PATENT SPECIFICATION (11) 1 590 169

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(19)

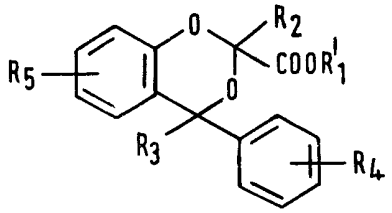
(54) 1,3-BENZODIOXINE DERIVATIVES, PROCESSES FOR PREPARING THEM AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(71) We, ROUSSEL-UCLAF, a French Body Corporate, of 35 Boulevard des Invalides, Paris 7 eme, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statements:—

This invention relates to 1,3 - benzodioxine derivatives, processes for preparing them and pharmaceutical compositions containing them.

The derivatives are pharmacologically active, and may be useful in medicine.

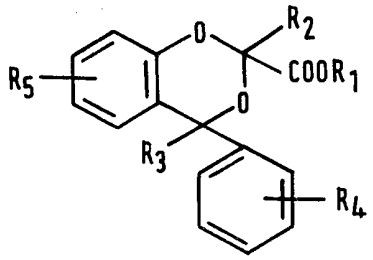
In one aspect this invention provides 1,3 - benzodioxine derivatives, which are compounds of the general formula:



(I')

(wherein R'_1 represents a hydrogen atom, an alkyl radical containing from 1 to 5 carbon atoms, a 2,3 - dihydroxypropyl radical, a (2,2 - dimethyl - 1,3 - dioxolan - 4 - yl) - methyl radical or a dialkylaminoalkyl radical of which the alkyl radicals contain from 1 to 4 carbon atoms; R_2 represents a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms; R_3 represents a hydrogen atom, an alkyl radical containing from 1 to 5 carbon atoms or a phenyl radical; and R_4 and R_5, which may be the same or different, each represent a hydrogen atom or a halogen atom) an alkali-metal, alkaline-earth metal, aluminium, ammonium and quaternary ammonium salts thereof where R'_1 represents a hydrogen atom; and, acid addition salts thereof where R'_1 represents a dialkylaminoalkyl radical.

This invention also provides 1,3 - benzodioxine derivatives, which are compounds of the general formula:



(I)

(wherein R_1 and R_2, which may be the same or different, each represent a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms; R_3 represents a hydrogen atom, an alkyl radical containing from 1 to 5 carbon atoms or a phenyl radical; and R_4 and R_5, which are the same or different, each represent a hydrogen atom or a halogen atom) and alkali-metal, alkaline-earth metal, aluminium, ammonium and quaternary ammonium salts thereof where R_1 represents a hydrogen atom.

Each compound of general formula I or I' has one or two asymetric carbon atoms—one at the 2-position of the benzodioxine ring and, depending on the nature of substituents R_3 and R_4, possibly one at the 4-position. Thus the 1—3 benzodioxine derivatives may consist of 2 or 4 stereoisomers, existing in the form of one or two pairs of enantiomers respectively. Unless stated otherwise, references herein to a benzodioxine derivative of this invention extend to that derivative in the form of any one stereoisomer or in the form of a mixture between two or more stereoisomers, and thus extend to mixtures of racemic and optically-active forms in any proportion.

The mixtures preferably consist of two optical enantiomers, or two optically active diastereoisomers, in any proportion.

Where the compounds of general formula I and I' contain an alkyl radical containing from 1 to 5 carbon atoms this is generally a methyl, ethyl, *n*-propyl, *i* - propyl, *n* - butyl, *i* - butyl, *t* - butyl or *n* - pentyl radical. Where they contain a halogen atom, this is generally a chlorine, bromine or fluorine atom.

The alkali-metal or alkaline-earth metal salts of the compounds of general formula I or I', wherein R_1 or R_1' represents a hydrogen atom, are conveniently sodium, potassium, lithium or calcium salts. The quaternary ammonium salts may be formed with amines commonly used for such purposes, for example, with monoalkylamines such as methylamine, ethylamine and propylamine; with dialkylamines such as dimethylamine, diethylamine and di - *n* - propylamine and with trialkylamines such as triethylamine; they may also be formed with piperidine, morpholine, piperazine and pyrrolidine.

The acid addition salts of the compounds of general formula I', wherein R_1' represents a dialkylaminoalkyl radical are conveniently formed with inorganic acids such as hydrochloric, hydrobromic, hydriodic, nitric, sulphuric or phosphoric acid, organic acids such as acetic, maleic, fumaric, succinic or tartaric acid, alkylmonosulphonic acids such as methanesulphonic acid, ethanesulphonic acid or propanesulphonic acid, and alkyldisulphonic acids such as α,β - ethanedisulphonic acid.

A preferred group of 1,3 - benzodioxine derivatives of the invention are those of general formula I wherein R_1 and R_2, which may be the same or different, each represent a hydrogen atom or a methyl radical, R_3 represents a hydrogen atom, a methyl radical or a phenyl radical, R_4 represents a hydrogen atom and R_5 represents a hydrogen atom or a chlorine atom; and where possible their alkali-metal, alkaline-earth metal, aluminium, ammonium and quaternary ammonium salts. Of these, the derivatives wherein R_2 represents a hydrogen atom and R_5 represents a chlorine atom are especially preferred.

The 1,3 - benzodioxine derivatives of the invention that are named in the Examples hereinafter are particularly preferred (in the form of one stereoisomer or a mixture of stereoisomers), especially the following:—

6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid;

6 - chloro - 2,4 - dimethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid;

6 - chloro - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid;

6 - chloro - 4,4 - diphenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid;

4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid;

methyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate;

methyl 6 - chloro - 4,4 - diphenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate;

ethyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate;

sodium 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate;

methyl 6 - chloro - 4 - (3 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate;

6 - chloro - 4 - (3 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid;

methyl 6 - chloro - 4 - [(1 - methyl)ethyl] - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate;

methyl 6 - chloro - 4 - [(1,1 - dimethyl)ethyl] - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate;

methyl 6 - fluoro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate;

methyl 6 - chloro - 4 - ethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate;

methyl 6 - chloro - 4 - (4 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

As stated before, the benzodioxine derivatives of the invention may consist of two pairs of enantiomers. In the Examples, a racemic mixture of one pair of enantiomers of a derivative is named isomer A, and a racemic mixture of the other pair is named isomer B; the isomers are distinguished by the differences in their physical properties, as set out in the Examples. In cases where the isomers are thus distinguished isomer A is the preferred isomer.

The isomer A of the following compounds, as obtained in the Examples, is especially preferred:

methyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate;

methyl 6 - chloro - 4 - (3 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate;

ethyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate;

6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid;

6 - chloro - 2,4 - dimethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid;

sodium 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate and

6 - chloro - 4 - (3 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid.

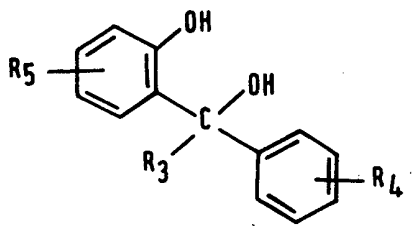
Other preferred derivatives of the invention are the piperidine quaternary ammonium salts of isomer A or isomer B of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid, and the enantiomers d and l of isomers A or B—preferably isomer A—of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid.

As derivatives of general formula I', (2,2 - dimethyl - 1,3 - dioxolan - 4 - yl) - methyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate;

2,3 - dihydroxy - propyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate; and

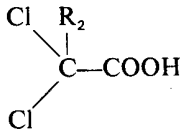
2 - (diethylamino) - ethyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate, together with its acid addition salts, are preferred.

In another aspect, this invention provides a process for preparing alkali-metal salts of the compounds of general formula I wherein R_1 represents a hydrogen atom, in which process a compound of general formula:



(II)

(wherein R_3, R_4 and R_5 are as defined hereinbefore) is reacted with an alkali-metal salt of an acid of general formula:



(III)

(wherein R_2 is as defined hereinbefore) in the presence of a basic condensation promoting agent, to give the desired salt.

The alkali-metal salt of the acid of general formula III is conveniently a sodium, potassium or lithium salt.

The basic condensation promoting agent present in the reaction mixture may advantageously be an alkali-metal alkylate such as sodium methylate, sodium ethylate or sodium t - butylate; an alkali-metal hydride such as sodium hydride or potassium hydride; an alkali-metal amide such as sodium amide, potassium amide or lithium amide; or sodium; and it is preferably reacted with the compound of general formula II before being brought into contact with the alkali-metal salt of the acid of general formula III.

It is preferred to perform the condensation in an organic solvent, such as benzene, toluene, xylene, ethyl ether, dioxan, dimethylformamide, tetrahydrofuran or hexamethyl phosphorotriamide, or in a mixture of these solvents. Also, the reaction medium may advantageously contain a catalyst, for instance a crown ether, such as dibenzo - 18 - crown - 6, dicyclohexyl - 18 - crown - 6 or 18 - crown - 6; the crown ethers are preferably used in conjunction with an organic solvent such as dioxan.

The reaction may be carried out at any temperature from −10°C to the reflux temperature of the reaction mixture.

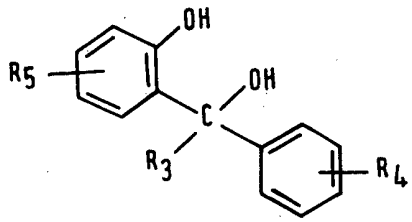
The formed alkali-metal salt of the compounds of general formula I may thereafter be treated with an acid to obtain the corresponding acid of general formula I in which R_1 represents a hydrogen atom. The treatment may be carried out as indicated hereinafter in the Examples.

The acid of general formula I thus formed may in turn be converted into its alkali-metal, alkaline-earth-metal, aluminium, ammonium or quaternary ammonium salts by reaction with an appropriate base.

The base, which is of course chosen with regard to the salt it is desired to form, may be, for example, sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, aluminium hydroxide, sodium ethylate, potassium ethylate or ammonia; or an amine such as methylamine, ethylamine, propylamine, diethylamine, di - n - propyl - amine, propylamine, dimethylamine, diethylamine, di - n - propyl - amine, triethylamine, piperidine, morpholine, piperazine or pyrrolidine.

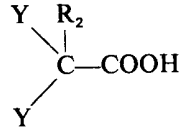
Preferably the salifying reaction is carried out in a solvent or a mixture of solvents such as water, ethyl ether, ethanol, acetone or ethyl acetate.

This invention also provides an alternative process for preparing alkali-metal salts of the compounds of general formula I wherein R_1 represents a hydrogen atom, in which process a compound of general formula:



(II)

(wherein R_3, R_4 and R_5 are as defined hereinbefore) is reacted with an alkali-metal salt of an acid of general formula:



(III')

(wherein Y represents a bromine atom or an iodine atom and R_2 is as defined

hereinbefore) in the presence of a basic condensation promoting agent to give the desired salt.

This alternative process is directly analogous to that described above employing the di-chloride of general formula III, and the methods mentioned as preferable for that reaction apply equally well to the alternative process. The formed alkali-metal salt may naturally be converted into the corresponding acid, and optionally thereafter into corresponding alkali-metal, alkaline-earth-metal, aluminium, ammonium and quaternary ammonium salts, by the methods described hereinbefore.

The esters of general formula I in which R_1 represents an alkyl radical containing from 1 to 5 carbon atoms may be prepared by esterification of an acid of general formula I in which R_1 represents a hydrogen atom to obtain the desired ester.

The esterification may be performed by reacting an alcohol of general formula:

R'OH

(wherein R' represents an alkyl radical containing from 1 to 5 carbon atoms) with the acid or a functional derivative thereof—for instance the acid chloride. Where an acid of general formula I is employed, the reaction should preferably be performed in an acidic medium, for instance in the presence of an acid such as hydrochloric acid or p-toluene sulphonic acid, or in the presence of an acid resin. The functional derivatives employed may be prepared from the acid by methods well known in the art.

The esterification may alternatively be effected by transesterification, or, where R_1 represents a methyl radical, by the action of diazomethane on the acid in an organic solvent.

Where diastereoisomers of the 1,3 - benzodioxine derivatives of the invention exist, it is sometimes advantageous to separate them in the form of their esters—that is the compounds of general formula I wherein R_1 represents an alkyl radical containing from 1 to 5 carbon atoms. In such cases, each diastereoisomeric ester may be hydrolysed separately to form the corresponding acid which thereafter may be treated to form any other corresponding diastereomeric derivatives of the invention. The hydrolysis may be performed by employing the methods set out hereinafter in the Examples.

In a further aspect, this invention provides a process for preparing the compounds of formula I' wherein R_1' represents a (2,2 - dimethyl - 1,3 - dioxolan - 4 - yl) - methyl radical or a dialkylaminoalkyl radical of which the alkyl radicals contain from 1 to 4 carbon atoms, and R_2, R_3, R_4 and R_5 are as defined hereinbefore, in which process an acid of general formula I in which R_1 represents a hydrogen atom, or a functional derivative thereof, is reacted with an alcohol of formula $R_1'OH$, wherein R_1' is as just defined, to obtain the desired compound of general formula I.

The functional derivative of the acid of general formula I employed in the above process may be any of those commonly used for such purposes—for example, an ester or an acid halide thereof; but whatever the functional derivative is, it may be prepared from the acid by methods well known in the art.

The reaction is preferably carried out in an organic solvent such as benzene, toluene, xylene or ethyl ether.

The compound of general formula II used as starting material in the process may naturally be prepared by any of the processes described herein.

The formed compound of general formula I' wherein R_1' represents a (2,2 - dimethyl - 1,3 - dioxolan - 4 - yl) - methyl radical, may thereafter be treated with a hydrolysing agent to obtain the corresponding compound of general formula I' wherein R_1' represents a 2,3 - dihydroxy - propanyl radical. The hydrolysing agent employed is preferably an acid, for example, hydrochloric acid.

The formed compound of general formula I' wherein R_1' represents a dialkylaminoalkyl radical may thereafter be treated with an acid to form its corresponding acid addition salt. The treatment may be carried out in a manner well known in the art.

The remaining 1,3 - benzodioxine derivatives of general formula I' may be prepared by the processes described above for the preparation of the compounds of general formula I.

The invention further provides a process for preparing compounds of general

formula I wherein R_4 and R_5 each represent a hydrogen atom, which process comprises treating a compound of general formula I wherein either one of R_4 and R_5 represents a chlorine atom and the other represents a hydrogen atom, or both R_4 and R_5 represent a chlorine atom, with hydrogen in the presence of a catalyst to obtain the desired product of general formula I.

The catalyst employed in the above process is preferably palladium; and the process is advantageously carried out in an alkaline medium with an organic solvent. The base employed may be for example an amine such as triethylamine, trimethylamine dimethylaniline or pyridine, and the organic solvent may be for example an alcohol such as ethanol, methanol or isopropanol.

The compounds of general formula II, used as a starting material in the processes for the preparation of the benzodioxine derivatives of general formula I or I', may or may not have an asymetric carbon atom, depending on the nature of the substituents R_3 and R_4. The reaction of a compound of general formula II not containing an asymetric carbon atom, with a compound of formula III or III' above, according to the invention, will result in an alkali-metal salt of a compound of general formula I containing a single asymmetric carbon atom, in the form of a racemic mixture; the mixture may then if desired be resolved into its optical enantiomers by methods known in the art such as, for example, the formation of salts with optically-active bases.

Each enantiomer may then independently be subjected to subsequent process steps to convert it into any of the other 1,3 - benzodioxine derivatives of the invention. Alternatively, the unresolved racemic mixture could be converted step by step into other derivatives of the invention, with the option after each step of resolving the mixture and carrying on the process thereafter with separate enantiomers.

An alkali-metal salt of general formula I, which is obtained from a compound of general formula II containing an asymmetric carbon atom, contains two asymmetric carbon atoms. Consequently it exists in the form of two pairs of enantiomers, each pair itself being a racemic mixture. The pairs of enantiomers (which could be identified by the prefixes cis and trans) may be obtained separately by methods well known in the art, for example by selective crystallisation, by counter-current separation or by chromatography on a column. Once separated, each pair of enantiomers may then itself at any time be resolved into separate optical enantiomers by the methods described above. The separation and resolution may, as before, be performed after any process step, the separated pair of enantiomers or single enantiomer thereafter being treated independently.

The different isomeric forms obtained may of course be mixed so as to constitute a particular desired mixture.

The 1,3 - benzodioxine derivatives of the invention have interesting pharmacological properties: they display marked hypolipaemiant activity, and they reduce the amount of plasma in lipids, triglycerides and cholesterol. Thus they may be useful in medicine, especially in the treatment of acute or chronic hyperlipaemia, cardiac insufficiency of atheromatose origin and chronic anginal conditions. However, before any of the derivatives of this invention are used in medicine, they should preferably be formed into pharmaceutical compositions by association with suitable pharmaceutically acceptable vehicles.

Accordingly, in yet another aspect this invention provides pharmaceutical compositions containing one or more of the compounds of general formula I or I', and where possible, their pharmaceutically acceptable alkali-metal, alkaline-earth-metal, ammonium, aluminium, quaternary-ammonium or acid-addition salts, in association with a suitable pharmaceutically acceptable vehicle.

The term "pharmaceutically acceptable" is used herein to exclude any possibility that the nature of the vehicle or of the salts of the compounds of the invention, considered of course in relation to the route by which the composition is intended to be administered, could be harmful to the patient. The choice of a suitable mode of presentation, together with an appropriate vehicle, is believed to be within the competence of those accustomed to the preparation of pharmaceutical formulations. It is preferred for the compositions to contain any of the 1,3 - benzodioxine derivatives mentioned hereinbefore as being preferred.

The compositions of this invention may be administered by the digestive or parenteral route, and in respect of these routes, the "pharmaceutical vehicle" is preferably:—

a) the ingestible excipient of a plain or sugar coated tablet, the ingestible container of a capsule, preferably a gelatin capsule; the ingestible pulverulent solid

carrier of a powder or granules; or the ingestible liquid medium of a syrup, solution, suspension or elixir,

b) a sterile injectable liquid solution or suspension medium, or

c) a base material which when appropriately shaped forms a suppository.

Whilst the modes of presentation just listed represent those most likely to be employed, they do not necessarily exhaust the possibilities.

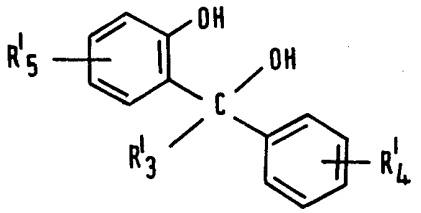
The compounds of this invention may preferably be administered in the form of tablets, capsules or granules; of injectable solutions or suspensions dispensed in single-dose ampoules or multi-dose phials; and of suppositories or implants.

The excipients employed as vehicles in the above forms are those generally employed for such purposes, for example, talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous liquids such as fatty substances of animals or vegetable origin, paraffin derivatives or glycols; optionally compounded with various wetting, dispersing or emulsifying agents and/or preservatives.

Whilst the dosages of the pharmacologically active ingredient will depend upon the route by which the compositions are to be administered, the person treated, the complaint concerned and the medicament administered, nevertheless, by way of general indication, it may be said that the useful dose ranges from 0.05 to 1.0 g of active principle per day for an adult by the oral route.

The majority of the compounds of general formula II used as starting materials in the preparation of the 1,3 - benzodioxine derivatives of the invention are known; but some are, we believe, new compounds, viz:

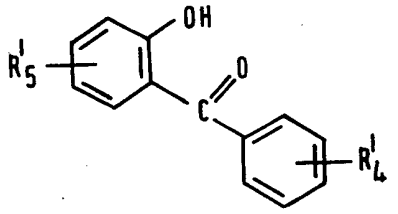
5 - chloro - 2 - hydroxy - α - methyl - α - phenyl - benzenemethanol, and the compounds of general formula:



(II'_A)

wherein R'_4 represents a chlorine atom, R'_5 represents a chlorine atom or fluorine atom, and R'_3 represents an alkyl radical containing from 1 to 4 carbon atoms, with the proviso that R'_3 is not a methyl radical when R'_5 represents a chlorine atom.

The compounds of general formula II'_A may be prepared by the reaction of a benzophenone derivative of general formula:

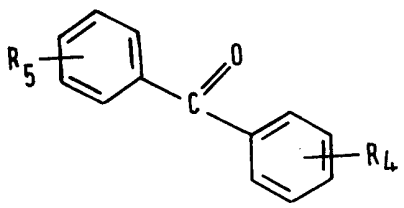


(wherein R'_5 and R'_4 are as defined above) with an organomagnesium derivative of general formula:

$$R'_3—Mg—Hal$$

(wherein R'_3 is as defined above and Hal represents a chlorine or bromine atom) in an organic solvent to obtain the desired compound of general formula II'_A. The reaction may be performed by a method illustrated hereinafter in the Examples.

Other compounds of general formula II wherein R_3 represents an alkyl radical containing from 1 to 5 carbon atoms or a phenyl radical may be prepared by an analagous process performed in an organic solvent, which comprises reacting a benzophenone derivative of general formula:



(IV)

(wherein R_4 and R_5 are as defined hereinbefore) with an organomagnesium derivative of general formula:

$$R_3—Mg—Hal$$

wherein R_3 and Hal are as defined hereinbefore.

Compounds of general formula II wherein R_3 represents a hydrogen atom may be prepared by reduction of an appropriate benzophenone derivative of general formula III in an organic solvent. The reducing agent may be for example a mixed hydride.

The following examples and formulations are given, though only by way of illustration, to show some preferred aspects of the invention.

Example 1

6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid (Mixture of the Two Diastereoisomeric Racemates)

One mixes, whilst agitating, 8.1 g of sodium amide and 100 ml of toluene, adds, drop by drop whilst agitating, a solution obtained by dissolving 24.9 g of 5 - chloro - 2 - hydroxy - α - methyl - α - phenyl benzene methanol in 250 ml of toluene, takes the mixture to reflux for 4 hours 30 minutes, brings the mixture to ambient temperature, adds, in small portions whilst agitating, 18 g of potassium dichloracetate, adds 20 ml of hexamethylphosphorotriamide, takes to reflux for 5 hours, cools the mixture to ambient temperature and adds slowly 10 ml of ethyl acetate then, drop by drop, 250 ml of water. One recovers the aqueous phase, extracts the organic phase again with 3×100 ml of water and combines the different aqueous extracts which one washes with 3×100 ml of ether. One acidifies the aqueous extraction phase which contains the potassium salt of the product expected by bubbling in sulphur dioxide and one extracts with 4×100 ml of ether. One washes the ethereal extraction phase with 3×50 ml of water. One dries the organic phase over magnesium sulphate, treats with active charcoal and evaporates the solvent under vacuum. One obtains 24 g of crude product which one crystallises from 100 ml of a mixture of cyclohexane and benzene 90:10, dries the drystals obtained and obtains 15.2 g of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid. M.Pt. equals 142°C.

Analysis: ($C_{16}H_{13}ClO_4$)					
Calculated:	C%	63.06	H%	4.30	Cl% 11.63
Found:		63.3		4.4	11.5

The 5 - chloro - 2 - hydroxy - α - methyl - α - phenyl benzene methanol used at the start of the preparation of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid can be prepared in the following manner:

one disperses, whilst agitating, 14 g of magnesium turnings in 100 ml of anhydrous ether, adds, drop by drop and under agitation, a solution obtained by dissolving 76 g of methyl iodide in 200 ml of anhydrous ether, takes to reflux for 1 hour, cools to the temperature of 15—20°C, then adds, at this temperature, a solution obtained by dissolving 59 g of 5 - chloro - 2 - hydroxy benzophenone in 250 ml of anhydrous benzene, partly distils off the ether, then takes to reflux again for 2 hours. One then cools the mixture to a temperature of 5—10°C and adds, drop by drop, 250 ml of 3N hydrochloric acid.

One decants and recovers the organic phase, then washes the aqueous phase with 2×100 ml of benzene.

One washes the organic extraction phase with water, then with a saturated solution of sodium bicarbonate, then finally with 2×50 ml of water. One dries the organic phase on magnesium sulphate, then evaporates off the solvent under vacuum, obtains 58.9 g of crystals which one takes up with petroleum ether (B.Pt.

60—80°C) and obtains 53 g of 5 - chloro - 2 - hydroxy - α - methyl - α - phenyl benzene methanol. M.Pt. equals 106°C.

Analysis: ($C_{14}H_{13}ClO_2$)			
Calculated:	C% 67.61	H% 5.27	Cl% 14.26
Found:	67.8	5.4	14.2

Example 2

Isomers A and B of Methyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

One prepares a solution of 2.25 g of diazomethane in 150 ml of methylene chloride, cools this solution to 5°C, adds thereto, drop by drop at 5°C, a solution obtained by dissolving 3.3 g of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid, in the form of a mixture of the two diastereoisomeric racemates obtained in Example 1, in 75 ml of methylene chloride. One agitates for one hour at ambient temperature, then leaves the solution to stand for 24 hours. One then adds 10 ml of acetic acid, then one evaporates the solvent under vacuum. One recovers 4.2 g of methyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate in the form of a mixture of the two diastereoisomeric racemates.

One subjects the residue obtained to chromatography through a column of silica, eluting with a mixture of ethyl ether and petroleum ether (B.Pt. equals 60—80°C) (20:80) and obtains 1 g of isomer A of methyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate. M.Pt. equals 114—115°C.

Analysis: ($C_{17}H_{15}ClO_4$)			
Calculated:	C% 64.06	H% 4.74	Cl% 11.12
Found:	63.9	4.7	11.4

N.M.R. Spectrum (base frequency of the apparatus used: 60 Hz).
—CH_3 at 117 hz;
—$COOCH_3$ at 232 hz;
—hydrogen at position 2 at 311 hz;
—aromatics from 410 to 445 hz.

One also obtains 0.6 g of isomer B of methyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate. M.Pt. equals 102°C.

Analysis: ($C_{17}H_{15}ClO_4$)			
Calculated:	C% 64.06	H% 4.74	Cl% 11.12
Found:	64.0	4.8	11.13

N.M.R. Spectrum (base frequency of the apparatus used: 60 hz).
—CH_3 at 125 hz;
—$COOCH_3$ at 228 hz;
—hydrogen at position 2 at 341 hz;
—aromatics from 405 to 455 hz.

Example 3

Isomer A of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid

One mixes 14 g of isomer A of methyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate obtained in Example 2 and, 2.8 g of pelleted potassium hydroxide, 32 ml of water and 160 ml of methanol, agitates for 22 hours at ambient temperature, adds 320 ml of water, washes the aqueous phase with 2 times 160 ml of ether, then acidifies the aqueous solution with a 2N solution of hydrochloric acid, extracts the precipitate obtained with 3 times 320 ml of ether, washes the organic extraction phase with 2 times 160 ml of water, dries it on magnesium sulphate and brings to dryness. One obtains 15 g of crystals. One recrystallises 3.9 g of them from 100 ml of a mixture of ethyl acetate and cyclohexane (20:80) and dries. One obtains 3.3 g of isomer A of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid. M.Pt. equals 175—176°C.

Analysis: ($C_{16}H_{13}ClO_4$)			
Calculated:	C% 63.06	H% 4.30	Cl% 11.63
Found:	63.3	4.6	11.3

N.M.R. Spectrum (base frequency: 60 hz)
—CH_3 at 117 hz;
—hydrogen at position 2 at 313 hz;
—COOH at 468 hz;
—aromatics from 412 to 443 hz.

Example 4

Isomer B of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid

One mixes 5.3 g of isomer B of methyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate obtained in Example 2 and 10 ml of water, 1.2 g of pelleted potassium hydroxide and 50 ml of methanol, agitates for 20 hours at ambient temperature, adds 200 ml of water, washes the aqueous phase with 2 times 80 ml of ether, then acidifies the aqueous solution with a 2N solution of hydrochloric acid, extracts with 3 times 100 ml of ether, combines the extracts, washes the extract with 2 times 80 ml of water, dries the ethereal phase on magnesium sulphate, evaporates the solvent under vacuum and obtains 4.8 g of crystals which one recrystallises from a mixture of cyclohexane and ethyl acetate (80:20), dries and obtains 4.4 g of isomer B of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid. M.Pt. equals 171°C.

Analysis: ($C_{16}H_{13}O_4Cl$)			
Calculated:	C% 63.06	H% 4.30	Cl% 11.63
Found:	63.1	4.4	11.7

N.M.R. Spectrum (base frequency: 60 hz)
—CH_3 at 124 hz;
—COOH at 329 hz;
—hydrogen at position 2 at 341 hz;
—aromatics from 408 to 445 hz.

Example 5

6 - chloro - 2,4 - dimethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid (Mixture of the Two Diastereoisomeric Racemates)

One mixes, whilst agitating, 8 g of sodium amide and 100 ml of toluene, adds, drop by drop at ambient temperature, a suspension obtained by dispersing 24.9 g of 5 - chloro - 2 - hydroxy - α - methyl - α - phenyl benzene methanol in 250 ml of toluene, takes the mixture to reflux for 6 hours, cools the mixture to ambient temperature, adds, in small portions, 17 g of sodium dichloro 2,2 - propionate, takes to reflux again for 6 hours, cools to ambient temperature and adds 700 mls of water. One acidifies by adding a N solution of hydrochloric acid and renders alkaline again by adding a saturated solution of sodium bicarbonate. One recovers the aqueous extraction phase which one washes with 3 times 100 ml of ether, acidifies the aqueous extract by adding 2N solution of hydrochloric acid and extracts with 3 times 100 ml of ether, combines the organic extracts which one washes with 3 times 80 ml of water and dries on magnesium sulphate, then one evaporates the solvent under vacuum and obtains 23 g of 6-chloro - 2,4 - dimethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid. M.pt. equals 181°C.

Analysis: ($C_{17}H_{15}ClO_4$)			
Calculated:	C% 64.06	H% 4.74	Cl% 11.12
Found:	64.0	4.8	11.2

Example 6

Isomers A and B of Methyl 6 - chloro - 2,4 - dimethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

One mixes 23 g of 6 - chloro - 2,4 - dimethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid in the form of a mixture of the two diastereoisomeric racemates A and B obtained in Example 5, 100 g of Redex "CF" (strong sulphonic acid cationic resin) and 250 ml of methanol, takes to reflux to 20 hours, cools to ambient temperature, vacuum-filters the resin, rinses it with solvent and concentrates the filtrate under vacuum. One obtains 20 g of crude product which one chromatographs on a column of silica under 1.5 kg pressure, eluting with a mixture of ethyl ether and petroleum ether (B.Pt. 60—80°C) (20:80) and obtains

1.7 g of isomer A of methyl 6 - chloro - 2,4 - dimethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate. M.Pt. equals 134°C.

Analysis: ($C_{18}H_{17}ClO_4$)

Calculated:	C% 64.96	H% 5.15	Cl% 10.65
Found:	65.2	5.2	10.9

N.M.R. Spectrum (base frequency: 60 hz)
—The CH_3's at 103 and 113 hz;
—$COOCH_3$ at 172 hz;
—aromatics from 419 to 447 hz.

One also obtains 8.2 g of isomer B (in the form of an oil) of methyl 6 - chloro - 2,4 - dimethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

Analysis: ($C_{18}H_{17}ClO_4$)

Calculated:	C% 64.96	H% 5.15	Cl% 10.65
Found:	65.8	5.1	10.8

N.M.R. Spectrum (base frequency: 60 hz)
—The CH_3's at 106 and 117 hz;
—$COOCH_3$ at 224 hz;
—aromatics from 415 to 455 hz.

Example 7

Isomer A of 6 - chloro - 2,4 - dimethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid

One mixes 1.6 g of isomer A of methyl 6 - chloro - 2,4 - dimethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate obtained in Example 6, 20 ml of methanol, 2 ml of water and 0.56 g of pelleted potassium hydroxide, agitates the mixture for 48 hours at ambient temperature, adds 100 ml of water, recovers the aqueous phase which one washes with 3 times 50 ml of ether, acidifies the aqueous solution by adding a 2N solution of hydrochloric acid and extracts with 4 times 50 ml of ether, combines the ethereal extracts which one washes with 3 times 50 ml of water, then dries on magnesium sulphate. One evaporates the solvent under vacuum and obtains 1.5 g of product which one recrystallises from 80 ml of cyclohexane and obtains 1.2 g of isomer A of 6 - chloro - 2,4 - dimethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid. M.Pt. equals 184°C.

Analysis: ($C_{17}H_{15}O_4Cl$)

Calculated:	C% 64.06	H% 4.74	Cl% 11.12
Found:	64.1	4.8	11.1

N.M.R. Spectrum (base frequency: 60 hz)
—The CH_3's at 101.5 hz and 113 hz;
—COOH at 342 hz;
—aromatics from 412 to 442 hz.

Example 8

Isomer B of 6 - chloro - 2,4 - dimethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid

One mixes 8 g of isomer B of methyl 6 - chloro - 2,4 - dimethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate obtained in Example 6, 80 ml of methanol, 8 ml of water and 2.8 g of pelleted potassium hydroxide, agitates for 24 hours at ambient temperature, adds 150 ml of water, and recovers the aqueous phase which one washes with 3 times 60 ml of ether. One acidifies the aqueous solution by adding a 2N solution of hydrochloric acid and extracts with 4 times 60 ml of ethyl ether. One combines the ethereal extracts and washes them with 2 times 80 ml of water, then dries on magnesium sulphate and evaporates the solvent under vacuum and obtains 7.2 g of product which one recrystallises from 80 ml of cyclohexane. One dries and obtains 4.5 g of isomer B of 6 - chloro - 2,4 - dimethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid. M.Pt. equals 125°C.

Analysis: ($C_{17}H_{15}O_4Cl$)

Calculated:	C% 64.06	H% 4.74	Cl% 11.12
Found:	64.2	5.0	11.2

N.M.R. Spectrum (base frequency: 60 hz)
—The CH_3's at 104 and 119 hz;
—The aromatics from 417 to 455 hz;
—COOH at ≃540 hz.

Example 9

6 - chloro - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid

One mixes 10.35 g of sodium amide and 100 ml of toluene, introduces, drop by drop at ambient temperature and under agitation, a solution obtained by dissolving 30.1 g of 5 - chloro - 2 - hydroxy - α - phenyl benzene methanol in 200 ml of anhydrous toluene, agitates for 2 hours at ambient temperature, takes the mixture to reflux for 6 hours, cools the mixture to ambient temperature and adds, in small portions, 22.3 g of potassium dichloracetate, adds 20 ml of hexamethylphosphoramide, agitates for 20 hours at ambient temperature, takes the mixture to reflux of the toluene for 4 hours, allows to return to ambient temperature adds 20 ml of ethyl acetate, then slowly 20 ml of water. One recovers the aqueous phase, extracts the organic phase again with 3 times 100 ml of water and combines the different aqueous extracts which one washes with 3 times 100 ml of ether. One acidifies the aqueous extraction phase which contains the potassium salt of the product expected by bubbling in sulphur dioxide, extracts with 3 times 100 ml of ether, combines the extracts, washes with 3 times 100 ml of water, dries on magnesium sulphate, treats with active charcoal, evaporates the solvent under vacuum and obtains 24 g of crude product which one dissolves in cyclohexane, obtains crystals which one recrystallises from 520 ml of a mixture of benzene and cyclohexane (7:3) and obtains 5.3 g of 6 - chloro - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid. M.Pt. equals 194°C.

Analysis: ($C_{15}H_{11}ClO_4$)

Calculated:	C% 61.97	H% 3.81	Cl% 12.20
Found:	62.2	3.9	12.1

N.M.R. Spectrum (base frequency: 60 hz)
—The hydrogens at positions 2 and 4 at 343.5 hz and 364 hz;
—COOH at ≃514 hz;
—aromatics from 398 to 442.5 hz.

Example 10

6 - chloro - 4,4 - diphenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid

One mixes 12.4 g of 5 - chloro - 2 - hydroxy - α,α - diphenyl benzene methanol, 150 ml of toluene and 3.2 g of sodium amide, takes the mixture to reflux for 6 hours, cools to ambient temperature and adds 6.8 g of potassium dichloracetate, takes to reflux again for 6 hours, cools to ambient temperature and adds 300 ml of water. One acidifies slightly by adding a N solution of hydrochloric acid, then renders alkaline by adding a saturated solution of sodium bicarbonate. One washes with 2 times 100 ml of methylene chloride, then acidifies by adding a 2N solution of hydrochloric acid, extracts with 3 times 100 ml of ether, combines the ethereal extracts, washes with 2 times 80 ml of water, then dries on magnesium sulphate and treats with active charcoal. After evaporating the solvent under vacuum one obtains 7 g of product which one recrystallises from 300 ml of benzene. One obtains 4.6 g of 6 - chloro - 4,4 - diphenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid. M.Pt. equals 226°C.

Analysis: ($C_{21}H_{15}O_4Cl$)

Calculated:	C% 68.76	H% 4.12	Cl% 9.67
Found:	69.1	4.3	9.5

N.M.R. Spectrum (base frequency: 60 hz)
—hydrogen at position 2 at 325 hz;
—COOH at ≃313 hz;
—aromatics from 405 to 443 hz.

Example 11

Isomer A of Methyl - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

One introduces into a hydrogenizing cell 1.3 g of 10% palladium on active charcoal, 11.8 g of the isomer A of methyl 6 - chloro - 4 - methyl - 4 - phenyl -

[4H - 1,3 - benzodioxin - 2 - carboxylate obtained in Example 2 and, 500 ml of ethanol and 10 ml of triethylamine and agitates the suspension under a current of hydrogen at ambient temperature. One washes the catalyst with methylene chloride, then concentrates the filtrate under vacuum, takes up the residue in 100 ml of water, adds 50 ml of a 2N solution of hydrochloric acid and extracts with 3 times 150 ml of methylene chloride, combines the extracts, washes them with 2 times 100 ml of water, dries on calcium chloride then, after treatment with active charcoal, evaporates the solvent under vacuum and obtains 9.7 g of expected product.

A sample of this product was recrystallised from methanol. M.Pt. equals 124°C.

Analysis: ($C_{17}H_{16}O_4$)

Calculated:	C% 71.82	H% 5.67
Found:	72.1	5.8

N.M.R. Spectrum (base frequency: 60 hz)
—hydrogen at position 2 at 312 hz;
—$COOCH_3$ at 231 hz;
—CH_3 geminal to phenyl: 117 hz;
—aromatics from 410 to 450 hz.

Example 12

Isomer A of 4 - methyl - 4 - phenyl - 1,3 - benzodioxin - 2 - carboxylic Acid

One mixes, under agitation, 9.7 g of isomer A of methyl 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate obtained in Example 11, 4 g of pelleted potassium hydroxide, 10 ml of water and 90 ml of methanol, maintains under agitation for 16 hours at ambient temperature, adds 400 ml of water, washes the aqueous phase with 2 times 100 ml of methylene chloride, acidifies the aqueous phase by adding a 2N solution of hydrochloric acid, extracts with 3 times 150 ml of methylene chloride, combines the extracts, washes with twice 80 ml of water, dries on calcium chloride, evaporates the solvent under vacuum, recovers 8 g of product which one recrystallises from a mixture of ethyl acetate and cyclohexane (20:80) and obtains 5.1 g of isomer A of 4 - methyl - 4 - phenyl - 1,3 - benzodioxin - 2 - carboxylic acid. M.Pt. equals 163°C.

Analysis: ($C_{16}H_{14}O_4$)

Calculated:	C% 71.10	H% 5.22
Found:	71.1	5.3

N.M.R. Spectrum (base frequency: 60 hz)
—CH_3 at 119 hz;
—hydrogen at position 2 at 316 hz;
—COOH at 534 hz;
—aromatics from 418 to 450 hz.

Example 13

Isomer B of methyl - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

One introduces into a hydrogenizing cell 1.3 g of 10% palladium on active charcoal, 12.8 g of the isomer B of methyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate obtained in Example 2 and 10 ml of triethylamine and 200 ml of ethanol, passes a continuous current of hydrogen and agitates the suspension at ambient temperature for about two hours. One filters, rinses the catalyst with methylene chloride, evaporates the filtrate under vacuum, takes up the residue in 80 ml of water, adds 70 ml of a 2N solution of hydrochloric acid, extracts with 3 times 100 ml of methylene chloride, combines the extracts and washes them with 3 times 50 ml of water, dries on calcium chloride and evaporates the solvent under vacuum. One obtains 10.2 g of expected product.

A sample of this product is recrystallised from methanol. M.Pt. equals 137°C.

Analysis: ($C_{17}H_{16}O_4$)

Calculated:	C% 71.82	H% 5.67
Found:	71.8	5.8

N.M.R. Spectrum (base frequency: 60 hz)
—CH_3 at 128 hz;

—$COOCH_3$ at 234 hz;
—hydrogen at position 2 at 347 hz;
—aromatics from 410 to 465 hz.

Example 14

Isomer B of 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid

One mixes under agitation 10.2 g of the isomer B of methyl 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate obtained in Example 13, 4 g of pelleted potassium hydroxide, 10 ml of water and 90 ml of ethanol, maintains under agitation for 16 hours at ambient temperature, adds 500 ml of water, washes the aqueous phase with twice 80 ml of methylene chloride, acidifies the aqueous phase by adding a 2N solution of hydrochloric acid, extracts with 3 times 100 ml of methylene chloride, washes with twice 80 ml of water, dries on calcium chloride, evaporates the solvent under vacuum, obtains 9 g of product which one recrystallises from a mixture of ethyl acetate and cyclohexane (20:80) and obtains 6.7 g of expected product. M.Pt. equals 153°C.

Analysis: ($C_{16}H_{14}O_4$)

Calculated:	C% 71.10	H% 5.22
Found:	71.1	5.3

N.M.R. Spectrum (base frequency: 60 hz)
—CH_3 at 128 hz;
—hydrogen at position 2 at 348 hz;
—aromatics from 410 to 460 hz.

Example 15

Methyl 6 - chloro - 4,4 - diphenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

One mixes, by agitation, 11 g of 6 - chloro - 4,4 - diphenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid obtained in Example 10, 50 g of Redex "CF" (strong sulphonic acid cationic resin) and 200 ml of methanol, takes to reflux for 16 hours, cools to ambient temperature, vacuum-filters the resin, washes it with ether and concentrates the filtrate under vacuum.

One takes up the crude product obtained in 200 ml of ether, washes the organic phase with 100 ml of a 5% solution of sodium bicarbonate, then with twice 100 ml of water. One dries the ethereal phase on magnesium sulphate, treats with active charcoal, evaporates the solvent and obtains 6.3 g of product which one recrystallises from 140 ml of cyclohexane. One dries and obtains 5.1 g of expected product. M.Pt. equals 172°C.

Analysis: $C_{22}H_{17}H_4Cl$

Calculated:	C% 69.38	H% 4.50	Cl% 9.31
Found:	69.7	4.6	9.3

N.M.R. Spectrum (base frequency: 60 MHz) (deuterochloroform)
—$COOCH_3$ at 230 Hz;
—aromatics from 406 to 443 Hz;
—hydrogen at position 2 at 324 Hz.

Example 16

Isomer A of ethyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

Stage A: Isomer A of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid Chloride

One mixes, by agitating, 4.9 g of the isomer A of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid obtained in Example 3 and 50 ml of anhydrous benzene, cools the suspension to a temperature of 10°C, then adds, drop by drop, 2.3 ml of triethylamine, then adds, drop by drop, at the same temperature, a solution of 1.5 ml of thionyl chloride in 25 ml of anhydrous benzene, takes the solution to reflux for two hours, cools to ambient temperature, vacuum-filters the precipitate and recovers the expected product in solution.

Stage B: Isomer A of Ethyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

One mixes 3 ml of absolute ethanol, 50 ml of anhydrous benzene and 2.3 ml of triethylamine, adds, drop by drop at ambient temperature, the solution of acid

chloride obtained in Stage A, maintains under agitation for twenty hours at ambient temperature, vacuum-filters and washes the triethylamine hydrochloride precipitate with cold benzene, washes the filtrate with twice 40 ml of water, dries the organic phase on calcium chloride, treats with active charcoal, evaporates the solvent under vacuum, obtains 9 g of crude product which one recrystallises from 30 ml of hexane and obtains, after drying, 4 g of expected product. M.Pt. equals 92°C.

Analysis: $C_{18}H_{17}O_4Cl$

Calculated:	C% 64.97	H% 5.15	Cl% 10.65
Found:	65.1	5.3	10.8

N.M.R. Spectrum (deuterochloroform) (base frequency: 60 MHz)
—CH_3 of C_2H_5 at 72.5—79.5—87 Hz;
—CH_3 at position 4 at 116 Hz;
—CH_2 of C_2H_5 at 247.5—255—262—269 Hz;
—hydrogen at position 2 at 308 Hz;
—aromatics from 412 to 441 Hz.

Example 17

Isomer A of Sodium 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

One mixes 0.6 g of sodium hydroxide and 250 ml of absolute ethanol, adds at ambient temperature 4.6 g of the isomer A of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid obtained in Example 3, one takes to boiling for 5 minutes, filters, cools to ambient temperature, adds to the filtrate 500 ml of ether and maintains under agitation for sixteen hours at ambient temperature. One filters and obtains, after drying, 3.8 g of expected product. M.Pt. equals 160°C.

Analysis: $C_{16}H_{12}O_4ClNa$

Calculated:	C% 58.82	H% 3.70	Cl% 10.85
Found:	58.5	3.8	10.7

Example 18

d and *l* Isomers of the Isomer A of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid

1) Isomer *l*

Stage A: *l* 1 - p - nitrophenyl - 2 - amino - 1,3 - propanediol salt of the Isomer *l* of the Isomer A of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid

One mixes 15.2 g of isomer A of the 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid obtained in Example 3, 16.2 g of *l* 1 - p - nitrophenyl - 2 - amino - 1,3 - propanediol and 800 ml of ethyl acetate.

One takes the mixture to reflux and maintains the refluxing after precipitation of the salt formed for five minutes. One brings to ambient temperature, vacuum-filters the precipitate obtained, rinses it with ethyl acetate, dries under vacuum and recovers 10 g of crude product. [One keeps the mother liquors for the separation of the crude isomer *d* (see further on)].

One recrystallises the 10 g of crude product obtained from isopropanol and finally obtains 6.4 g of expected product. M.Pt. equals 218°C.

$[\alpha]_D^{20}=-84°\pm2°$ (c=1%, ethanol).

A sample of this product is recrystallised from a little isopropanol. M.Pt. equals 218°C.

$[\alpha]_D^{20}=-84.5°\pm2°$ (c=1%, ethanol).

Stage B: *l* Isomer of the Isomer A of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid

One puts the salt thus purified, obtained in Stage A above, into suspension in 150 ml of N hydrochloric acid, then one extracts with three times 75 ml of ether, washes the organic extraction phase with three times 50 ml of water and dries on magnesium sulphate. One evaporates the solvent under vacuum, obtains 3.5 g of crude product which one crystallises from cyclohexane, obtains 2.7 g of crystals which one purifies by recrystallisation from cyclohexane and obtains 2.3 g of crystals melting at 113—114°C then recrystallising and melting at 128°C. One recrystallises again from 80 ml of cyclohexane and obtains 1.8 g of expected product melting at 113°C.

One obtains, from the mother liquors of previous recrystallisations, 0.5 g of expected product. One collects these 0.5 g of product and the 1.8 g of product obtained above, recrystallises the 2.3 g of product from 50 ml of cyclohexane maintaining the refluxing of the solvent for twenty minutes and then obtains 2 g of expected product. M.Pt. equals 140°C.

(The variations in the different melting points recorded for the expected product are probably due to variations in crystalline structure.)

Analysis: $C_{16}H_{13}ClO_4$

	C%	H%	Cl%
Calculated:	63.06	4.30	11.63
Found:	63.2	4.4	11.6

N.M.R. Spectrum (deuterochloroform) (base frequency: 60 MHz).
—CH_3 at 116.5 Hz;
—hydrogen at position 2 at 313 Hz;
—aromatics from 415 to 443 Hz;
—OH at about 540 Hz.

Rotatory Power
$[\alpha]_D^{20}=-157°\pm2.5°$ (c=1%, ethanol 95°).

2) Isomer *d*

Stage A: *d* Isomer of the Isomer A of Crude 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid

One takes up the ethyl acetate mother liquors from salifying the isomer A of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid with *l* 1 - p - nitrophenyl - 2 - amino - 1,3 - propanediol.

One concentrates the solution under vacuum, recovers 17.8 g of crude product which one treats with 200 ml of 2N hydrochloric acid, extracts with three times 100 ml of ether, washes the organic phase with twice 50 ml of water, dries on magnesium sulphate and concentrates under vacuum. One obtains 8.4 g of residue which one takes up with 150 ml of a mixture of cyclohexane and ethyl acetate (70:30) and takes to reflux, allows to cool, vacuum-filters the residual starting racemic acid which crystallises out, concentrates the filtrate under vacuum and obtains 7 g of crude expected product.

Stage B: *d* 1 - p - nitrophenyl - 2 - amino - 1,3 - propanediol Salt of the *d* Isomer of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid

One takes up the residue obtained above in 300 ml of ethyl acetate and adds to the solution 7.4 g of *d* 1 - p - nitrophenyl - 2 - amino - 1,3 - propanediol.

One takes the suspension to reflux, allows to cool, after precipitation of the salt formed, to ambient temperature, vacuum-filters the precipitate and rinses with a little ethyl acetate. One obtains, after drying, 11.4 g of expected product melting at 200°C.

One recrystallises from 1.1 litres of isopropanol, obtains 6.2 g of expected product. M.Pt. equals 218°C, which one recrystallises from 800 ml of isopropanol and obtains 5 g of expected product. M.Pt. equals about 218°C.

Stage C: *d* Isomer of the Isomer A of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid

One takes up the salt obtained above in 150 ml of water, acidifies with 2N hydrochloric acid, extracts with twice 100 ml of ether, washes the organic extraction phase with twice 50 ml of water, dries on magnesium sulphate and evaporates the solvent under vacuum; one obtains 2.9 g of crude product which one takes up in a mixture of ethyl ether and petroleum ether (B.Pt. 60—80°C) (20:80).

Finally, after separation, one obtains 2.4 g of expected product. M.Pt. equals 128°C.

$[\alpha]_D^{20}=+153°\pm2°5$ (c=1%, ethanol).

One recrystallises this product from 100 ml of cyclohexane and obtains 2 g of expected product. M.Pt. equals 128°C.

$[\alpha]_D^{20}=+153°\pm2°5$ (c=1%, ethanol).

One recrystallises again from 60 ml of cyclohexane and obtains finally 1.7 g of expected product. M.Pt. equals 140°C.

(As for the isomer *l* the isomer *d* has several melting points. This is probably due to variations in crystalline structure.)

Analysis: $C_{16}H_{13}ClO_4$

	C%	H%	Cl%
Calculated:	63.06	4.30	11.63
Found:	63.2	4.3	11.6

N.M.R. Spectrum (deuterochloroform) (base frequency: 60 MHz)
—CH_3 at 117 Hz;
—monosubstituted phenyl at 440 Hz;
—aromatics 413 to 440 Hz;
—OH at 485 Hz;
—hydrogen at 2 at 312.5 Hz.

Rotatory Power
$[\alpha]_D^{20}=+154°5\pm2°5$ (c=1%, ethanol).

Example 19

6 - chloro - 4 - (3 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid (Mixture of the Diastereoisomeric Racemates)

One mixes, whilst agitating, 10 g of sodium amide and 200 ml of anhydrous toluene, then adds, at ambient temperature and in small portions, a suspension obtained by dissolving 28.3 g of 1 - [5 - chloro - 2 - hydroxyphenyl] - 1 - [3 - chlorophenyl] ethanol in 250 ml of toluene, then one takes the mixture to reflux for six hours (one adds 1 g more of sodium amide to the mixture). After cooling to ambient temperature one adds, in small portions whilst agitating, 25 g of potassium dichloracetate and takes the mixture again to reflux for six hours. After a return to ambient temperature one adds slowly 150 ml of water, then 150 ml of 2N HCl. One recovers the organic phase then one extracts the aqueous phase again with twice 100 ml of ether. One washes the organic extraction phase with twice 100 ml of water. One extracts the organic phase with a saturated solution of sodium bicarbonate then with twice 100 ml of water. One washes the aqueous extraction phase with three times 100 ml of ether, then one acidifies the aqueous phase slowly with a 2N solution of HCl. One then extracts the aqueous phase with three times 150 ml of ether. One washes the organic extraction phase with twice 75 ml of water. One treats it with active charcoal and dries it on magnesium sulphate. One evaporates the solvent under vacuum and one obtains finally 29.3 g of expected product.

N.M.R. Spectrum (deuterochloroform) (base frequency: 60 MHz)
—CH_3 at 117 and 125.5 Hz;
—hydrogen at position 2 at 315.5 and 346 Hz;
—aromatics 412 to 455 Hz;
—COOH at 588 Hz.

The 1 - [5 - chloro - 2 - hydroxyphenyl] - 1 - [3 - chlorophenyl] - ethanol used at the start of the preparation of 6 - chloro - 4 - (3 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid can be prepared in the following manner:

One disperses whilst agitating 11 g of magnesium turnings in 100 ml of anhydrous ether and adds, drop by drop at ambient temperature and under agitation, a solution obtained by dissolving 64 g of methyl iodide in 100 ml of anhydrous ether. One maintains gentle refluxing of the solvent during the addition and continues the refluxing for one hour, brings back to ambient temperature, then adds, drop by drop over twenty-five minutes, a solution of 31.7 g of (5 - chloro - 2 - hydroxyphenyl)(3 - chlorophenyl) - methanone in 100 ml of anhydrous ether and 150 ml of anhydrous benzene.

One distils off the ether, adds 250 ml of anhydrous benzene then takes the solution to reflux for four hours.

One cools the mixture to ambient temperature and, maintaining at this temperature by means of an ice bath, one hydrolyzes by means of a N solution of hydrochloric acid.

One recovers the organic phase, extracts the aqueous phase again with twice 80 ml of ether, washes the organic extraction phase with three times 80 ml of water, dries the organic phase on magnesium sulphate, then evaporates the solvent under vacuum.

One then obtains 31.5 g of expected product which one recrystallises from 750 ml of cyclohexane.

One obtains finally 25.5 g of expected product. M.Pt. equals 125°C.

Analysis: $C_{14}H_{12}O_2Cl_2$			
Calculated:	C% 59.38	H% 4.27	Cl% 25.04
Found:	59.2	4.3	24.9

The [5 - chloro - 2 - hydroxyphenyl][3 - chlorophenyl]methanone used at the start of the preparation of 1 - [5 - chloro - 2 - hydroxyphenyl] - 1 - [3 - chlorophenyl]ethanol above can be prepared thus:

Stage A: 4 - chlorophenyl - 3 - chlorobenzoate

One mixes, whilst agitating, 5.87 g of 4 - chlorophenol, 46.1 g of triethylamine and 250 ml of anhydrous benzene, cools to 10°C, adds, drop by drop, a solution of 80 g of 3 - chlorophenyl carboxylic acid chloride in 100 ml of anhydrous benzene, maintains under agitation at ambient temperature for one night, filters, recovers the filtrate and brings to dryness. One obtains 122 g of crude product which one crystallises from 200 ml of a mixture of ethyl ether and petroleum ether (B.Pt. 60—80°C) (20:80).

One obtains 116 g of expected product. M.Pt. equals 72°C.

Analysis: $C_{13}H_8Cl_2O_2$			
Calculated:	C% 58.45	H% 3.02	Cl% 26.55
Found:	58.5	3.0	26.2

Stage B: [5 - chloro - 2 - hydroxyphenyl][3 - chlorophenyl]methanone

One mixes, under agitation, 64.5 g of 4-chlorophenyl 3 - chlorobenzoate obtained in the previous stage and 32 g of aluminium chloride, heats the mixture gradually, under agitation, to 160°C, maintains at this temperature for thirty minutes, brings back to ambient temperature, takes up the crude product obtained with methylene chloride, hydrolyzes the organic solution slowly at the beginning with 250 ml N hydrochloric acid, decants the organic phase, then extracts the aqueous phase with twice 70 ml of methylene chloride, washes the organic extraction phase with three times 70 ml of water, dries the organic phase on calcium chloride then evaporates the solvent under vacuum. One obtains finally 60 g of crude product which one crystallises from a mixture of ethyl ether and petroleum ether (B.Pt. 60—80°C) (20:80).

One vacuum-filters, dries and obtains 41.3 g of expected product.

One recrystallises a sample of this product from cyclohexane. M.Pt. equals 72°C.

Analysis: $C_{13}H_8Cl_2O_2$			
Calculated:	C% 58.45	H% 3.02	Cl% 26.55
Found:	58.4	3.2	26.6

Example 20

Isomers A and B of Methyl 6 - chloro - 4 - (3 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

One mixes, whilst agitating, 29.3 g of 6 - chloro - 4 - (3 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid in the form of a mixture of the two diastereoisomeric racemates obtained in Example 19, 300 ml of methanol and 30 g of strong sulphonic acid cationic resin, takes to reflux for twenty hours under agitation, cools to ambient temperature, vacuum-filters the resin, rinses it with methanol and concentrates the filtrate under vacuum. One obtains 20 g of crude product which one chromatographs on a column of silica under pressure eluting with a mixture of ethyl ether and petroleum ether (B. Pt. 60—80°C) (20:80) and obtains after fractionating and evaporating off the solvent:

9.5 g of expected isomer A, of which one purifies 4 g by recrystallisation from methanol: one obtains 3.2 g of purified expected isomer A. M.Pt. equals 112°C.

Analysis: $C_{17}H_{13}O_4Cl_2$			
Calculated:	C% 57.97	H% 3.72	Cl% 20.13
Found:	57.9	4.0	19.8

N.M.R. Spectrum (deuterochloroform) (base frequency: 90 MHz)
—CH_3 at 172 Hz;
—$COOCH_3$ at 345 Hz;
—hydrogen at position 2 at 461.5 Hz;
—aromatics from 623 to 660 Hz.
and 8.4 g of expected isomer B, in the form of crude product.

Analysis: $C_{17}H_{13}O_4Cl_2$

Calculated:	C% 57.97	H% 3.72	Cl% 20.13
Found:	58.2	4.0	20.1

N.M.R. Spectrum (deuterochloroform) (base frequency: 90 MHz)
—CH_3 at 184 Hz;
—$COOCH_3$ at 343.5 Hz;
—hydrogen at position 2 at 509 Hz;
—aromatics from 612 to 674 Hz.

Example 21

Isomer A of 6 - chloro - 4 - (3 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid

One mixes, whilst agitating, 6.5 g of isomer A of methyl 6 - chloro - 4 - (3 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate obtained in Example 20, 2.8 g of pelleted potassium hydroxide, 10 ml of water and 100 ml of methanol, agitates the mixture for sixteen hours at ambient temperature, adds 200 ml of water, washes the aqueous solution with twice 50 ml of ether, acidifies the aqueous solution with a 2N solution of hydrochloric acid, extracts the aqueous phase with three times 80 ml of ether, washes the organic extraction phase with twice 50 ml of water, dries the ethereal phase on magnesium sulphate, evaporates the solvent under vacuum and obtains 6.1 g of product which one recrystallises from 100 ml of cyclohexane. One obtains 3.6 g of expected product. M.Pt. equals 131°C.

Analysis: $C_{16}H_{12}O_4Cl_2$

Calculated:	C% 56.66	H% 3.57	Cl% 20.90
Found:	56.7	3.7	20.6

N.M.R. Spectrum (deuterochloroform) (base frequency: 60 MHz)
—CH_3 at 174.5 Hz;
—hydrogen at position 2 at 466.5 Hz;
—aromatics=peaks from 625 to 665 Hz.

Example 22

Isomer B of 6 - chloro - 4 - (3 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid

One mixes, whilst agitating, 5.3 g of isomer B of methyl 6 - chloro - 4 - (3 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate obtained in Example 20, 2.4 g of pelleted potassium hydroxide, 10 ml of water and 100 ml of methanol, agitates the mixture for one night at ambient temperature, adds 250 ml of water, then washes the aqueous phase with twice 80 ml of ether, acidifies the aqueous solution with a 2N solution of hydrochloric acid, extracts the aqueous phase with three times 800 ml of ether, washes the organic phase with twice 50 ml of water, dries the ethereal phase on magnesium sulphate, concentrates under vacuum and obtains 5.3 g of expected product which one recrystallises from 110 ml of a mixture of cyclohexane and ethyl acetate (80:30). One obtains 4 g of purified expected product. M.Pt. equals 177°C.

Analysis: $C_{16}H_{12}O_4Cl_2$

Calculated:	C% 56.66	H% 3.87	Cl% 20.90
Found:	56.8	3.8	20.9

N.M.R. Spectrum (deuterochloroform) (base frequency: 90 MHz)
—CH_3 at 185.5 Hz;
—hydrogen at position 2 at 510 Hz;
—aromatics=from 610 to 673 Hz.

Example 23

6 - chloro - 4 - [1 - methyl)ethyl] - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid (Mixture of the Two Diastereoisomeric Racemates)

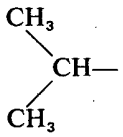
One mixes, whilst agitating, 8.1 g of 50% sodium hydride in oil, 60 ml of anhydrous dioxan and 360 mg of dibenzo - 18 - crown - 6 of the type described in "Synthesis", 1976, page 168, adds, maintaining the solution at ambient temperature, over 10 minutes and whilst agitating, a solution of 3.66 ml of dichloracetic acid in 60 ml of anhydrous dioxan, then adds, at ambient temperature, a solution of 8.7 g of 5 - chloro - α - [(1 - methyl)ethyl] - 2 - hydroxy - α - phenyl benzene methanol in 30 ml of anhydrous dioxan, heats the suspension for 10 hours at 90—100°C, brings to ambient temperature, adds, drop by drop whilst cooling with a bath of iced water, 500 ml of water, washes the aqueous phase with twice 200 ml of ether and extracts the ethereal phase with three times 100 ml of 2N sodium hydroxide. One acidifies the aqueous phase with 2N hydrochloric acid and one extracts the acid released with three times 150 ml of ether, washes the ethereal phase with three times 100 ml of water, extracts the acid formed in the form of the sodium salt by extracting the ethereal phase with a saturated solution of sodium bicarbonate, then with three times 100 ml of water, washes the aqueous extraction phase with twice 80 ml of ether, acidifies by adding 2N hydrochloric acid, extracts the acid thus released with three times 150 ml of ether, washes the organic extraction phase with three times 80 ml of water, dries and treats with active charcoal, brings to dryness and obtains 8.8 g of expected product in the form of an oil.

N.M.R. Spectrum (deuterochloroform) (base frequency of the apparatus 60 MHz)

—hydrogen at position 2 at 323 Hz (peak corresponding to the isomer A),

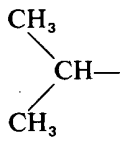
—hydrogen at position 2 at 335 Hz (peak corresponding to the isomer B),

—the two CH_3 of the radical



from 49 to 69 Hz,

—the hydrogen of the radical



from 100 to 190 Hz,

—aromatics from 410 to 465 Hz,

—OH at 490 Hz.

The 5 - chloro - α - [(1 - methyl)ethyl] - 2 - hydroxy - α - phenyl benzene methanol used at the start of the preparation above was prepared as follows:

One mixes, by agitation, 21.4 g of magnesium turnings, 200 ml of anhydrous ether and 2 ml of isopropyl bromide.

One agitates until the expected magnesium derivative is formed, then adds, drop by drop so as to maintain gentle refluxing and at ambient temperature, a solution of 110.8 g of isopropyl bromide in 400 ml of anhydrous ether. When the addition is finished one continues the refluxing for two hours. In addition one mixes 58.2 g of [(5 - chloro - 2 - hydroxy)phenyl]phenyl methanone and 600 ml of anhydrous benzene, then adds, drop by drop at ambient temperature, 520 ml of the magnesium derivative solution prepared above.

One distils off the ether replacing it gradually with benzene. One continues the refluxing for six hours.

After cooling to ambient temperature one pours the reaction mixture onto one litre of a 10% iced solution of ammonium chloride. One decants the organic phase and extracts the aqueous phase with twice 150 ml of ether. One collects the organic phases, washes them with three times 100 ml of water, dries, treats with active charcoal and evaporates off the solvent under vacuum. One obtains 74 g of crude product which one chromatographs on a column of silica eluting with methylene chloride; after fractionating one obtains 18 g of crude product which one takes up

with 50 ml of cyclohexane. One obtains 8.7 g of expected product. M.Pt. equals 114°C.

One purifies a sample of this product by recrystallisation from cyclohexane. M.Pt. equals 118°C.

Analysis: ($C_{18}H_{17}O_2Cl$)

Calculated:	C% 69.43	H% 6.19	Cl% 12.81
Found:	69.7	6.2	12.8

N.M.R. (deuterochloroform) (base frequency of the apparatus used=60 MHz)
—the $2CH_3$ of the radical (1 - methyl)ethyl at 48—55 Hz and 63—70 Hz,

— CH— at ≃165 Hz (multiplet),

—OH of the methanol at 165 Hz,
—OH of the 2-hydroxy at 537 Hz,
—aromatics from 395 to 455 Hz.

Example 24

Isomer A of Methyl 6 - chloro - 4 - [(1 - methyl)ethyl] - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

Stage A: Chloride of 6 - chloro - 4 - [(1 - methyl)ethyl] - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid (Mixture of Racemates)

One mixes, whilst agitating, 8.8 g of 6 - chloro - 4 - [(1 - methyl)ethyl] - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid obtained in Example 23 and 100 ml of anhydrous benzene, adds, maintaining at ambient temperature, 3.7 ml of triethylamine, 3.8 ml of thionyl chloride and 25 ml of anhydrous benzene, takes the mixture to reflux for three hours, cools to ambient temperature, vacuum-filters and washes the precipitate with a little anhydrous benzene and recovers the filtrate which contains the expected product.

Stage B: Isomer A of Methyl 6 - chloro - 4 - [(1 - methyl)ethyl] - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

One mixes, whilst agitating, 50 ml of anhydrous benzene, 4 ml of anhydrous methanol and 3.7 ml of triethylamine, adds, drop by drop at ambient temperature, the filtrate obtained in Stage A above, agitates the mixture for 50 hours at ambient temperature, vacuum-filters and washes the precipitate with a little benzene, recovers the filtrate and washes with 2N sodium hydroxide then with water until neutral pH. One dries the organic phase, treats with active charcoal, brings to dryness, obtains 7.3 g of crude product which one crystallises from methanol, vacuum-filters, dries the crystals obtained and recovers 4.5 g of expected product which one purifies by recrystallising twice from methanol. One obtains 1.8 g of purified expected product. M.Pt. equals 114—115°C.

Analysis: $C_{19}H_{19}ClO_4$

Calculated:	C% 65.80	H% 5.52	Cl% 10.22
Found:	65.8	5.6	10.2

N.M.R. (deuterochloroform) (base frequency: 90 MHz)
—the two CH_3 of the radical (1 - methyl)ethyl at 74 and 77 Hz,
—the —CH— of the radical (1 - methyl)ethyl from 187 to 239 Hz,

—$COOCH_3$ at 351 Hz,
—hydrogen at position 2 at 479 Hz,
—aromatics: peaks from 616 to 681 Hz.

Example 25

6 - chloro - 4 - [(1,1 - dimethyl)ethyl] - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid (Mixture of the Two Diastereoisomeric Racemates)

One mixes, whilst agitating, 12.8 g of 50% sodium hydride in oil, 100 ml of anhydrous dioxan and 600 mg of dibenzo 18 - crown - 6, then adds, drop by drop maintaining the solution at ambient temperature, a solution of 5.82 ml of dichloracetic acid in 100 ml of dioxan, maintains the suspension at ambient temperature, adds, drop by drop, a solution of 14.1 g of 5-chloro - α - (1,1 - dimethyl)ethyl - 2 - hydroxy - α - phenyl benzene methanol in 100 ml of dioxan, then heats the mixture to 80°C for six hours, cools to ambient temperature and

maintains at this temperature with a bath of iced water, one adds 400 ml of water, extracts the aqueous phase with 600 ml of ether, extracts with three times 100 ml of 0.1N sodium hydroxide, acidifies the aqueous extraction phase with 2N hydrochloric acid, extracts with three times 150 ml of ether, washes the organic extraction phase with three times 100 ml of water, extracts the acid in the form of the sodium salt by means of a saturated solution of sodium bicarbonate, then with three times 100 ml of water and collects the aqueous extracts.

One washes the aqueous phase with three times 100 ml of ether, acidifies the aqueous phase with 2N hydrochloric acid, extracts with four times 150 ml of ether, washes the ethereal phase with three times 100 ml of water, dries the ethereal phase on magnesium sulphate, treats with active charcoal, brings to dryness and obtains 9.1 g of crude expected product.

N.M.R. (deuterochloroform) (base frequency of the apparatus: 60 MHz)
—hydrogen at position 2 at 317 Hz (isomer A),
—hydrogen at position 2 at 340 Hz (isomer B),
—(1,1 - dimethyl)ethyl at 63 and 65 Hz,
—aromatics from 415 to 472 Hz,
—OH at 527 Hz.

The 5 - chloro - o - (1,1 - dimethyl)ethyl - 2 - hydroxy - α - phenyl benzene methanol used at the start of the preparation above was obtained as follows:

One mixes 40.2 g of (5 - chloro - 2 - hydroxy phenol)phenyl methanone and 400 ml of anhydrous ether, adds, drop by drop at ambient temperature, 192 g of a solution of t - butyllithium in pentane, agitates for two hours at ambient temperature, distils off the ether replacing it gradually with 600 ml of anhydrous benzene, takes the solution to reflux of the benzene for sixteen hours, cools to ambient temperature, pours onto one litre of an iced 10% solution of ammonium chloride, eliminates the organic phase by decanting, extracts the aqueous phase with twice 100 ml of ether, washes the organic phase with twice 70 ml of water, dries on magnesium sulphate, treats with active charcoal, brings to dryness, obtains 50 g of crude product (in the form of an oil) which one chromatographs on a column of silica eluting with methylene chloride and obtains by fractionation 14.1 g of product of which one recrystallises a sample from cyclohexane. M.Pt. equals 146°C.

Analysis: $C_{17}H_{19}O_2Cl$

Calculated:	C% 70.22	H% 6.59	Cl% 12.19
Found:	70.5	6.7	11.9

N.M.R. (deuterochloroform) (base frequency: 60 MHz)
—OH of the 2 - hydroxy radical at 530 Hz,
—OH of the methanol at 175 Hz,
—[(1,1 - dimethyl)ethyl] radical at 75 Hz,
—aromatics of the phenyl radical at α of the methanol from 420 to 455 Hz,
—other aromatics from 400 to 455 Hz.

Example 26

Isomer A of Methyl 6 - chloro - 4 - [(1,1 - dimethyl)ethyl] - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

Stage A: 6 - chloro - 4 - [(1,1 - dimethyl)ethyl] - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid Chloride (Mixture of the Racemates)

One mixes 9.1 g of the mixture of the diastereoisomeric racemates of 6 - chloro - 4 - [(1,1 - dimethyl)ethyl] - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid prepared as indicated in Example 25 and 100 ml of anhydrous benzene.

One then adds gradually, maintaining at ambient temperature, 3.7 ml of triethylamine then, drop by drop, a solution of 6.2 g of thionyl chloride in 25 ml of anhydrous benzene, takes to reflux for three hours, cools to ambient temperature, vacuum'filters and washes the precipitate with anhydrous benzene, recovers the filtrate and concentrates the solution under vacuum to obtain a volume of solution of 30 ml.

Stage B: Isomer A of Methyl 6 - chloro - 4 - [(1,1 - dimethyl)ethyl] - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

One mixes, whilst agitating, 3 ml of methanol, 50 ml of anhydrous benzene and 3.7 ml of triethylamine, cools to 15—20°C, adds, drop by drop at this temperature,

the solution obtained in Stage A above to which one has added 30 ml of anhydrous benzene, agitates for sixteen hours at ambient temperature, vacuum-filters and washes the precipitate with anhydrous benzene.

One concentrates the filtrate under vacuum and obtains 6.5 g of crude product which one chromatographs on a column of silica eluting with a mixture of ethyl ether and petroleum ether (B.Pt. 60—80°C (20:80) and obtains, after fractionation, then evaporation of the solvent, the crude expected product which one crystallises from 20 ml of methanol and obtains, after drying, the expected product. M.Pt. equals 85°C.

Analysis: $C_{20}H_{21}ClO_4$

	C%	H%	Cl%
Calculated:	66.57	5.87	9.82
Found:	66.5	6.0	10.0

N.M.R. (deuterochloroform) (base frequency: 60 MHz)
—(1,1 - dimethyl)ethyl at 62 Hz,
—$COOCH_3$ at 117 Hz,
—hydrogen at position 2 at 338 Hz,
—aromatics: peaks from 412 to 468 Hz.

Example 27

6 - fluoro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid (Mixture of the Diastereoisomeric Racemates)

One mixes, under an atmosphere of argon, 25 g of sodium hydride, 350 cm³ of anhydrous dioxan and 1.55 g of dibenzo - 18 - crown - 6, adds over one hour, a solution of 16.5 cm³ of dichloracetic acid in 150 cm³ of dioxan, then at the end of the reaction adds, over one hour at 22°C, a solution of 31 g of α - phenyl - α - methyl(5 - fluoro - 2 - hydroxy)phenyl methanol in 150 cm³ of anhydrous dioxan, one heats to about 80°C, agitates for six hours at 80—85°C, cools, pours onto an ice-water mixture, extracts with ether, acidifies the aqueous phase, extracts the aqueous phase with ether, washes the ethereal phase with water, extracts the ethereal phase with sodium bicarbonate, washes with methylene chloride, acidifies the alkaline phases, extracts with methylene chloride, washes with water, dries on magnesium sulphate and brings to dryness under vacuum. One obtains 29.5 g of crude expected product (in the form of an oil).

N.M.R.
—hydrogen at position 2 at 310 Hz and CH_3 at 117 Hz (peak corresponding to the isomer A of the acid obtained),
—hydrogen at position 2 at 339 Hz and CH_3 at 126 Hz (peak corresponding to the isomer B of the acid obtained),
—aromatics from 400 to 450 Hz,
—OH at 505 Hz.

The α - phenyl - α - methyl(5 - fluoro - 2 - hydroxy)phenyl methanol used at the start of the preparation above was prepared as follows:

One mixes, under an atmosphere of argon, whilst agitating, 13.3 g of magnesium turnings, 50³ of anhydrous ether, then slowly a solution of 34.7 cm³ of methyl iodide in 250 cm³ of anhydrous ether, then heats for one hour to reflux. One then adds 220 cm³ of this magnesium derivative solution obtained to a solution of 30 g of α - phenyl)5 - fluoro - 2 - hydroxy)phenyl methanone in 150 cm³ of anhydrous benzene, distils off the ether whilst replacing it with anhydrous benzene, then agitates for four hours at about 78°C, cools, pours onto a solution of ammonium chloride, extracts with ether, washes with water, dries on magnesium sulphate and brings to dryness under vacuum. One obtains 32 g of crude expected product.

One recrystallises a sample of this product from cyclohexane. M.Pt. equals 122°C.

Analysis: $C_{14}H_{13}FO_2$

	C%	H%	F%
Calculated:	72.40	5.64	8.18
Found:	72.4	5.6	8.2

Example 28

Isomer A of Methyl 6 - fluoro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

One mixes, whilst agitating, 29.5 g of the mixture of racemates of 6 - fluoro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid obtained

in Example 27, 300 cm³ of methanol and 130 g of acid resin, then takes to and maintains at reflux for 24 hours. One cools, treats with active charcoal, filters, rinses with methanol, brings to dryness, takes up with ether, washes the ethereal phase with three times 200 cm³ of bicarbonate then with water, dries on magnesium sulphate, brings to dryness under vacuum and obtains 23.8 g of crude product which one takes up with 200 cm³ of methanol. One obtains 5 g of product which one recrystallises from 20 cm³ of methanol. One obtains 4.4 g of expected product. M.Pt. equals 95°C.

Analysis: $C_{17}H_{15}FO_4$

Calculated:	C% 67.54	H% 5.00	F% 6.28
Found:	67.7	5.0	6.2

N.M.R. (deuterochloroform) (frequency of the apparatus: 90 MHz)
—CH_3 at 171 Hz,
—$COOCH_3$ at 345 Hz,
—hydrogen at position 2 at 463 Hz,
—aromatics: peaks from 615 to 680 Hz.

Example 29

Isomer A of (2,2 - dimethyl - 1,3 - dioxolan - 4 - yl)methyl - 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

Stage A: Chloride of the Isomer A of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid

One mixes, by agitating, 4.9 g of isomer A of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid obtained in Example 3 and 50 ml of anhydrous benzene, cools to about 10°C, and adds, drop by drop at this temperature, 1.66 g of triethylamine. One then adds, at this temperature and drop by drop, a solution of 2.5 g of thionyl chloride in 25 ml of anhydrous benzene, then one takes to reflux for two hours. One cools the suspension to ambient temperature, vacuum-filters the precipitate and recovers the filtrate which contains the expected product.

Stage B: Isomer A of (2,2 - dimethyl - 1,3 - dioxolan - 4 - yl)methyl - 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

One mixes, whilst agitating, 2.25 g of (2,2 - dimethyl - 1,3 - dioxolan - 4 - yl)methanol 50 ml of anhydrous benzene and 2.3 ml of triethylamine and adds, drop by drop at ambient temperature, the filtrate recovered in Stage A above. One agitates for twenty hours at ambient temperature. One filters, washes the filtrate with a 10% solution of sodium carbonate, then washes with water until neutral pH.

One dries the benzene phase on calcium chloride and treats with active charcoal, evaporates the solvent under vacuum and obtains 4.5 g of crude product which one chromatographs on a column of silica eluting with methylene chloride. One obtains, after fractionation, 2 g of crude expected product in the form of a colourless gum.

Analysis: $C_{22}H_{23}O_6Cl$

Calculated:	C% 63.08	H% 5.53	Cl% 8.46
Found:	62.0	5.5	8.9

N.M.R. (deuterochloroform) (base frequency of the apparatus: 60 MHz)
—the CH_3 of 2,2 - dimethyl dioxolan at ≃81—82 Hz,
—CH_3 at position 4 at 115 Hz,
—$COO—CH_2—\underset{\underset{O}{|}}{CH}—\underset{\underset{O}{|}}{CH_2}$ from 215 to 260 Hz,
—aromatics from 411 to 441 Hz.

Example 30

Hydrochloride of the Isomer A of 2 - (diethylamino)ethyl - 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

One takes to reflux under an atmosphere of nitrogen, whilst agitating, a mixture of 6.2 g of isomer A of methyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate obtained as indicated in Example 16, 100 ml of anhydrous toluene and 2.6 g of diethylamino ethanol and a very small amount of sodium hydride. One maintains at reflux for three hours, cools, adds 5 ml of a 4N

solution of hydrochloric acid in ether, adds 200 ml of anhydrous ether, filters, washes with ether, dries and obtains 3.7 g of product which one takes up with 20 ml of isopropanol at 60°C, treats with active charcoal, cools, adds 50 ml of ether, filters, dries and obtains 2.7 g of expected product. M.Pt. equals 110°C.

Analysis: $C_{22}H_{27}Cl_2NO_4$				
Calculated:	C% 60.00	H% 6.18	Cl% 16.10	N% 3.18
Found:	59.6	6.4	15.9	3.4

Example 31

6 - chloro - 4 - ethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid (Mixture of the Two Diastereoisomeric Racemates)

One mixes, under agitation, 250 cm³ of liquid ammonia, which one has condensed, with about 100 mg of ferric nitrate and 4.8 g of sodium which one adds in small portions, one then adds, over one hour thirty minutes at 28—30°C, a solution of 26.2 g of 5 - chloro - α - ethyl - 2 - hydroxy - α - phenyl benzene methanol in 200 cm³ of anhydrous toluene, increases the temperature and dries off the ammonia released, heats to reflux for three hours, adds 100 cm³ of toluene and, at 50°C, 18 g of potassium dichloroacetate, maintains for one night at reflux and adds 9 g of potassium dichloroacetate, agitates for a further two hours at reflux, cools, pours into water, eliminates the organic phase, acidifies the aqueous phase and extracts with ether, washes the ethereal phase with three times 500 cm³ of water, extracts the ethereal phase with three times 300 cm³ of sodium bicarbonate, washes with twice 500 cm³ of ether, acidifies the aqueous phase with concentrated hydrochloric acid, extracts with three times 500 cm³ of ether, washes with water, dries on magnesium sulphate, brings to dryness under vacuum and obtains 27 g of crude expected product. The 5 - chloro - α - ethyl - 2 - hydroxy - α - phenyl benzene methanol used at the start of the preparation of the product of Example 31 above can be prepared as indicated in Example 23 but using, in place of the isopropyl bromide, ethyl iodide. M.Pt. equals 85°C.

Example 32

Isomers A and B of Methyl 6 - chloro - 4 - ethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

One used for the preparation and the isolation of the two diastereoisomeric racemates A and B of methyl 6 - chloro - 4 - ethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate—starting with the mixture of the isomers A and B of the corresponding acids, a mixture obtained in Example 31—the same technique as that described in Example 20.

One thus obtained, from 26 g of the mixture of the isomers A and B obtained in Example 31:

4.5 g of expected isomer A which one recrystallises from methanol at reflux. One obtains 3.5 g of purified expected isomer A. M.Pt. equals 128°C.

Analysis: $C_{18}H_{17}ClO_4$			
Calculated:	C% 64.96	H% 5.15	Cl% 10.65
Found:	65.0	5.2	10.4

N.M.R. Spectrum (deuterochloroform) (base frequency: 60 MHz)
—ethyl at 4 at 44—51—58 Hz, 110 to 160 Hz,
—$COOCH_3$ at 232 Hz,
—hydrogen at position 2 at 314 Hz,
—aromatics of the 1,3 - benzodioxin nucleus from 415 to 450 Hz,
—phenyl at 4 at 445 Hz,
and 4 g of expected isomer B. M.Pt. equals 108°C.

Example 33

6 - chloro - 4 - (4 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid (Mixture of the Two Diastereoisomeric Racemates)

One mixes, under agitation, 250 cm³ of dioxan, 1.6 g of dibenzo - 18 - crown - 6 and 25 g of sodium hydride, then, over 45 minutes, one adds a solution of 16 cm³ of dichloroacetic acid in 100 cm³ of dioxan, then, over one hour one adds, at 30°C, a solution of 36.6 g of 5 - chloro - 2 - hydroxy - α - methyl - α - (4 - chlorophenyl)benzene methanol in 150 cm³ of dioxan, heats to 80°C for five minutes, cools, pours onto a mixture of ice and water, extracts with three times 500

cm^3 of ether, acidifies the aqueous phase with concentrated hydrochloric acid, extracts with three times 500 cm^3 of ether, extracts the ethereal phase with sodium bicarbonate, acidifies the aqueous phase and extracts with four times 300 cm^3 of ether, washes with water, dries on magnesium sulphate, brings to dryness under vacuum and obtains 40 g of crude expected product.

N.M.R. Spectrum (deuterochloroform) (base frequency: 60 MHz)
—hydrogen at position 2 at 309 Hz,
—CH_3 at 116 Hz, this corresponds to one of the expected isomers (isomer A)
—hydrogen at position 2 at 340 Hz,
—CH_3 at 124 Hz, this corresponds to the other expected isomer (isomer B),
—aromatics from 405 to 445 Hz,
—OH at 510 Hz.

The 5 - chloro - 2 - hydroxy - α - methyl - α - (4 - chlorophenyl)benzene methanol used at the start of the preparation above can be prepared as follows:

One mixes, under magnetic agitation and under an atmosphere of argon:

13.5 g of 2 - hydroxy - 5 - chloro acetophenone and 130 cm^3 of anhydrous ether, cools externally with a bath of iced water, introduces, drop by drop maintaining the internal temperature between 10 and 20°C, 330 cm^3 of an ethereal solution, freshly prepared and filtered, of the magnesium derivative of 1 - chloro - 4 - bromobenzene titrating 0.46 mole/litre and maintains under agitation for one night at ambient temperature. One chills the yellow suspension and introduces, drop by drop, 125 cm^3 of iced 2N aqueous hydrochloric acid, decants, washes the organic phase with water, dries on sodium sulphate, treats with active charcoal, vacuum-filters and brings to dryness under vacuum, one dissolves the residue in 100 cm^3 of cyclohexane and allows to crystallise under agitation, vacuum-filters the precipitate, makes it into a paste with a little cyclohexane, dries it in the oven and obtains 19.3 g of expected product. M.Pt. equals 130°C.

Analysis: $C_{14}H_{12}O_2Cl_2$					
Calculated:	C%	59.38	H%	4.27	Cl% 25.04
Found:		59.7		4.3	24.7

Example 34

Isomer A of Methyl 6 - chloro - 4 - (4 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate

One mixes 40 g of the mixture of the diastereoisomeric racemates of 6 - chloro - 4 - (4 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid, a mixture as obtained in Example 33, 400 cm^3 of methanol and 180 g of strong sulphonic resin, agitates at reflux for eighteen hours, cools, vacuum-filters, washes four times with 300 cm^3 of ether, brings to dryness under vacuum, takes up the residue with 500 cm^3 of ether, washes with three times 300 cm^3 of sodium bicarbonate, then with four times 500 cm^3 of water, dries on magnesium sulphate, brings to dryness under vacuum and obtains 35.5 g of product. One treats the product obtained with 100 cm^3 of methanol, leaves for one night at ambient temperature, vacuum-filters, washes with iced methanol, obtains 10 g of product which one recrystallises from 60 cm^3 of methanol, leaves for one night at ambient temperature and obtains 9.1 g of expected isomer A. M.Pt. equals 108°C.

Analysis: $C_{17}H_{14}Cl_2O_4$					
Calculated:	C%	57.81	H%	4.0	Cl% 20.0
Found:		58.0		4.0	19.9

N.M.R. Spectrum (deuterochloroform) (base frequency: 60 MHz)
—CH_3 at 115 Hz,
—$COOCH_3$ at 231 Hz,
—hydrogen at position 2 at 308 Hz,
—aromatics from 412 to 442 Hz.

Example 35

6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid (Mixture of the Two Diastereoisomeric Racemates)

One mixes 4 g of sodium amide and 50 ml of anhydrous toluene and adds, drop by drop at ambient temperature, a solution of 9.95 g of 5 - chloro - 2 - hydroxy - α - methyl - α - phenyl benzene methanol in 150 ml of anhydrous toluene. One

takes the mixture to reflux for six hours, cools to ambient temperature, introduces 10.25 g of potassium dibromoacetate and takes to reflux again for six hours. One cools and one takes up with 200 ml of water, decants, extracts the organic phase with twice 80 ml of water, washes the aqueous phase with twice 80 ml of ether and acidifies the aqueous solution with 40 ml of 2N hydrochloric acid.

There is formed a precipitate which one extracts with three times 100 ml of ether. One washes the organic phases with twice 80 ml of water and re-extracts the expected acid three times with 50 ml of a 5% saturated aqueous solution of sodium bicarbonate.

One washes the organic extraction phase with three times 80 ml of ether and one acidifies the alkaline solution with 90 ml of a 2N solution of hydrochloric acid. One extracts the expected acid with four times 100 ml of ether. One washes the organic phase with water, dries on magnesium sulphate in the presence of active charcoal, eliminates the solvent under vacuum and obtains 7.85 g of crude product which one takes up in hexane. One vacuum-filters and dries the crystals obtained and obtains 6 g of expected product. M.Pt. equals 144°C.

N.M.R. (deuterochloroform) (base frequency: 60 MHz)
—CH_3 at 117 Hz,
—hydrogen at position 2 at 312 Hz, (corresponding to the isomer A),
—CH_3 at 125.5 Hz,
—hydrogen at position 2 at 342.5 Hz (corresponding to the isomer B)
—aromatics from 405 to 450 Hz,
—OH at ≃350 Hz.

Example 36

6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid (Mixture of the two diastereoisomeric Racemates)

One mixes 10 cm³ of dioxan and 1.35 g of 50% sodium hydride in oil; at 15°C one adds 60 mg of dibenzo - 18 - crown - 6 then, over five minutes, 0.61 cm³ of dichloracetic acid and 10 cm³ of dioxan.

One introduces, over ten minutes at about 20°C, 1.25 g of 2 - hydroxy - 5 - chloro - α - methyl benzhydrol and 5 cm³ of dioxan.

One then heats for six hours to about 80°C, then cools to about 20°C, adds 2 cm³ of methanol, pours into iced water, extracts three times with ethyl acetate and washes five times with iced 0.1N sodium hydroxide. One combines the aqueous phases, acidifies them to pH 1 with a 2N solution of hydrochloric acid, extracts three times with methylene chloride, dries and brings to dryness and recovers the crude expected product.

Example 37

Piperidine Salt of the Isomer A of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid

One dissolves the mixture of the two diastereoisomeric racemates of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid obtained in Example 36 above in 4 cm³ of ethyl acetate and adds, at 10°C, 0.8 cm³ of piperidine. The expected piperidine salt crystallises out upon scratching. One vacuum-filters after 15 minutes washes with ethyl acetate, then with ether, dries to 20°C under vacuum and obtains 855 mg of expected product.

One recovers the mother liquor of crystallisation and dilutes it with methylene chloride, washes with iced N hydrochloric acid, dries and brings to dryness, takes up the residue with 12 cm³ of methylene chloride and adds 0.6 cm³ of boron trifluoride etherate, leaves to stand for half an hour at 20°C, pours onto ice, washes twice with water, re-extracts with methylene chloride, dries and brings to dryness, takes up with 2 cm³ of ethyl acetate and 0.4 cm³ of piperidine, allows to crystallise and isolates 545 mg of expected product. A fresh operation carried out in the same manner, starting with the mother liquor of crystallisation (isomerisation with boron trifluoride, addition of piperidine) enables one to recover 130 mg more of expected product. One has therefore obtained, in toto 1.53 g of expected product. M.Pt. equals ≃165°C.

Example 38

Isomer A of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic Acid

One takes up the 1.53 g of piperidine salt obtained in Example 37 above with a mixture of methylene chloride and N hydrochloric acid, washes, dries, treats with

active charcoal, concentrates by adding cyclohexane until a volume of 3 cm^3 is reached, vacuum-filters, washes with cyclohexane, dries at 40°C under vacuum and obtains 1.1 g of expected product. M.Pt. equals 175°C.

This product is identical to the isomer A obtained in Example 3.

Formulation 1

One prepared compressed tablets corresponding to the following formula:

	mg
6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid (in the form of isomer A)	300
Excipient q.s. for one compressed tablet up to	500

(Detail of the excipient: lactose, starch, talc, magnesium stearate).

Formulation 2

One prepared gelatin capsules corresponding to the following formula:

	mg
Methyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate (in the form of isomer A)	25
Excipient q.s. for one gelatin capsule up to	500

(Detail of the excipient: talc, magnesium stearate, Aerosil—Registered Trade Mark).

Formulation 3

One prepared compressed tablets corresponding to the formula:

	mg
Isomer A as obtained in Example 21	300
Excipient q.s. for one compressed tablet up to	500

(Detail of the excipient: talc, magnesium stearate, Aerosil).

Formulation 4

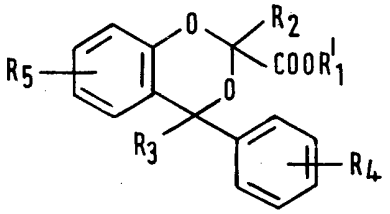
One prepared gelatin capsules corresponding to the general formula:

	mg
Isomer *d* as obtained in Example 18	250
Excipient q.s. for one gelatin capsule up to	500

(Detail of the excipient: talc, magnesium stearate, Aerosil).

WHAT WE CLAIM IS:—

1. 1,3 - benzodioxine derivatives, which are compounds of the general formula:

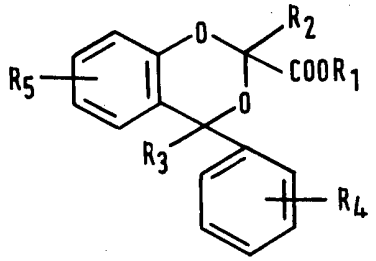


(I')

(wherein R'_1 represents a hydrogen atom, an alkyl radical containing from 1 to 5 carbon atoms, a 2,3 - dihydroxypropyl radical, a (2,2 - dimethyl - 1,3 - dioxolan - 4 - yl) - methyl radical or a dialkylaminoalkyl radical of which the alkyl radicals contain from 1 to 4 carbon atoms; R_2 represents a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms; R_3 represents a hydrogen atom, an alkyl radical containing from 1 to 5 carbon atoms or a phenyl radical; and R_4 and R_5, which may be the same or different, each represent a hydrogen atom or a

halogen atom) and alkali-metal, alkaline-earth-metal, aluminium, ammonium and quaternary ammonium salts thereof where R_1' represents a hydrogen atom; and, acid addition salts thereof where R_1' represents a dialkylaminoalkyl radical.

2. 1,3 - benzodioxine derivatives, which are compounds of the general formula:



(I)

(wherein R_3, R_4 and R_5 are as defined in Claim 1 and R_1 and R_2, which may be the same or different, each represent a hydrogen atom or an alkyl radical containing from 1 to 5 carbon atoms) and alkali-metal, alkaline-earth-metal, aluminium, ammonium and quaternary ammonium salts thereof where R_1 represents a hydrogen atom.

3. A derivative as claimed in Claim 2, which is a compound of general formula I wherein R_1 and R_2, which may be the same or different, each represent a hydrogen atom or a methyl radical, R_3 represents a hydrogen atom, a methyl radical or a phenyl radical, R_4 represents a hydrogen atom and R_5 represents a hydrogen atom or a chlorine atom; and alkali-metal, alkaline-earth-metal, aluminium, ammonium and quaternary ammonium salts thereof where R_1 represents a hydrogen atom.

4. A derivative as claimed in Claim 3, in which R_2 of general formula I represents a hydrogen atom and R_5 represents a chlorine atom.

5. 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid.

6. 6 - chloro - 2,4 - dimethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid.

7. 6 - chloro - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid.

8. 6 - chloro - 4,4 - diphenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid.

9. 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid.

10. Methyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

11. Methyl 6 - chloro - 4,4 - diphenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

12. Ethyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

13. Sodium 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

14. Methyl 6 - chloro - 4 - (3 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

15. 6 - chloro - 4 - (3 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid.

16. Methyl 6 - chloro - 4 - [(1 - methyl)ethyl] - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

17. Methyl 6 - chloro - 4 - [(1,1 - dimethyl)ethyl] - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

18. Methyl 6 - fluoro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

19. Methyl 6 - chloro - 4 - ethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

20. Methyl 6 - chloro - 4 - (4 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

21. Isomer A of methyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

22. Isomer A of methyl 6 - chloro - 4 - (3 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

23. Isomer A of ethyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

24. Isomer A of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid.

25. Isomer A of 6 - chloro - 2,4 - dimethyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid.

26. Isomer A of sodium 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

27. Isomer A of 6 - chloro - 4 - (3 - chlorophenyl) - 4 - methyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid.

28. The piperidine quaternary ammonium salts of isomer A or isomer B of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid.

29. d and l enantiomers of isomers A or B of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid.

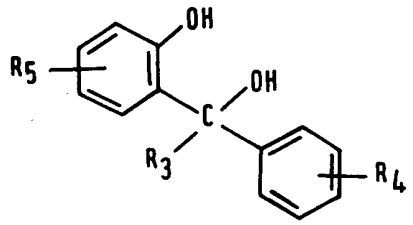
30. d and l enantiomers of isomer A of 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylic acid.

31. (2,2 - dimethyl - 1,3 - dioxolan - 4 - yl) - methyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

32. 2,3 - dihydroxy - propyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate.

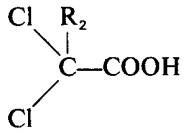
33. 2 - (diethylamino) - ethyl 6 - chloro - 4 - methyl - 4 - phenyl - [4H] - 1,3 - benzodioxin - 2 - carboxylate, and its acid addition salts.

34. A process for preparing alkali-metal salts of the compounds of general formula I wherein R_1 represents a hydrogen atom, in which process a compound of general formula:



(II)

(wherein R_3, R_4 and R_5 are as defined in Claim 2) is reacted with an alkali-metal salt of an acid of general formula:



(III)

(wherein R_2 is as defined in Claim 2) in the presence of a basic condensation promoting agent, to give the desired salt.

35. A process as claimed in Claim 34, in which the basic condensation promoting agent present in the reaction mixture is an alkali-metal alkylate, an alkali-metal hydride, an alkali-metal amide, or sodium.

36. A process as claimed in Claim 34 or Claim 35, in which the basic condensation promoting agent is reacted with the compound of general formula II before being brought into contact with the alkali-metal salt of the acid of general formula III.

37. A process as claimed in any of Claims 34 to 36, in which the reaction between the compounds of general formulae II and III is performed in an organic solvent.

38. A process as claimed in any of Claims 34 to 37, in which the reaction medium of the compounds of general formulae II and III additionally contains a catalyst.

39. A process as claimed in Claim 38, in which the catalyst is a crown ether, and the reaction is performed in a dioxane solvent.

40. A process as claimed in any of Claims 34 to 39, in which the reaction between the compounds of general formulae II and III is performed at any temperature from −10°C to the reflux temperature of the reaction mixture.

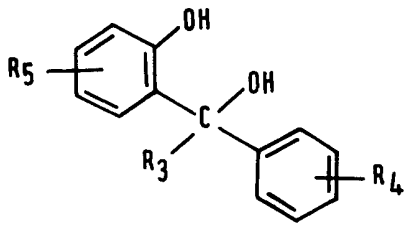
41. A process as claimed in any of Claims 34 to 40, in which the formed alkali-metal salt of the compound of general formula I is thereafter treated with an acid to

obtain the corresponding acid of general formula I in which R_1 represents a hydrogen atom.

42. A process as claimed in Claim 41, in which the formed acid of general formula I is in turn converted into its alkali-metal, alkaline-earth-metal, aluminium, ammonium or quaternary ammonium salts by reaction with an appropriate base.

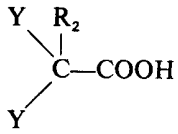
43. A process as claimed in Claim 42, in which the conversion is carried out in a solvent.

44. An alternative process for preparing alkali-metal salts of the compounds of general formula I wherein R_1 represents a hydrogen atom, in which process a compound of general formula:



(II)

(wherein R_3, R_4 and R_5 are as defined in Claim 2) is reacted with an alkali-metal salt of an acid of general formula:



(III')

(wherein Y represents a bromine atom or an iodine atom and R_2 is as defined in Claim 2) in the presence of a basic condensation promoting agent to give the desired salt.

45. A process as claimed in Claim 44 in which the reaction is performed using methods analogous to those defined in any of Claims 35 to 40 in relation to the analagous process defined in Claim 34.

46. A process as claimed in Claim 44 or Claim 45, in which the formed alkali-metal salt is converted into the corresponding acid, and optionally thereafter into corresponding alkali-metal, alkaline-earth-metal, aluminium, ammonium and quaternary ammonium salts, by methods identical to those defined in Claims 41 to 43.

47. A process for preparing the esters of general formula I in which R_1 represents an alkyl radical containing from 1 to 5 carbon atoms, in which an acid of general formula I wherein R_1 represents a hydrogen atom is esterified to obtain the desired ester.

48. A process as claimed in Claim 47, in which the esterification is performed by reacting an alcohol of general formula:

R'OH

(wherein R' represents an alkyl radical containing from 1 to 5 carbon atoms) with the acid or a functional derivative thereof.

49. A process as claimed in Claim 48 in which, where an acid of general formula I is employed, the reaction is performed in an acidic medium.

51. A process as claimed in Claim 47, in which the esterification is effected by transesterification of the acid.

52. A process as claimed in Claim 47, in which, where R_1 represents a methyl radical, the esterification is effected by the action of diazomethane on the acid in an organic solvent.

53. A process as claimed in any of Claims 47 to 52, in which the acid of general formula I is prepared by the process claimed in Claim 41.

54. A process as claimed in any of Claims 47 to 52, in which the acid of general formula I is prepared by the process claimed in Claim 46.

55. A process as claimed in any of Claims 47 to 54, in which diastereoisomers of the formed esters are separately hydrolysed to form a corresponding diastereomeric acid of general formula I.

56. A process for preparing the compounds of formula I' wherein R_1' represents a (2,2 - dimethyl - 1,3 - dioxolan - 4 - yl) - methyl radical or a dialkylaminoalkyl radical of which the alkyl radicals contain from 1 to 4 carbon atoms, and R_2, R_3. R_4 and R_5 are as defined in Claim 1, in which process an acid of general formula I in which R_1 represents hydrogen atom, or a functional derivative thereof, is reacted with an alcohol of formula $R_1'OH$, wherein R_1' is as just defined, to obtain the desired compound of general formula I.

57. A process as claimed in Claim 56, in which the functional derivative of the acid of general formula I employed is an ester or an acid halide thereof.

58. A process as claimed in Claim 56 or Claim 57, in which the reaction is carried out in an organic solvent.

59. A process as claimed in any of Claims 56 to 58, in which the formed compound of general formula I' wherein R_1' represents a (2,2 - dimethyl - 1,3 - dioxolan - 4 - yl) - methyl radical, is thereafter treated with a hydrolysing agent to obtain the corresponding compound of general formula I' wherein R_1' represents a 2,3 - dihydroxy - propyl radical.

60. A process as claimed in Claim 59, in which the hydrolysing agent employed is hydrochloric acid.

61. A process as claimed in any of Claims 56 to 58, in which the formed compound of general formula I' wherein R_1' represents a dialkylaminoalkyl radical of which the alkyl radicals contain from 1 to 4 carbon atoms is thereafter treated with an acid to form its corresponding acid addition salt.

62. A process as claimed in any of Claims 56 to 61, in which the acid of general formula I used as starting material is prepared by the process claimed in Claim 41.

63. A process as claimed in any of Claims 56 to 61, in which the acid of general formula I used as starting material is prepared by the process claimed in Claim 46.

64. A process for preparing compounds of general formula I wherein R_4 and R_5 each represent a hydrogen atom, which process comprises treating a compound of general formula I wherein either one of R_4 and R_5 represents a chlorine atom and the other represents a hydrogen atom, or both R_4 and R_5 represent a chlorine atom, with hydrogen in the presence of a catalyst to obtain the desired product of general formula I.

65. A process as claimed in Claim 64, in which the catalyst employed is palladium.

66. A process as claimed in Claim 64 or Claim 65 in which the treatment is carried out in an alkaline medium containing an organic solvent.

67. A process as claimed in any of Claims 64 to 66, in which the starting material of general formula I is prepared by a process claimed in any of Claims 34 to 55.

68. A process for preparing a 1,3-benzodioxine derivative as claimed in Claim 1, substantially as described herein with reference to any one of the Examples 1 to 38.

69. Pharmaceutical compositions containing one or more of the compounds of general formula I or I', and where possible, their pharmaceutically acceptable alkali-metal, alkaline-earth-metal, ammonium, aluminium, quaternary-ammonium or acid-addition salts, as defined in any of Claims 1, 3 to 10, 21, 24 and 25 in association with a suitable pharmaceutically acceptable vehicle.

70. Pharmaceutical compositions containing one or more of the compounds of general formula I or I', and where possible, their pharmaceutically acceptable alkali-metal, alkaline-earth-metal, ammonium, aluminium, quaternary-ammonium or acid-addition salts, as defined in any of Claims 2, 11 to 20, 22, 23 and 26 to 33 in association with a suitable pharmaceutically acceptable vehicle.

71. A pharmaceutical composition substantially as described herein with reference to any one of the Formulations.

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