-chloro-4-cyclohexylphenylglycolate or N-isopropyl 3-chloro-4-cyclohexylphenylglycolamide, then the products prepared are *d* ethyl α-bromo-3-chloro-4-cyclohexyl-phenylglycolate, *l* ethyl α-bromo-3-chloro-4-cyclohexylphenylglycolate or N-isopropyl α-bromo-3-chloro-4cyclohexylphenylglycolamide.

When the above procedure is followed using the various glycolates and glycolamides of this invention, then the corresponding α-bromacetates and α-bromacetamides are prepared.

EXAMPLE 47

When the α-bromacetates of Example **46** are hydrolyzed according to the procedures of Examples 40–42, then the corresponding dl, *d* and *l* α-bromo-3-chloro-4-cyclohexylphenylacetic acid compounds and the various α-bromoacetic acids are prepared.

EXAMPLE 48

When the α-bromacetic acid compounds are reacted according to the procedures of Examples 43–44, then the corresponding α-bromoacetic acid salts are prepared.

EXAMPLE 49

Ethyl α-fluoro-3-chloro-4-cyclohexylphenylacetate

A mixture of 118 g. (0.33 moles) of ethyl α-bromo-3-chloro-4-cyclohexylphenylacetate 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-3-chloro-4-cyclohexyl-phenylacetate.

When ethyl α-bromo-3-chloro-4-cyclohexylphenylacetate in the above procedure is replaced by *d* ethyl α-bromo-3-chloro-4-cyclohexylphenylacetate, L ethyl α-bromo-3-chloro-4-cyclohexylphenylacetate or N-isopropyl α-bromo-3-chloro-4-cyclohexylphenylacetamide, then the products prepared are *d* ethyl α-fluoro-3-chloro-4-cyclohexylphenylacetate, l ethyl α-fluoro-3-chloro-4-cyclohexylphenylacetate or N-isopropyl α-fluoro-3,5-dichloro-4-cyclohexylphenylacetamide.

When the above procedure is followed using the various α-bromoacetates and α-bromoacetamides of this invention, then the corresponding α-fluoroacetates and α-fluoroacetamides are prepared.

EXAMPLE 50

When the α-fluoroacetates of Example 49 are hydrolyzed according to the procedures of Examples 40–42, then the corresponding α-fluoro-3-chloro-4-cyclohexylphenylacetic acid compound and the various α-fluoroacetic acids are prepared.

EXAMPLE 51

When the α-fluoroacetic acid compounds are reacted according to the procedures of Examples 43–44, then the corresponding α-fluoroacetic acid salts are prepared.

EXAMPLE 52

Ethyl α-iodo-3-chloro-4-cyclohexylphenylacetate

A mixture of 40.5 g. (0.1 moles) of ethyl α-bromo-3-chloro-4-cyclohexylphenylacetate and 150 g. 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-3- chloro-4-cyclohexylphenylacetate.

When ethyl α-bromo-3-chloro-4-cyclohexylphenylacetate in the above procedure is replaced by *d* ethyl α-bromo-3-chloro-4-cyclohexylphenyl-acetate, *l* ethyl α-bromo-3-chloro-4-cyclohexylphenylacetate or N-isopropyl α-bromo-3,5-dichloro-4-cyclohexylphenylacetamide, then the products prepared are *d* ethyl α-iodo-3-chloro-4-cyclohexylphenylacetate, *l* ethyl α-iodo-3-chloro-4-cyclohexylphenylacetate or N-isopropyl α-iodo-3-chloro-4-cyclohexylphenylacetamide.

When the above procedure is followed using the various α-bromoacetates and α-bromoacetamides of this invention then the corresponding α-iodoacetates and α-iodoacetamides are prepared.

EXAMPLE 53

When the α-iodoacetates of Example 52 are hydrolyzed according to the procedures of Examples 40–42, then the corresponding α-iodo-3-chloro-4-cyclohexylphenylacetic acid compound and the various α-iodoacetic acids are prepared.

EXAMPLE 54

When the α-iodoacetic acid compounds are reacted according to the procedures of Examples 43–44, then the corresponding α-iodoacetic acid salts are prepared.

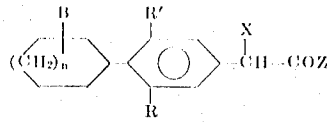
EXAMPLE 55

When the procedures of Examples 46–50 are followed but the starting materials used are those below, then the corresponding products are prepared.

STARTING MATERIAL	PRODUCT	EXAMPLE
3-fluoro-4-cyclohexylphenylglycolate	α-bromo-3-fluoro-4-cyclohexylphenylacetic acid	46,47
3-bromo-4-cyclohexylphenylglycolate	α-dibromo-4-cyclohexylphenylacetic acid	46,47
3-nitro-4-cyclohexylphenylglycolate	αbromo-3-nitro-4-cyclohexylphenylacetic acid	46,47
3-trifluoromethyl-4-cyclohexylphenylglycolate	α-bromo-3-trifluoromethyl-4-cyclohexylphenylacetic acid	46,47
3-cyano-4-cyclohexylphenylglycolate	α-bromo-3-cyano-4-cyclohexylphenylacetic acid	46,47
3-methylsulfonyl-4-cyclohexylphenylglycolate	α-bromo-3-methylsulfonyl-4-cyclohexylphenylacetic acid	46,47
3-chloro-5-fluoro-4-cyclohexylphenylglycolate	α-bromo-3-chloro-5-fluoro-4-cyclohexylphenylacetic acid	46,47
3,5-dichloro-4-cyclohexylphenylglycolate	α-bromo-3,5-dichloro-4-cyclohexylphenylacetic acid	46,47
3-chloro-5-bromo-4-cyclohexylphenylglycolate	α-bromo-3-chloro-5-bromo-4-cyclohexylphenylacetic acid	46,47
3-chloro-5-nitro-4-cyclohexylphenylglycolate	α-bromo-3-chloro-5-nitro-4-cyclohexylphenylacetic acid	46,47
3-chloro-5-trifluoromethyl-4-cyclohexylphenylglycolate	α-bromo-3-chloro-5-trifluoromethyl-4-cyclohexylphenylacetic acid	46,47
3-chloro-5-cyano-4-cyclohexylphenylglycolate	α-bromo-3-chloro-5-cyano-4-cyclohexylphenylacetic acid	46,47
3-chloro-5-methylsulfonyl-4-cyclohexylphenylglycolate	α-bromo-3-chloro-5-methylsulfonyl-4-cyclohexylphenylacetic acid	46,47
3-chloro-4-cyclopentylphenylglycolate	α-bromo-3-chloro-4-cyclopentylphenylacetic acid	46,47
3-nitro-4-cyclopentylphenylglycolate	α-bromo-3-nitro-4-cyclopentylphenylacetic acid	46,47
3,5-dichloro-4-cyclopentylphenylglycolate	α-bromo-3,5-dichloro-4-cyclopentylphenylacetic acid	46,47
3-chloro-5-nitro-4-cyclopentylphenylglycolate	-bromo-3-chloro-5-nitro-4-cyclopentylphenylacetic acid	46,47
3-chloro-4-cycloheptylphenylglycolate	-bromo-3-chloro-4-cycloheptylphenylacetic acid	46,47
3-nitro-4-cycloheptylphenylglycolate	-bromo-3-nitro-4-cycloheptylphenylacetic acid	46,47
3,5-dichloro-4-cycloheptylphenylglycolate	-bromo-3,5-dichloro-4-cycloheptylphenylacetic acid	46,47
3-chloro-5-nitro-4-cycloheptylphenylglycolate	-bromo-3-chloro-5-nitro-4-cycloheptylphenylacetic acid	46,47
3-fluoro-4-cyclohexylphenylglycolate	,3-difluoro-4-cyclohexylphenylacetic acid	49,50
3-bromo-4-cyclohexylphenylglycolate	-fluoro-3-bromo-4-cyclohexylphenylacetic acid	49,50
3-nitro-4-cyclohexylphenylglycolate	-fluoro-3-nitro-4-cyclohexylphenylacetic acid	49,50
3-trifluoromethyl-4-cyclohexylphenylglycolate	-fluoro-3-trifluoromethyl-4-cyclohexylphenylacetic acid	49,50
3-cyano-4-cyclohexylphenylglycolate	-fluoro-3-cyano-4-cyclohexylphenylacetic acid	49,50
3-methylsulfonyl-4-cyclohexylphenylglycolate	-fluoro-3-methylsulfonyl-4-cyclohexylphenylacetic acid	49,50
3-chloro-5-fluoro-4-cyclohexylphenylglycolate	-fluoro-3-chloro-5-fluoro-4-cyclohexylphenylacetic acid	49,50
3,5-dichloro-4-cyclohexylphenylglycolate	-fluoro-3,5-dichloro-4-cyclohexylphenylacetic acid	49,50
3-chloro-5-bromo-4-cyclohexylphenylglycolate	-fluoro-3-chloro-5-bromo-4-cyclohexylphenylacetic acid	49,50
3-chloro-5-trifluoromethyl-4-cyclohexylphenylglycolate	-fluoro-3-chloro-5-trifluoromethyl-4-cyclohexylphenylacetic acid	49,50
3-chloro-5-cyano-4-cyclohexylphenylglycolate	-fluoro-3-chloro-5-cyano-4-cyclohexylphenylacetic acid	49,50
3-chloro-5-methylsulfonyl-4-cyclohexylphenylglycolate	-fluoro-3-chloro-5-methylsulfonyl-4-cyclohexylphenylacetic acid	49,50
3-chloro-4-cyclopentylphenylglycolate	-fluoro-3-chloro-cyclopentylphenylacetic acid	49,50
3-nitro-4-cyclopentylphenylglycolate	-fluoro-3-nitro-4-cyclopentylphenylacetic acid	49,50
3,5-dichloro-4-cyclopentylphenylglycolate	-fluoro-3,4-dichloro-4-cyclopentylphenylacetic acid	49,50
3-chloro-5-nitro-4-cyclopentylphenylglycolate	-fluoro-3-chloro-5-nitro-4-cyclopentylphenylacetic acid	49,50
3-chloro-4-cycloheptylphenylglycolate	-fluoro-3-chloro-4-cycloheptylphenylacetic acid	49,50
3-nitro-4-cycloheptylphenylglycolate	-fluoro-3-nitro-4-cycloheptylphenylacetic acid	49,50
3,5-dichloro-4-cycloheptylphenylglycolate	-fluoro-3,5-dichloro-4-cycloheptylphenylacetic acid	49,50
3-chloro-5-nitro-4-cycloheptylphenylglycolate	-fluoro-3-chloro-5-nitro-4-cycloheptylphenylacetic acid	49,50

We claim:

1. A compound of the formula



where:

n is 0–2;

B is hydrogen or loweralkyl;

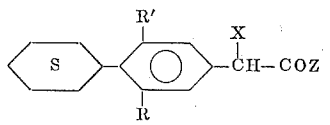
R is halo, nitro, loweralkylsulfonyl, trifluoromethyl or cyano;

R′ is fluoro, chloro, bromo, trifluoromethyl, cyano, nitro or loweralkylsulfonyl

X is halo;

Z is —OH, loweralkoxy, phenyl loweralkoxy, —OM where M is an alkali, alkaline earth or aluminum metal or an ammonium salt which is pharmaceutically acceptable.

2. A compound of the formula



where:

R is chloro, bromo, nitro, methylsulfonyl, trifluoromethyl or cyano;

R′ is chloro, bromo or nitro

X is fluoro, chloro or bromo; and

Z is —OH loweralkoxy, phenyl loweralkoxy or —OM where M is an alkali, alkaline earth or aluminum metal or an ammonium salt which is pharmaceutically acceptable.

3. A compound according to claim 2 which is dextrorotatory.

4. A compound according to claim 2 which is levorotatory.

5. A compound according to claim 2 of the formula

where:

R is chloro,
bromo,
nitro,
methylsulfonyl,
trifluoromethyl or cyano;

R′ is chloro,
bromo or
nitro.

6. A compound according to claim 5 which is dextrorotatory.

7. A compound according to claim 5 which is levorotatory.

8. A compound according to claim 5 where:
R is chloro and R′ is chloro thus forming α,3,5-trichloro-4-cyclohexylphenylacetic acid.

9. A compound according to claim 5 where:
R is bromo and R′ is chloro thus forming α,3-dichloro-5-bromo-4-cyclohexylphenylacetic acid.

10. A compound according to claim 5 where:
R is nitro and R′ is chloro thus forming α,3-dichloro-5-nitro-4-cyclohexylphenylacetic acid.

11. A compound according to claim 5 where:
R is methylsulfonyl and R′ is chloro thus forming α,3-dichloro-5-methylsulfonyl-4-cyclohexylphenylacetic acid.

12. A compound according to claim 5 where:
R is trifluoromethyl and R′ is chloro thus forming α,3-dichloro-5-trifluoromethyl-4-cyclohexylphenylacetic acid.

13. A compound according to claim 5 where:
R is cyano and R′ is chloro thus forming α,3-dichloro-5-cyano-4-cyclohexylphenylacetic acid.

14. A compound according to claim 5 where:
R is bromo and R′ is bromo thus forming α-chloro-3,5-dibromo-4-cyclohexylphenylacetic acid.

15. A compound according to claim 5 where:
R is nitro and R′is bromo thus forming α-chloro-3-bromo-5-nitro-4-cyclohexylphenylacetic acid.

16. A compound according to claim 5 where:
R is methylsulfonyl and R′ is bromo thus forming α-chloro-3-bromo-5-methylsulfonyl-4-cyclohexylphenylacetic acid.

17. A compound according to claim 5 where:
R is trifluoromethyl and R′ is bromo thus forming α-chloro-3-bromo-5-trifluoromethyl-4-cyclohexylphenylacetic acid.

18. A compound according to claim 5 where:
R is cyano and R′ is bromo thus forming α-chloro-3-bromo-5-cyano-4-cyclohexylphenylacetic acid.

19. A compound according to claim 5 where:
R is nitro and R′ is nitro thus forming α-chloro-3,5-dinitro-4-cyclohexylphenylacetic acid.

20. A compound according to claim 5 where:
R is methylsulfonyl and R′ is nitro thus forming α-chloro-3-methylsulfonyl 5-nitro-4-cyclohexylphenylacetic acid.

21. A compound according to claim 5 where:
R is trifluoromethyl and R′ is nitro thus forming α-chloro-3-nitro-5-trifluoromethyl-4-cyclohexylphenylacetic acid.

22. A compound according to claim 5 where:
R is cyano and R′ is nitro thus forming α-chloro-3-cyano-5-nitro-4-cyclohexylphenylacetic acid.

23. A compound according to claim 6 where:
R is chloro and R′ is chloro thus forming *d* α,3,5-trichloro-4-cyclohexylphenylacetic acid.

24. A compound according to claim 7 where:
R is chloro and R′ is chloro thus forming *l* α,3,5-trichloro-4-cyclohexylphenylacetic acid.

25. A compound according to claim 6 where:
R is bromo and R′ is chloro thus forming *d* α,3-dichloro-5-bromo-4-cyclohexylphenylacetic acid.

26. A compound according to claim 7 where:
R is bromo and R′ is chloro thus forming l α,3-dichloro-5-bromo-4-cyclohexylphenylacetic acid.

27. A compound according to claim 6 where:
R is nitro and R′ is chloro thus forming d α,3-dichloro-5-nitro-4-cyclohexylphenylacetic acid.

28. A compound according to claim 7 where:
R is nitro and R′ is chloro thus forming *l* α,3-dichloro-5-nitro-4-cyclohexylphenylacetic acid.

29. A compound according to claim 6 where:
R is methylsulfonyl and R′ is chloro thus forming *d* α,3-dichloro-5-methylsulfonyl-4-cyclohexylphenylacetic acid.

30. A compound according to claim 7 where:
R is methylsulfonyl and R′ is chloro thus forming l α,3-dichloro-5-methylsulfonyl-4-cyclohexylphenylacetic acid.

31. A compound according to claim 6 where:
R is trifluoromethyl and R′ is chloro thus forming *d* α,3-dichloro-5-trifluoromethyl-4-cyclohexylphenylacetic acid.

32. A compound according to claim 7 where:
R is trifluoromethyl and R′ is chloro thus forming *l* α,3-dichloro-5-trifluoromethyl-4-cyclohexylphenylacetic acid.

33. A compound according to claim 6 where:
R is cyano and R′ is chloro thus forming *d* α,3-dichloro-5-cyano-4-cyclohexylphenylacetic acid.

34. A compound according to claim 7 where:
R is cyano and R′ is chloro thus forming l α,3-dichloro-5-cyano-4-cyclohexylphenylacetic acid.

35. A compound according to claim 6 where:
R is bromo and R′ is bromo thus forming *d* α-chloro-3,5-dibromo-4-cyclohexylphenylacetic acid.

36. A compound according to claim 7 where:
R is bromo and R′ is bromo thus forming *l* α-chloro-3,5-dibromo-4-cyclohexylphenylacetic acid.

37. A compound according to claim 6 where:
R is trifluoromethyl and R′ is bromo thus forming *d* α-chloro-3-bromo-5-trifluoromethyl-4-cyclohexylphenylacetic acid.

38. A compound according to claim 7 where:
R is trifluoromethyl and R′ is bromo thus forming *l* α-chloro-3-bromo-5-trifluoromethyl-4-cyclohexyl-

phenylacetic acid.

39. A compound according to claim **8** which is the sodium salt.

40. A compound according to claim **8** which is the diethylammonium salt.

41. A compound according to claim **23** which is the sodium salt.

42. A compound according to claim **24** which is the diethylammonium salt.

* * * * *

UNITED STATES PATENT OFFICE

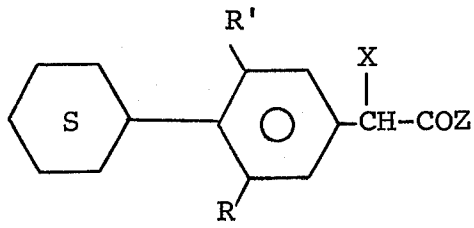
CERTIFICATE OF CORRECTION

Patent No. 3,852,323 Dated December 3, 1974

Inventor(s) Diamond et al.

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 74, lines 50-57, Insert the following formula:



Signed and Sealed this

ninth Day of *December 1975*

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents and Trademarks