

PATENT SPECIFICATION

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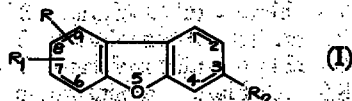
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(54) DIBENZOFURAN DERIVATIVES

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESSELLSCHAFT, a Swiss Company of 124-184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to dibenzofuran derivatives, as well as to a process for the manufacture thereof and pharmaceutical preparations containing same.

The dibenzofuran derivatives provided by this invention are compounds of the general formula



wherein R represents a hydrogen or halogen atom or a hydroxy, cyano, lower alkyl, hydroxy - (lower alkyl), lower alkoxy, acyl, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group; R₁ represents a halogen atom or a cyano, lower alkyl, hydroxy - (lower alkyl), lower alkoxy, acyl, acylamido, benzyloxy, lower alkylthio, trifluoromethyl, hydroxy, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl,

di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group, or R and R₁ on adjacent carbon atoms together represent a lower alkylenedioxy group; and R₂ represents the grouping



in which A represents a cyano, hydroxy, lower alkoxy, amino - (lower alkoxy), mono(lower alkyl) - amino - (lower alkoxy) or di(lower alkyl)amino - (lower alkoxy) group or the grouping —C(O)—B, wherein B represents a hydrogen atom or a hydroxy, carboxy, lower alkoxy, amino, hydroxyamino, mono(lower alkyl)amino, di(lower alkyl)amino, amino - (lower alkoxy), mono(lower alkyl) - amino - (lower alkoxy) or di(lower alkyl)amino - (lower alkoxy) group; X and Y each represent a hydrogen atom or a lower alkyl group and n stands for 1 to 7,

and salts thereof.

The compounds of formula I and pharmaceutically acceptable salts thereof are useful as anti-inflammatory, analgesic and anti-rheumatic agents.

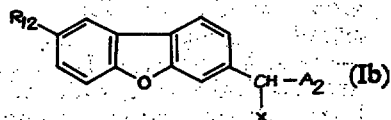
The pharmaceutically unacceptable salts of the compounds of formula I can be converted into compounds of formula I or into pharmaceutically acceptable salts thereof.

As used in this description and in the accompanying claims, the term "lower alkyl"

denotes a straight-chain or branched-chain hydrocarbon group containing 1-7 carbon atoms (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, neopentyl, pentyl and heptyl). The term "lower alkoxy" denotes an alkyl ether group in which the alkyl group is as defined earlier (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy and pentoxy). The term "lower alkylthio" denotes an alkyl thioether group in which the alkyl group is as defined earlier (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio and pentylthio). The term "halogen" denotes bromine, chlorine, fluorine and iodine, with bromine and chlorine being preferred. The term "acyl" denotes a "lower alkanoyl" group derived from an aliphatic carboxylic acid containing 1-7 carbon atoms (e.g. formyl, acetyl and propionyl) and an "aroyl" group derived from an aromatic carboxylic acid (e.g. benzoyl). The term "lower alkylene" denotes a straight-chain or branched-chain alkylene group containing 1-7 carbon atoms (e.g. methylene, ethylene, propylene, butylene and methyl - methylene). The term "lower alkylenedioxy" preferably denotes methylenedioxy.

Examples of mono(lower alkyl)amino groups are methylamino and ethylamino. Examples of di(lower alkyl)amino groups are dimethylamino and diethylamino. Examples of amino - (lower alkoxy) groups are aminomethoxy and aminoethoxy. Examples of mono(lower alkyl)amino - (lower alkoxy) groups are methylaminomethoxy and ethylaminomethoxy. Examples of di(lower alkyl)amino - (lower alkoxy) groups are dimethylaminomethoxy and diethylaminomethoxy. Examples of di(lower alkyl)sulfamoyl groups are dimethylsulfamoyl and diethylsulfamoyl.

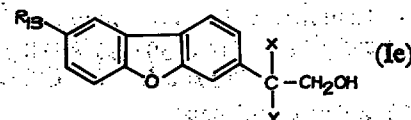
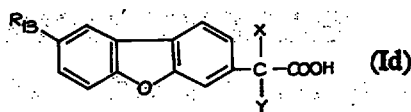
Preferred dibenzofuran derivatives provided by this invention are compounds of the general formula



wherein R_{12} represents a halogen atom or a hydroxy, lower alkyl, lower alkoxy, benzyloxy, nitro, amino, lower alkanoyl-amido or trifluoromethyl group, A_2 represents a cyano, hydroxymethyl or hydroxy group or the grouping $-C(O)-B_2$, wherein B_2 represents a hydrogen atom or a hydroxy, lower alkoxy, amino, hydroxyamino, mono(lower alkyl)amino, di(lower alkyl)amino or di(lower alkyl)amino - (lower alkoxy) group, and X represents a hydrogen atom or a lower alkyl group, and their pharmaceutically acceptable salts.

Particularly preferred dibenzofuran derivatives provided by this invention are compounds of the general formulae

and



wherein R_{13} represents a halogen atom or a lower alkyl or lower alkoxy group, preferably a halogen atom or a lower alkyl group and most preferably a halogen atom, and X and Y have the significance given earlier, and their pharmaceutically acceptable salts.

Preferred compounds of formula I are:

8 - chloro - α - methyl dibenzofuran - 3 - acetic acid,

(+) - 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid,

(-) - 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid,

2 - (8 - chloro - 3 - dibenzofuranyl) - propanol,

2 - (8 - chloro - 3 - dibenzofuranyl) ethanol,

8 - chloro - dibenzofuran - 3 - acetic acid,

8 - chloro - dibenzofuran - 3 - acetamide and

8 - chloro - α - methyl dibenzofuran - 3 - acetaldehyde.

Examples of compounds of formula I are:

8 - chloro - dibenzofuran - 3 - acetic acid,

8 - chloro - dibenzofuran - 3 - acetic acid ethyl ester,

8 - methoxy - dibenzofuran - 3 - acetic acid,

8 - nitro - dibenzofuran - 3 - acetic acid,

7 - methoxy - dibenzofuran - 3 - acetic acid,

7 - chloro - dibenzofuran - 3 - acetic acid,

8 - methyl - dibenzofuran - 3 - acetic acid,

6 - chloro - dibenzofuran - 3 - acetic acid,

8,9 - dichloro - dibenzofuran - 3 - acetic acid,

α - methyl - dibenzofuran - 3 - acetic acid,

8 - carbethoxy - dibenzofuran - 3 - acetic acid,

7 - methyl - dibenzofuran - 3 - acetic acid,

7,8 - dichloro - dibenzofuran - 3 - acetic acid,

8 - chloro - 9 - methyl - dibenzofuran - 3 - acetic acid,

8 - difluoromethylsulfonyl - dibenzofuran - 3 - acetic acid,

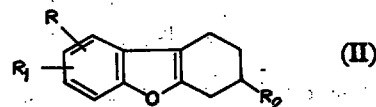
2 - (8 - chloro - 3 - dibenzofuranyl) propanol methyl ether,

8 - chloro - 7 - methyl - dibenzofuran - 3 - acetic acid,

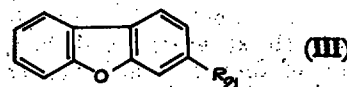
- 8 - sulfamoyl - dibenzofuran - 3 - acetic acid,
 8 - benzoyl - dibenzofuran - 3 - acetic acid,
 8 - fluoro - dibenzofuran - 3 - acetic acid,
 8 - trifluoromethyl - dibenzofuran - 3 - acetic acid,
 6,7 - dichloro - dibenzofuran - 3 - acetic acid,
 9 - chloro - 8 - sulfamoyl - dibenzofuran - 3 - acetic acid,
 8 - methylthio - dibenzofuran - 3 - acetic acid,
 8 - ethyl - dibenzofuran - 3 - acetic acid,
 8 - chloro - dibenzofuran - 3 - acetic acid dimethylaminoethyl ester,
 8 - methyl - dibenzofuran - 3 - acetic acid ethyl ester,
 8 - dimethylsulfamoyl - dibenzofuran - 3 - acetic acid,
 8 - carboxy - dibenzofuran - 3 - acetic acid,
 8 - iodo - dibenzofuran - 3 - acetic acid,
 8 - chloro - N,N - dimethyl - dibenzofuran - 3 - acetamide,
 8 - cyano - dibenzofuran - 3 - acetic acid,
 8 - acetyl - dibenzofuran - 3 - acetic acid,
 8 - chloro - dibenzofuran - 3 - acetic acid dimethylaminoethyl ester hydrochloride,
 8 - benzyloxy - dibenzofuran - 3 - acetic acid,
 7,8 - methylenedioxy - dibenzofuran - 3 - acetic acid,
 8 - hydroxy - dibenzofuran - 3 - acetic acid,
 7 - chloro - dibenzofuran - 3 - acetic acid ethyl ester,
 9 - chloro - dibenzofuran - 3 - acetic acid ethyl ester,
 8 - bromo - dibenzofuran - 3 - acetic acid ethyl ester,
 8 - acetamido - dibenzofuran - 3 - acetic acid ethyl ester,
 8 - chloro - dibenzofuran - 3 - propionic acid ethyl ester,
 8 - chloro - α,α - dimethyl - dibenzofuran - 3 - acetic acid ethyl ester,
 8 - chloro - α - methyl - dibenzofuran - 3 - acetic acid dimethylaminoethyl ester,
 8 - chloro - α - methyl - dibenzofuran - 3 - acetamide,
 8 - trifluoromethyl - dibenzofuran - 3 - acetic acid ethyl ester,
 6,7 - dichloro - dibenzofuran - 3 - acetic acid ethyl ester,
 8,9 - dichloro - dibenzofuran - 3 - acetic acid ethyl ester,
 8 - methylthio - dibenzofuran - 3 - acetic acid ethyl ester,
 8 - carbethoxy - dibenzofuran - 3 - acetic acid ethyl ester,
 8 - fluoro - dibenzofuran - 3 - acetic acid ethyl ester,
 α - methyl - dibenzofuran - 3 - acetic acid ethyl ester,

- 8 - N,N - dimethylsulfamoyl - dibenzofuran - 3 - acetic acid ethyl ester,
 8 - cyano - dibenzofuran - 3 - acetic acid ethyl ester,
 7,8 - dichloro - dibenzofuran - 3 - acetic acid ethyl ester, and
 8 - nitro - dibenzofuran - 3 - acetic acid ethyl ester.

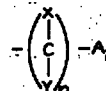
According to the process provided by the present invention, the dibenzofuran derivatives aforesaid (i.e. the compounds of formula I and their salts) are manufactured by reacting a compound of the general formula



wherein R, R₁ and R₂ have the significance given earlier, with an aromatising agent; or chlorinating or brominating a compound of the general formula

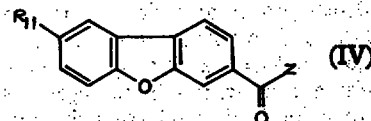


wherein R₂₁ represents the grouping



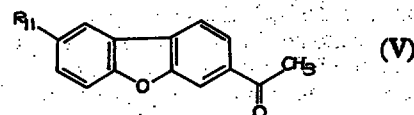
in which A₁ represents a cyano or lower alkoxy group or the grouping $-\text{C}(\text{O})-\text{B}_1$, in which B₁ represents a hydroxy, lower alkoxy or di(lower alkyl)-amino group, and n, X and Y have the significance given earlier,

to yield a corresponding compound of formula I in which R₁ represents a chlorine or bromine atom, R represents a hydrogen atom and R₂ has any of the values accorded to R₂₁; or simultaneously reducing and saponifying a compound of the general formula



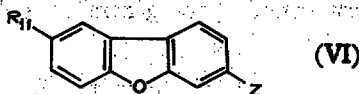
wherein R₁₁ represents a chlorine or bromine atom and Z represents a carbo - (lower alkoxy) group,

to yield a corresponding compound of formula I in which R represents a hydrogen atom, R₁ has either of the values accorded to R₁₁ and R₂ represents a carboxymethyl group; or reacting a compound of the general formula



wherein R_{11} has the significance given earlier,

with an amine having a boiling point in the range of from 100°C to 200°C, in the presence of sulfur and saponifying the resulting compound to yield a corresponding acid of formula I in which R represents a hydrogen atom, R_1 has either of the values accorded to R_{11} and R_2 represents a carboxymethyl group; or reducing a compound of the general formula



wherein R_{11} and Z have the significance given earlier,

to yield a corresponding alcohol of formula I in which R represents a hydrogen atom, R_1 has either of the values accorded to R_{11} and R_2 represents a hydroxymethyl group; for the manufacture of an acid of formula I in which B represents a hydroxy group, saponifying an ester of formula I in which B represents a lower alkoxy group; if desired, reducing an ester of formula I in which at least one of R, R_1 and $-C(O)-B$ represents a carbo - (lower alkoxy) group to the corresponding alcohol in which the carbo - (lower alkoxy) group is replaced by the hydroxymethyl group; if desired, converting a hydroxy group denoted by B in an acid of formula I into an amino group; if desired, dehydrating an amide of formula I in which A represents a carbamoyl group to the corresponding nitrile; if desired, esterifying an acid of formula I in which B represents a hydroxy group, or a salt thereof with a base, or converting the group B in such an acid or salt thereof into an amino - (lower alkoxy) or mono(lower alkyl)amino - (lower alkoxy) or di(lower alkyl)amino - (lower alkoxy) group; if desired, deacylating an acylamido group denoted by R_1 to an amino group; if desired, halogenating an acid of formula I in which B represents a hydroxy group to yield a corresponding acid halide and hydrogenating the resulting acid halide to yield a corresponding aldehyde of formula I in which B represents a hydrogen atom; if desired, converting the group denoted by A in an alcohol of formula I in which A represents a hydroxymethyl group or the group denoted by A in an ester of formula I in which A represents a carbo - (lower alkoxy) group into the formyl group; if desired, appropriately alkylating an amino group denoted by R or R_1 in a compound of formula I to yield a compound of formula I in which R or R_1 represents a di(lower alkyl)amino group; if desired, dealkylating a lower alkoxy group denoted by R, R_1 or A contained in an ether of formula I to a hydroxy group; if desired, transforming a hydroxy group denoted by A contained in an alcohol of formula I into

a lower alkoxy, amino - (lower alkoxy), mono - (lower alkyl)amino - (lower alkoxy) or di - (lower alkyl)amino - (lower alkoxy) group; if desired, replacing the hydroxy group denoted by A in an alcohol of formula I in which R represents a hydrogen or halogen atom or a hydroxy, cyano, lower alkyl, lower alkoxy, acyl, lower alkylthio, trifluoromethyl, carboxy, carbo - (lower alkoxy), nitro, amino, mono - (lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group, R_1 represents a halogen atom or a cyano, lower alkyl, lower alkoxy, acyl, acylamido, lower alkylthio, trifluoromethyl, hydroxy, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group or R and R_1 on adjacent carbon atoms together represent a lower alkylenedioxy group, by a halogen atom and reacting the compound obtained with an alkali metal cyanide to yield a corresponding compound of formula I in which A represents a cyano group; if desired, saponifying a nitrile of formula I in which R represents a hydrogen or halogen atom or a hydroxy, cyano, lower alkyl, hydroxy - (lower alkyl), lower alkoxy, acyl, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino or difluoromethylsulfonyl group, R_1 represents a halogen atom or a cyano, lower alkyl, hydroxy - (lower alkyl), lower alkoxy, acyl, acylamido, benzyloxy, lower alkylthio, trifluoromethyl, hydroxy, carboxy, carbo - (lower alkoxy), nitro, amino, mono - (lower alkyl)amino, di(lower alkyl)amino or difluoromethylsulfonyl group or R and R_1 on adjacent carbon atoms together represent a lower alkylenedioxy group with the proviso that at least one of A, R and R_1 represents a cyano group, to the corresponding acid in which a cyano group is replaced by a carboxy group; if desired, appropriately alkylating a compound of formula I in which R represents a hydrogen or halogen atom or a hydroxy, cyano, lower alkyl, lower alkoxy, acyl, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group, R_1 represents a halogen atom or a cyano, lower alkyl, lower alkoxy, acyl, acylamido, benzyloxy, lower alkylthio, trifluoromethyl, hydroxy, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group or R and R_1 on adjacent carbon atoms together represent a lower alkylenedioxy group, n stands for 1, A represents a cyano group or the grouping $-C(O)-B$ in which B represents a hydrogen atom or a lower alkoxy group and at least one of X and Y

represents a hydrogen atom, to yield a corresponding compound of formula I in which at least one of X and Y represents a lower alkyl group; if desired, converting an acid or base of formula I into a salt; and, also if desired, resolving a racemate obtained into its optically active isomers and isolating the desired isomer.

A compound of formula II can be converted into a corresponding compound of formula I by reaction with an aromatising agent [e.g. p - chloranil, o - chloranil, 2,3 - dichloro - 5,6 - dicyanobenzoquinone (DDQ), sulfur, palladium-on-carbon and lead oxide] in the presence of a solvent [e.g. xylene, benzene, toluene, quinoline, dimethyl sulfoxide (DMSO) or dimethylformamide (DMF)]. The aromatisation is carried out at a temperature of from room temperature to the reflux temperature of the reaction mixture, preferably at the reflux temperature of the reaction mixture. The compound of formula I can be separated from the reaction mixture by known procedures; for example, by filtration, crystallisation or distillation.

A compound of formula I in which B represents a lower alkoxy group can be de-esterified to a corresponding compound of formula I in which B represents a hydroxy group by saponification according to known procedures; for example, by reaction with an alkali metal hydroxide (e.g. sodium hydroxide or potassium hydroxide) and subsequent treatment with a mineral acid (e.g. a hydrohalic acid such as hydrochloric acid). The de-esterification can be carried out in the presence of a solvent (e.g. an alkanol such as methanol or ethanol) at a temperature of from room temperature to the reflux temperature of the mixture, preferably at the reflux temperature of the mixture. The compound of formula I can be separated from the mixture by known procedures.

An ester of formula I in which A, R and/or R₁ represents a carbo - (lower alkoxy) group can be converted into a corresponding alcohol (e.g. a compound of formula I in which A represents a hydroxymethyl group) by known procedures. For example, an ester of formula I can be treated with a reagent such as lithium aluminium hydride at a temperature of from room temperature to the reflux temperature of the mixture. Thereafter, the corresponding alcohol which is formed can be separated by known procedures.

A compound of formula I in which R₁ represents an acylamido group can be converted into a corresponding compound of formula I in which R₁ represents an amino group by treatment with an inorganic acid (e.g. a hydrohalic acid such as hydrochloric acid) according to known conditions.

An acid of formula I in which B represents a hydroxy group or a salt of such an acid with a base can be converted into a compound of formula I in which B represents

an amino - (lower alkoxy), mono(lower alkyl)-amino - (lower alkoxy) or di(lower alkyl)-amino - (lower alkoxy) group according to known procedures. For example, a salt of an acid of formula I is reacted with an amino - (lower alkyl) halide, a mono(lower alkyl)-amino - (lower alkyl) halide or di(lower alkyl)-amino - (lower alkyl) halide, examples of which are aminoethyl chloride, methylaminoethyl bromide and diethylaminomethyl chloride, to yield the desired product. The temperature at which the reaction is carried out is not critical. Conveniently, the reaction is carried out at a temperature of from room temperature to the reflux temperature of the reaction mixture. Conveniently, the reaction can be carried out in a polar solvent such as dimethylformamide or dimethyl sulfoxide. The molar ratio of reactants is not critical. Preferably, the reactants are used in a 1:1 molar ratio.

An acid of formula I in which R₂ represents a carboxy group can be converted into a corresponding ester by known procedures. For instance, (a) an acid of formula I can be reacted with an alkanol (e.g. methanol, ethanol or propanol) at a temperature of from about room temperature to the reflux temperature of the reaction mixture, or (b) an alkali metal salt of an acid of formula I (e.g. the sodium salt) can be reacted with a substituted or unsubstituted alkyl halide under known conditions (e.g. in an inert solvent such as benzene, toluene or dimethylformamide at a temperature of from room temperature to the reflux temperature of the reaction mixture).

A compound of formula I in which R or R₁ represents an amino group can be converted into a corresponding compound in which R or R₁ represents a di(lower alkyl)-amino group according to known procedures; for example, using hydrogen at a pressure of from 1 atmosphere to several atmospheres and a catalyst such as Raney nickel, together with an appropriate alkyl aldehyde such as formaldehyde at a temperature of from room temperature to 100°C in a solvent (e.g. an alkanol such as methanol or ethanol).

A compound of formula I in which R, R₁ or A represents a lower alkoxy group can be converted into a corresponding compound in which R, R₁ or A represents a hydroxy group according to known procedures. For example, such a compound of formula I can be treated with a mineral acid (e.g. a hydrohalic acid such as hydrobromic acid) in a solvent (e.g. an alkanol such as ethanol or propanol) at a temperature of from room temperature to the reflux temperature of the reaction mixture. The conversion can also be carried out using a Lewis acid (e.g. aluminium tribromide, boron trifluoride or tin tetrachloride) in a solvent (e.g. benzene, toluene or dimethylformamide).

An alcohol of formula I in which A represents a hydroxy group can be converted into a corresponding compound of formula I in which A represents a lower alkoxy, amino - (lower alkoxy), mono(lower alkyl)amino - (lower alkoxy) or di(lower alkyl)amino - (lower alkoxy) group according to known procedures. For example, such an alcohol of formula I is treated with an alkali metal such as sodium. The resulting compound is then treated with a halide of the formula RX' , wherein X' represents a halogen atom and R represents a lower alkyl, amino - (lower alkyl), mono - (lower alkyl)amino - (lower alkyl) or di(lower alkyl)amino - (lower alkyl) group under known reaction conditions.

An acid of formula I in which B represents a hydroxy group can be converted into a corresponding amide in which B represents an amino group by reaction with a dehydrating agent such as 1,1' - carbonyldiimidazole followed by reaction of the resulting compound with ammonia. Preferably, the reaction is carried out at a temperature of from 0°C to 40°C in an aprotic solvent (e.g. tetrahydrofuran or dioxane) and under an inert atmosphere (e.g. an atmosphere of nitrogen).

An amide of formula I in which A represents a carbamoyl group can be converted into a corresponding nitrile in which A represents a cyanomethyl group by reaction with a halogenating agent such as phosphorus oxychloride followed by reaction of the resulting compound with a tertiary amine such as a tri(lower alkyl)amine (e.g. triethylamine). The first step of this reaction is preferably carried out at a temperature of from 0°C to 50°C , most preferably at about room temperature and with or without an inert solvent such as nitrobenzene or a haloalkane (e.g. tetrachloromethane). The second step of this reaction is preferably carried out at a temperature of from -10°C to $+10^{\circ}\text{C}$, preferably at about 0°C .

An acid of formula I in which B represents a hydroxy group can be converted into a corresponding acid halide by reaction with known reagents such as thionyl chloride or phosphorus oxychloride. Preferably, the reaction is carried out at a temperature of from 0°C to the reflux temperature of the reaction mixture and with or without an aprotic solvent such as nitrobenzene or a haloalkane (e.g. methylene chloride or tetrachloromethane). The resulting acid halide is then converted into a corresponding aldehyde of formula I in which B represents a hydrogen atom by the Rosenmund reaction (i.e. catalytic hydrogenation in the presence of a sulfur-containing palladium catalyst). Preferably, this reaction is carried out in an inert solvent such as dioxane or an aromatic hydrocarbon (e.g. benzene, toluene or xylene), at a pressure of

from 1 to 10 atmospheres and at a temperature of from 0°C to about 100°C .

An alcohol of formula I in which A represents a hydroxymethyl group can be converted into a corresponding aldehyde in which A represents a formyl group by reaction with an oxidising agent such as manganese dioxide. Preferably, the reaction is carried out in an aprotic solvent such as a haloalkane (e.g. methylene chloride or tetrachloromethane), an aromatic hydrocarbon (e.g. benzene, toluene or xylene), at a temperature of from 0°C to the reflux temperature of the reaction mixture, most preferably at about room temperature.

An ester of formula I in which A represents a carbo - (lower alkoxy) group can be converted into a corresponding aldehyde in which A represents a formyl group by selective reduction with sodium bis(2 - methoxyethoxy) - aluminium hydride. This reaction is preferably carried out in an aprotic solvent such as an ether (e.g. dioxane or tetrahydrofuran).

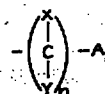
A compound of formula I in which R represents a hydrogen or halogen atom or a hydroxy, cyano, lower alkyl, lower alkoxy, acyl, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group, R_1 represents a halogen atom or a cyano, lower alkyl, lower alkoxy, acyl, acylamido, benzyloxy, lower alkylthio, trifluoromethyl, hydroxy, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group or R_1 and R_2 on adjacent carbon atoms together represent a lower alkylenedioxy group; n stands for 1; at least one of X and Y represents a hydrogen atom and A represents a cyano group or the grouping $-\text{C}(\text{O})-\text{B}$ in which B represents a hydrogen atom or a lower alkoxy group, can be appropriately alkylated to yield a corresponding compound of formula I in which at least one of X and Y represents a lower alkyl group. In a first step, the compound to be alkylated can be reacted with, e.g., an alkali metal amide or an alkali metal hydride, conveniently with sodium amide, in the presence of hexamethyl - phosphoric acid triamide or liquid ammonia. Where hexamethyl - phosphoric acid triamide is used, the reaction is conveniently carried out at a temperature of from 0°C to 100°C , with or without an aprotic solvent such as an ether (e.g. tetrahydrofuran or diethyl ether). Where liquid ammonia is used, the reaction is conveniently carried out at a temperature of from -70°C to the reflux temperature of the reaction mixture, with or without an aprotic solvent of the kind mentioned earlier. In a second step, the resulting alkali metal salt is treated with a haloalkane (e.g. iodomethane

or bromoethane), conveniently at a temperature in the range mentioned earlier.

A nitrile of formula I in which A represents a cyano group, R represents a hydrogen or halogen atom or a hydroxy, cyano, lower alkyl, lower alkoxy, acyl, lower alkylthio, trifluoromethyl, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group, R₁ represents a halogen atom or a cyano, lower alkyl, lower alkoxy, acyl, acylamido, lower alkylthio, trifluoromethyl, hydroxy, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group or R and R₁ on adjacent carbon atoms together represent a lower alkylenedioxy group, can be manufactured by treating a corresponding alcohol of formula I in which A represents a hydroxy group with a halogenating agent such as thionyl chloride or a hydrohalic acid (e.g. hydrochloric acid), with or without an inert solvent such as a haloalkane (e.g. dichloromethylene) at a temperature of from 0°C to the reflux temperature of the reaction mixture. The resulting halide is then reacted with an alkali metal cyanide (e.g. sodium or potassium cyanide), conveniently in a polar solvent (e.g. dimethyl sulfoxide) at a temperature of from 0°C to the reflux temperature of the reaction mixture.

An acid of formula I in which R represents a hydrogen or halogen atom or a hydroxy, cyano, lower alkyl, hydroxy - (lower alkyl), lower alkoxy, acyl, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino or difluoromethylsulfonyl group, R₁ represents a halogen atom or a cyano, lower alkyl, hydroxy - (lower alkyl), lower alkoxy, acyl, acylamido, benzyloxy, lower alkylthio, trifluoromethyl, hydroxy, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino or difluoromethylsulfonyl group or R and R₁ on adjacent carbon atoms together represent a lower alkylenedioxy group with the proviso that at least one of A, R and R₁ represents a carboxy group can be manufactured by saponifying a corresponding nitrile in which A, R or R₁ represents a cyano group. The saponification is conveniently carried out either using a strong acid such as a hydrohalic acid (e.g. hydrochloric acid) in a solvent such as a lower alkanol (e.g. n - butanol) or using a strong base such as an alkali metal hydroxide (e.g. sodium hydroxide) in a solvent such as a lower alkanolic acid (e.g. acetic acid) at a temperature of from 20°C to the reflux temperature of the mixture.

An 8 - (chloro or bromo) - dibenzofuran of formula I in which R₂ represents the grouping



wherein A₁ represents a cyano or lower alkoxy group or the grouping —C(O)—B

wherein B represents a hydroxy, lower alkoxy or di(lower alkyl)amino group, can be manufactured by chlorinating or brominating a corresponding dibenzofuran of formula III hereinbefore in the presence of a catalytic amount of iron powder. The chlorination or bromination is preferably carried out in a solvent such as a lower alkanolic acid (e.g. acetic acid) at a temperature of from 0°C to the reflux temperature of the mixture.

Alternatively, a compound of formula III can be treated with a halogenating agent such as sulfur chloride or N - bromosuccinimide, preferably in an inert solvent such as nitrobenzene, and at a temperature of from 20°C to the reflux temperature of the mixture.

A compound of formula I in which R represents a hydrogen atom, R₁ represents a chlorine or bromine atom in the 8-position and R₂ represents a carboxymethyl group can be manufactured by simultaneously reducing and saponifying a compound of formula IV hereinbefore. This procedure is conveniently carried out with hydrazine and an alkali hydroxide (e.g. potassium hydroxide) in the presence of a high boiling solvent such as diglyme or a glycol (e.g. ethylene glycol) at a temperature of from 100°C to the reflux temperature of the mixture.

Alternatively, an acid of formula I in which R represents a hydrogen atom, R₁ represents a chlorine or bromine atom in the 8-position and R₂ represents a carboxymethyl group can be manufactured from a compound of formula V hereinbefore by the Willgerodt reaction (i.e. by refluxing in an amine having a boiling point in the range from 100°C to 200°C such as morpholine in the presence of sulfur) and saponifying the resulting product with a mineral acid such as a halohydric acid (e.g. hydrochloric acid). The saponification is preferably carried out in a solvent such as a lower alkanolic acid (e.g. acetic acid) at a temperature of from 20°C to the reflux temperature of the mixture.

An alcohol of formula I in which R represents a hydrogen atom, R₁ represents a chlorine or bromine atom in the 8-position and R₂ represents a hydroxymethyl group can be manufactured by reducing a compound of formula VI hereinbefore. This reduction can be carried out in the same manner as described earlier in connection with the conversion of an ester of formula I in which A represents a carbo - (lower alkoxy) group into a corresponding alcohol of formula I in which A represents a hydroxymethyl group.

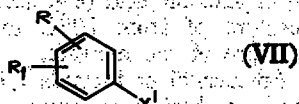
The compounds of formula I in which R or R₁ represents an amino, mono(lower alkyl)-amino or di(lower alkyl)amino group and/or in which B or A represents an amino - (lower alkoxy), mono(lower alkyl)amino - (lower alkoxy) or di(lower alkyl)amino - (lower alkoxy) group form addition salts with organic and inorganic acids, for instance with pharmaceutically acceptable acids. Examples of such salts are hydrohalides (e.g. hydrochloride, hydrobromide and hydroiodide), sulfate, nitrate and phosphate, alkylsulfonates and arylsulfonates such as ethanesulfonate, toluenesulfonate and benzenesulfonate, acetate, tartrate, maleate, citrate, benzoate, salicylate and ascorbate.

The compounds of formula I in which R or R₁ represents a carboxy group and/or B represents a hydroxy or carboxy group form salts with pharmaceutically acceptable bases. Examples of such bases are alkali metal hydroxides (e.g. sodium hydroxide and potassium hydroxide), alkaline earth metal hydroxides (e.g. calcium hydroxide and barium hydroxide), sodium alkoxides (e.g. sodium ethanolate and potassium ethanolate) and organic bases (e.g. piperidine, diethanolamine and N - methylglucamine). Also included within this invention are the aluminium salts of the compounds of formula I.

Since the compounds of formula I in which X and Y have different values possess an asymmetric carbon atom, they are ordinarily obtained as racemic mixtures. The resolution of such racemates into the optically active isomers can be carried out by known procedures. Some racemic mixtures can be precipitated as eutectics and can thereafter be separated. Chemical resolution is, however, preferred. By this method, diastereomers are formed from the racemic mixture with an optically active base such as d - α - methylbenzylamine which can be reacted with the carboxyl group. The diastereomers formed are separated by selective crystallisation and converted into the corresponding optical isomer.

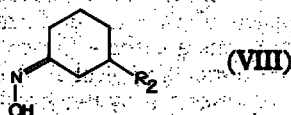
The starting materials of formula II can be prepared as follows:

A halobenzene of the general formula

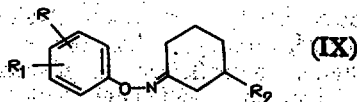


wherein X' represents a halogen atom, preferably a fluorine atom, and R and R₁ have the significance given earlier,

can be reacted with an oxime of the general formula



wherein R₂ has the significance given earlier, to yield an O-phenyl oxime of the general formula



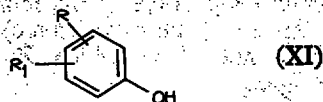
wherein R, R₁ and R₂ have the significance given earlier,

in a polar solvent such as dimethyl sulfoxide, dimethylformamide or hexamethylphosphoric acid triamide. The reaction temperature is not critical. Preferably, the reaction is carried out at a temperature of from room temperature to the reflux temperature of the reaction mixture. The molar ratio of the reactants is not critical. Preferably, they are reacted in a 1:1 molar ratio.

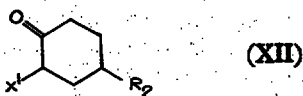
An O-phenyl oxime of formula IX is converted into a compound of formula II using, for example, an acidic catalyst such as an organic, inorganic or Lewis acid, examples of which are hydrochloric acid, sulfuric acid, phosphoric acid, zinc chloride, copper chloride and boron trifluoride, and various combinations thereof. Conveniently, the reaction can be carried out in a polar solvent such as an alkanol (e.g. methanol, ethanol or propanol), water or a hydrocarbon (e.g. benzene or toluene). The reaction temperature is not critical. Preferably, the reaction is carried out at a temperature of from room temperature to the reflux temperature of the reaction mixture. The separation of the desired compound of formula II from the reaction mixture can be carried out according to known techniques such as, for example, filtration, crystallisation or distillation.

A nitro group present in a compound of formula II can be converted into an amino group according to known procedures; for example, by catalytic reduction. An amino group can be converted into a diazonium salt grouping according to known procedures, for example, by reaction with sodium nitrite and a mineral acid such as a hydrohalic acid. A diazonium salt group can then be replaced by a halogen atom, a cyano, hydroxy or lower alkoxy group or a hydrogen atom according to known procedures; for example, by mixing a diazonium salt solution with, for example, a cuprous halide, cuprous cyanide, water, an alkanol or a reducing agent such as hypophosphorus acid, respectively, at room temperature or, occasionally, at an elevated temperature.

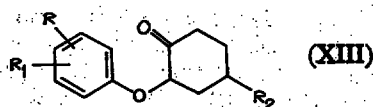
The compounds of formula II can also be prepared by reacting a compound of the general formula



wherein R and R₁ have the significance given earlier, with an appropriate haloketocycloalkane of the general formula



wherein X' and R₂ have the significance given earlier, to yield a compound of the general formula



wherein R, R₁ and R₂ have the significance given earlier.

The reaction is conveniently carried out in a non-polar solvent (e.g. a hydrocarbon such as benzene or toluene) or a polar solvent (e.g. dimethyl sulfoxide, dimethylformamide or hexamethylphosphoric acid triamide). The reaction temperature is not critical. Preferably, the reaction is carried out at a temperature of from room temperature to the reflux temperature of the reaction mixture. The molar ratio of the reactants is not critical. Preferably, they are reacted at a 1:1 molar ratio.

A compound of formula XIII can then be converted into a compound of formula II by thermal cyclisation or by using a cyclising agent such as polyphosphoric acid. Preferably, the reaction is carried out at a temperature of from -20°C to 120°C. The reaction can be conveniently carried out in the presence or absence of a solvent. An example of a convenient solvent is acetic acid.

The halobenzenes of formula VII are known compounds or can be prepared in an analogous manner to known compounds. Examples of such halobenzenes are:

- 4 - fluoronitrobenzene,
- 4 - fluorocyanobenzene, and
- 4 - fluoroacetophenone.

The oximes of formula VIII are known compounds or can be prepared in an analogous manner to known compounds. Examples of such oximes are:

- 3 - oxyiminocyclohexaneacetic acid methyl ester,
- 3 - oxyiminocyclohexaneacetic acid ethyl ester,
- 3 - oxyiminocyclohexaneacetic acid propyl ester, and
- 3 - oxyiminocyclohexaneacetic acid butyl ester.

The O-phenyl oximes of formula IX are

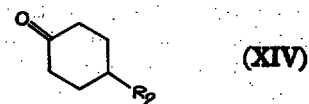
novel compounds. Examples of such O-phenyl oximes are:

- 3 - (4 - nitrophenoxyimino)cyclohexaneacetic acid and the methyl ester thereof,
- 3 - (2 - nitrophenoxyimino)cyclohexaneacetic acid and the methyl ester thereof,
- 3 - (4 - cyanophenoxyimino)cyclohexaneacetic acid, and
- 3 - (2 - trifluoromethylphenoxyimino)cyclohexaneacetic acid.

The compounds of formula XI are known compounds or can be prepared in an analogous manner to known compounds. Examples of such compounds are:

- 4 - chlorophenol,
- 5 - chlorophenol,
- 4 - nitrophenol and
- p - cresol.

The haloketocycloalkanes of formula XII can be prepared by halogenating a compound of the general formula



wherein R₂ has the significance given earlier.

The compounds of formula XIV are known compounds or can be prepared in an analogous manner to known compounds.

The halogenation is carried out according to known procedures; for example, using a halogen such as bromine in ether at a temperature of -10°C.

Examples of haloketocycloalkanes of formula XII are:

- 3 - bromo - 4 - ketocyclohexaneacetic acid, and
- 3 - bromo - 4 - ketocyclohexaneacetic acid ethyl ester.

Examples of compounds of formula XIII are:

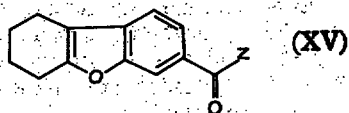
- 3 - (4 - chlorophenoxy) - 4 - oxocyclohexaneacetic acid and the ethyl ester thereof, and
- 3 - (4 - bromophenoxy) - 4 - oxocyclohexaneacetic acid and the methyl ester thereof.

The starting materials of formulae III and VI are known compounds or can be prepared in an analogous manner to known compounds.

The starting materials of formula IV can be prepared as follows:

1,2,3,4 - Tetrahydro - dibenzofuran can be reacted under the conditions of a Friedel-Crafts reaction with a mono(lower alkyl)

oxalate halide (e.g. monomethyl oxalate chloride) to yield a compound of the general formula



wherein Z represents a carbo - (lower alkoxy) group.

Such a compound can then be aromatised in a manner analogous to that described in connection with the aromatisation of a compound of formula II. The resulting dibenzofuran can then be converted into a compound of formula IV by treatment with chlorine or bromine in the presence of glacial acetic acid and in a solvent (e.g. dioxane or tetrahydrofuran), conveniently at a temperature of from 0°C to the reflux temperature of the mixture, preferably at about 50°C.

The starting materials of formula V can be prepared as follows:

8 - (Chloro or bromo) - dibenzofuran - 3 - carboxylic acid can be treated with a halogenating agent such as thionyl chloride or phosphorus oxychloride at a temperature of from 0°C to the reflux temperature of the mixture, with or without an aprotic solvent such as a haloalkane (e.g. methylene chloride).

The compounds of formula I and salts thereof with pharmaceutically acceptable bases and acids possess anti-inflammatory, analgesic and anti-rheumatic activity and are therefore useful as anti-inflammatory, analgesic and anti-rheumatic agents. The compounds of formula I also exhibit a significantly low incidence of ulcerogenic activity, which renders them highly desirable as anti-inflammatory, analgesic and anti-rheumatic agents. Their pharmacologically useful activities are demonstrated in warm-blooded animals using standard procedures.

For example, the anti-inflammatory activity is demonstrated in rats weighing 125-155 g. The test animals are given 10 ml of vehicle (Hilgar, A.G. and Hummel, D.J.: Endocrine Bioassay Data No. 1, p. 15, August 1964, Cancer Chemotherapy National Service Center, N.I.H.) which contains the test compound per kg of body weight. The animals are treated daily for 5 consecutive days. Three hours after the first treatment, 0.05 ml of an 0.5% suspension of heat-killed desiccated *Mycobacterium butyricum* in olive oil, which has been steam sterilised for 30 minutes, is injected into the right hind foot of each rat. The paw volume is measured immediately after the injection of the adjuvant and again 96 hours later. The difference is recorded as volume of oedema. The paw volume is measured by immersion of the paw into a column of mercury to an ink mark exactly at the level of the lateral malleolus. Per cent

inhibition is calculated by dividing the average control oedema minus the average treatment oedema by the average control oedema times 100. The per cent inhibition is plotted against dose on semi-logarithmic probability paper and the dose required to produce a 30% reduction in oedema is estimated therefrom and is expressed as ED₃₀.

When 8 - chloro - dibenzofuran - 3 - acetic acid, which has demonstrated an LD₅₀ of, for example, 775 mg p.o. in mice, is used as the test compound at a dosage of 0.03 gm p.o., an anti-inflammatory activity is observed (ED₅₀=1.6).

The analgesic activity is demonstrated, for example, using a method which is a modification of that described by Eddy (1950), Wolfe and MacDonald (1944) and Eddy and Leimbach (1952). The method determines the reaction time of mice dropped on to a hot plate maintained at 55°±0.5°C. Six groups of male mice (5 mice per group) weighing between 20-30 g are used. The initial reaction time of these mice is determined once, and the reaction time of each group is then averaged. The mice are then given the vehicle and/or the test compound by the oral, intraperitoneal or subcutaneous route. The average reaction time of each group is determined again at 30, 60 and 90 minutes after the administration and is compared with controls. Reaction time is recorded as per cent changes from control. All groups are averaged before and after treatment. A combined reaction time average (recorded as per cent change of reaction time threshold from controls) for all three periods is plotted against dose on graph paper and a curve is drawn. The ED₅₀ is read from this curve.

When 8 - chloro - dibenzofuran - 3 - acetic acid, which has demonstrated an LD₅₀ of, for example, 775 mg p.o. in mice, is used as the test compound, analgesic activity is observed at an ED₅₀ of 74.

The compounds of formula I, their enantiomers and pharmaceutically acceptable salts thereof as herein described have effects qualitatively similar to those of phenylbutazone and indomethacin which are known for their therapeutic uses and properties. Thus, they demonstrate a pattern of activity associated with anti-inflammatory agents of known efficacy and safety.

The compounds of formula I, their enantiomers and pharmaceutically acceptable salts thereof as herein described, can be incorporated into standard pharmaceutical dosage forms. For example, they are useful for oral or parenteral administration with the usual pharmaceutical adjuvant material such as organic or inorganic inert carrier materials which include water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums and polyalkyleneglycols. The pharmaceutical preparations can be made up in a solid form

(e.g. as tablets, troches, suppositories or capsules) or in liquid form (e.g. as solutions, suspensions or emulsions). Pharmaceutical adjuvant materials can be added. Such materials include preservatives, stabilisers, wetting or emulsifying agents, salts to change the osmotic pressure or to act as buffers. The pharmaceutical preparations can also contain other therapeutically active substances. The present invention thus provides a pharmaceutical preparation containing a dibenzofuran derivative of the present invention or a pharmaceutically acceptable salt thereof in association with a compatible pharmaceutical carrier.

The following Examples illustrate the process provided by the present invention:

Example 1

Manufacture of 8 - chloro - 3 - dibenzofuranacetic acid ethyl ester

A mixture of 7.23 g of 8 - chloro - 1,2,3,4 - tetrahydro - 3 - dibenzofuranacetic acid ethyl ester, 11.8 g of 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone and 150 ml of benzene is stirred at reflux temperature for 18 hours under an atmosphere of nitrogen and then cooled. The solid is removed by filtration and washed with benzene. The filtrate and washings are combined and concentrated under reduced pressure to yield 14.1 g of a dark oil which is dissolved in methylene chloride and filtered. The eluate is evaporated to 3.28 g of yellowish solid which is crystallised first from a mixture of ether and pentane and then from ether alone to give 1.35 g of 8 - chloro - 3 - dibenzofuranacetic acid ethyl ester of melting point 90°—91°C.

The 8 - chloro - 1,2,3,4 - tetrahydro - 3 - dibenzofuranacetic acid ethyl ester used as the starting material can be prepared as follows:

a) Preparation of 3 - bromo - 4 - oxocyclohexylacetic acid ethyl ester

4.48 ml of bromine are added dropwise to a solution of 16 g of 4 - oxocyclohexylacetic acid ethyl ester in 200 ml of ether stirred and cooled to -10°C. After 90 minutes, the ether solution is washed successively with two 100 ml portions of water, one 100 ml portion of saturated sodium bicarbonate and three 100 ml portions of water. The aqueous layers are extracted with two 100 ml portions of ether. The organic layers are combined, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give 23 g of 3 - bromo - 4 - oxocyclohexylacetic acid ethyl ester as a pale yellow oil.

b) Preparation of 3 - (4 - chlorophenoxy) - 4 - oxocyclohexylacetic acid ethyl ester

A mixture of 11.2 g of 4 - chlorophenol, 24 g of anhydrous potassium carbonate and 45 ml of dimethylformamide is stirred at

100°C for 10 minutes. After stirring and cooling for 2 hours, the mixture is treated dropwise over a period of 1 hour with a solution of 23 g of 3 - bromo - 4 - oxocyclohexylacetic acid ethyl ester in 45 ml of dimethylformamide, heated at 100°C for 1.25 hours and finally stirred at room temperature for 64 hours. The solid which forms is removed by filtration and washed with dimethylformamide. The filtrate and washings are combined and concentrated at 40°C under reduced pressure to give 33 g of an oil. This oil is mixed with 200 ml of water and extracted with three 200 ml portions of ether. The organic layers are washed successively with 200 ml of water, three 100 ml portions of 1-N sodium hydroxide and three 200 ml portions of water, dried over anhydrous sodium sulfate and evaporated to give 23 g of 3 - (4 - chlorophenoxy) - 4 - oxocyclohexylacetic acid ethyl ester as a yellow oil. A portion of the oil is distilled and yields the ester as a pale yellow oil of boiling point 178°C/0.55 mm.

c) Preparation of 8 - chloro - 1,2,3,4 - tetrahydro - 3 - dibenzofuranacetic acid ethyl ester

A mixture of 70 g of 3 - (4 - chlorophenoxy) - 4 - oxocyclohexylacetic acid ethyl ester and 700 g of polyphosphoric acid is stirred at room temperature for 2.75 hours under an atmosphere of nitrogen, allowed to stand for 1.5 hours and stirred on a steam-bath for 0.25 hour. The hot viscous mass which forms is decomposed by pouring on to ice and the resulting cold mixture is extracted with three 500 ml portions of water, three 100 ml portions of 1-N sodium hydroxide and four 100 ml portions of water and subsequently dried over anhydrous sodium sulfate. The solvent is evaporated to give 56.1 g of a turbid oil. A portion of this material is distilled to give 17.4 g of 8 - chloro - 1,2,3,4 - tetrahydro - 3 - dibenzofuranacetic acid ethyl ester of boiling point 166°—167°C/0.03 mm.

Example 2

Manufacture of 8 - chloro - 3 - dibenzofuranacetic acid

10 ml of 1-N sodium hydroxide are added to a solution of 568 mg of 8 - chloro - 3 - dibenzofuranacetic acid ethyl ester in 40 ml of hot ethanol. The solution is stirred at reflux temperature under an atmosphere of nitrogen for 2 hours and evaporated under reduced pressure. The residue is dried by a three-fold evaporation with benzene and is then digested repeatedly with methylene chloride. The solid is removed by filtration, dried and dissolved in hot water. The hot solution is treated with charcoal and filtered. The filtrate is adjusted to pH 1 with concentrated hydrochloric acid and the mixture cooled. The resulting solid is removed by filtration, dried and crystallised from

methanol/ether to give 179 mg of 8 - chloro - 3 - dibenzofuranacetic acid of melting point 221°—222°C.

Example 3

Manufacture of 2 - (8 - chloro - 3 - dibenzofuranyl)ethanol

A solution of 653 mg of 8 - chloro - 3 - dibenzofuranacetic acid ethyl ester in 75 ml of ether is added over a 15 minute period under an atmosphere of nitrogen to a suspension of 447 mg of lithium aluminium hydride in 100 ml of ether. The mixture is stirred at room temperature for 2.5 hours, then at reflux temperature for 8 hours and finally at room temperature for 10.5 hours, whereupon the mixture is cooled in an ice-water bath, decomposed with 10 ml of water and stirred in the cold for 2 hours. Diatomaceous earth and charcoal are added. The solids are removed by filtration and washed with ether. After evaporation of the filtrate and washings, crystallisation of the residue twice from methylene chloride/ether/pentane yields 229 mg of 2 - (8 - chloro - 3 - dibenzofuranyl)-ethanol of melting point 115.5°—117°C.

Example 4

Manufacture of 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid ethyl ester

A mixture of 3.15 g of distilled 8 - chloro - α - methyl - 1,2,3,4 - tetrahydro - 3 - dibenzofuranacetic acid ethyl ester (boiling point 146°—147°C/0.023 mm), 5.22 g of 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone and 125 ml of benzene is heated at reflux under an atmosphere of nitrogen for 18 hours, cooled and filtered. The filtrate is evaporated under reduced pressure and the residue dissolved in methylene chloride and filtered. The eluate is evaporated to give 2.55 g of oil which crystallises and has a melting point of 49°—57°C. Distillation yields 2.3 g of 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid ethyl ester of boiling point 131°C/0.023 mm and melting point 45°—55.5°C.

The 8 - chloro - α - methyl - 1,2,3,4 - tetrahydro - 3 - dibenzofuranacetic acid ethyl ester used as the starting material can be prepared as follows:

4.16 ml of bromine are added to a solution of 16 g of 2 - (4 - oxocyclohexyl)propionic acid ethyl ester in 125 ml of ether stirred and cooled to -10°C. The ether solution is washed with two 100 ml portions of water, 125 ml of saturated sodium bicarbonate and three 100 ml portions of ether. The organic layers are combined, treated with charcoal, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give 22.6 g of 2 - (3 - bromo - 4 - oxocyclohexyl)propionic acid ethyl ester as a yellow oil.

A mixture of 10.42 g of 4 - chlorophenol,

22.4 g of anhydrous potassium carbonate and 50 ml of dimethylformamide is stirred under an atmosphere of nitrogen at reflux for 15—20 minutes, cooled and treated over a period of 45 minutes with a solution of 22.5 g of 2 - (3 - bromo - 4 - oxocyclohexyl)propionic acid ethyl ester in 50 ml of dimethylformamide. The mixture is stirred at room temperature for 65 hours, at 100°C for 2 hours and, finally, at room temperature for 2.5 hours. The remaining solid is removed by filtration and washed with dimethylformamide. The filtrate is concentrated at 40°C under reduced pressure and the residue is partitioned between 500 ml of ether and 100 ml of water. The ether layer is washed with 100 ml of water, three 100 ml portions of 1-N sodium hydroxide and two 100 ml portions of water. The aqueous layers are extracted with two 250 ml portions of ether and the combined ether phases are treated with charcoal and dried over anhydrous sodium sulfate. The solids are removed by filtration and the filtrate evaporated under reduced pressure to give 19.7 g of 2 - [3 - (4 - chlorophenoxy) - 4 - oxocyclohexyl]propionic acid ethyl ester as a mixture of geometric isomers of boiling point ca 162°—168°C/0.4—0.5 mm.

A mixture of 3.69 g of distilled 2 - [3 - (4 - chlorophenoxy) - 4 - oxocyclohexyl]propionic acid ethyl ester (boiling point 167°—168°C/0.4 mm Hg) and 38 g of polyphosphoric acid is stirred for 12 hours under an atmosphere of nitrogen at room temperature and then for 20 minutes at 80°—85°C. The reaction mass is decomposed with 125 ml of ice and water and the resulting mixture extracted with three 150 ml portions of ether. The organic layers are washed successively with 100 ml of water, 100 ml of 1-N sodium hydroxide and three 100 ml portions of water and then dried with anhydrous sodium sulfate. The solids are removed by filtration and the filtrate evaporated to give 2.95 g of 8 - chloro - α - methyl - 1,2,3,4 - tetrahydro - 3 - dibenzofuranacetic acid ethyl ester as a mixture of diastereomers.

Example 5

Manufacture of 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid

A mixture of 1.78 g of 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid ethyl ester, 100 ml of ethanol and 30 ml of 1-N sodium hydroxide is stirred at reflux for 2 hours and concentrated under reduced pressure. The residue is dissolved in 125 ml of hot water and treated with charcoal and diatomaceous earth. The solids are removed by hot filtration and washed with water. The filtrate is stirred and cooled in ice-water while being acidified by the dropwise addition of 5 ml of concentrated hydrochloric acid. The precipitate is removed by filtration, washed with water and dried to give 1.36 g of a

solid. Crystallisation from ether/pentane, sublimation at 145°C/0.021 mm and recrystallisation from ether/pentane gives 620 mg of 8 - chloro - α - methylbenzofuran - 3 - acetic acid of melting point 159°—162°C.

Example 6

Manufacture of 2 - (8 - chloro - 3 - dibenzofuranyl)propanol

1 ml of a 70% solution in benzene of sodium bis(2 - methoxyethoxy) - aluminium hydride diluted with 5 ml of benzene is added over 10 minutes to a solution of 977 mg of 8 - chloro - α - methylbenzofuran - 3 - acetic acid ethyl ester in 50 ml of benzene which is stirred at room temperature under an atmosphere of nitrogen. The mixture is stirred at room temperature for 4.25 hours. During this time, 0.1 ml portions of the hydride reagent in 5—10 ml of benzene are added at 0.75 and 1.5 hours. After the addition of 5 ml of acetone and agitation for another 15 minutes, the mixture is decomposed by the gradual addition of 25 ml of water and stirred for an additional 20—25 minutes. The aqueous phase is separated and extracted with three 100 ml portions of benzene. The organic layers are washed with 25 ml of saturated sodium bicarbonate, four 25 ml portions of water and 25 ml of saturated sodium chloride, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residual oil is distilled to give 604 mg of 2 - (8 - chloro - 3 - dibenzofuranyl)propanol of boiling point 163°—164°C/0.4—0.5 mm Hg and melting point 60°—73°C.

Example 7

Manufacture of 8 - chloro - 3 - dibenzofuranacetamide

A solution of 9.45 g of 8 - chloro - 3 - dibenzofuranacetic acid in 225 ml of tetrahydrofuran is treated with 6.01 g of 98% 1,1' - carbonyldiimidazole and stirred 16 hours at room temperature under an atmosphere of nitrogen. Ammonia is passed into the resulting suspension for 3 hours and stirring is continued for an additional 1.5 hours. The solid is removed by filtration and washed with tetrahydrofuran and ether to give 8.14 g of 8 - chloro - 3 - dibenzofuranacetamide of melting point 258°—263°C. A sample crystallised from aqueous methanol and sublimed at 234°C/0.1 mm melts at 265.5°—266.5°C.

Example 8

Manufacture of 8 - chloro - 3 - dibenzofuranacetonitrile

905 mg of 8 - chloro - 3 - dibenzofuranacetamide are added in portions over a 15—20 minute period to 10 ml of phosphorus oxychloride which are stirred at room temperature under an atmosphere of nitrogen. The

suspension is stirred first at room temperature for 45 minutes and then in an ice-water bath for 10 minutes. Thereafter, the suspension is treated dropwise over a 15—20 minute period with 1.4 ml of triethylamine. After an additional 15 minutes of stirring in the cold, the mixture is heated on an oil-bath at 90°—100°C for 2 hours, cooled and concentrated *in vacuo*. The residue is treated with 25 ml of water and extracted four times with 75 ml portions of methylene chloride. The organic layers are washed with three 25 ml portions of water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue is redissolved in methylene chloride and the solution filtered. The eluates are evaporated to dryness and the residue crystallised from methylene chloride/ether to give 447 mg of 8 - chloro - 3 - dibenzofuranacetonitrile of melting point 175°—176°C.

Example 9

Manufacture of 8 - chloro - 3 - dibenzofuranacetic acid 2 - dimethylaminoethyl ester hydrochloride

A mixture of 1.0 g of 8 - chloro - 3 - dibenzofuranacetic acid, 1.17 g of anhydrous potassium carbonate and 50 ml of dimethylformamide is stirred for 1 hour at room temperature, cooled, treated with 1.22 g of dimethylaminoethyl chloride hydrochloride and then stirred for 16 hours at room temperature. The solid is removed by filtration and the filtrate concentrated *in vacuo* at below 40°C. The residue is diluted with 100 ml of water and extracted with three 100 ml portions of methylene chloride. The organic layers are washed once with 100 ml of 1-N sodium hydroxide, three times with 100 ml portions of water, dried over anhydrous magnesium sulfate and filtered. Concentration of the filtrate under reduced pressure yields an oil which is dissolved in methanol and acidified with hydrogen chloride. The solution is evaporated to dryness and the residue dried by azeotropic distillation (three times with benzene and once with methylene chloride). Crystallisation from methanol/ether gives 349 mg of 8 - chloro - 3 - dibenzofuranacetic acid 2 - dimethylaminoethyl ester hydrochloride of melting point 201°—202.5°C.

Example 10

Manufacture of 8 - chloro - 3 - dibenzofuranacetic acid methyl ester

A solution of 1.0 g of 8 - chloro - 3 - dibenzofuranacetic acid in 100 ml of methanol, saturated with hydrogen chloride at 0°C, is stirred for 16 hours at room temperature and then heated at reflux for 2 hours. Evaporation of the solvent under reduced pressure and crystallisation of the residue from ether/pentane gives 850 mg of 8 - chloro - 3 - dibenzofuranacetic acid methyl ester of melting point 126.5°—128°C.

Example 11

Manufacture of racemic 8,α - dimethyldibenzofuran - 3 - acetic acid

3.2 g of 8,α - dimethyl - 1,2,3,4 - tetrahydro - 3 - dibenzofuranacetic acid ethyl ester are dissolved in 100 ml of benzene and heated at reflux for 16 hours with 5.3 g of 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone. The mixture is cooled and the solid removed by filtration and washed with benzene. The dark filtrate is filtered and the eluate evaporated to give 2.4 g of crude 8,α - dimethyldibenzofuran - 3 - acetic acid ethyl ester of melting point 52°—62°C.

A solution of 2.35 g of the foregoing ester in 100 ml of ethanol is heated at reflux for 2.5 hours in a nitrogen atmosphere with 50 ml of 1-N potassium hydroxide and then evaporated. The residue is dissolved in water, treated with charcoal and filtered. The filtrate is acidified with 5—6 ml of concentrated hydrochloric acid and the resulting precipitate removed by filtration and dissolved in acetone. Evaporation of the acetone solution, removal of water by azeotropic distillation with benzene and crystallisation from ether/pentane gives 1.5 g of 8,α - dimethyldibenzofuran - 3 - acetic acid of melting point 151°—153.5°C (sintering at 142°C). Sublimation at 132°—140°C/0.035—0.065 mm yields pure acid as white crystals of melting point 155°—157°C.

The 8,α - dimethyl - 1,2,3,4 - tetrahydro - 3 - dibenzofuranacetic acid used as the starting material can be prepared as follows:

Sodium p - cresolate, prepared from 8.75 g of p - cresol and 4.37 g of sodium methylate, is suspended in 100 ml of benzene and stirred at 20°C while adding a solution of 2 - (3 - bromo - 4 - oxocyclohexyl)propionic acid ethyl ester in 70 ml of benzene. The resulting mixture is refluxed for 18 hours, cooled and washed successively with two 250 ml portions of water, two 150 ml portions of 1-N sodium hydroxide and two 150 ml portions of water. The aqueous layers are extracted with two 250 ml portions of benzene and the combined organic phases are dried over magnesium sulfate and evaporated to give 20.2 g of an oil which is distilled to yield 17.6 g of crude 2 - (3 - p - cresoxy - 4 - oxocyclohexyl)propionic acid ethyl ester of boiling point 48°C/0.4 mm.

A mixture of 14.8 g of crude 2 - (3 - p - cresoxy - 4 - oxocyclohexyl)propionic acid ethyl ester and 150 g of polyphosphoric acid is stirred at room temperature for 40 minutes, decomposed by the addition of ice and water and extracted with three 250 ml portions of ether. The organic layers are washed successively with two 200 ml portions of water, two 200 ml portions of saturated sodium bicarbonate solution and two 150 ml portions of water. The combined ether phases are dried over magnesium sulfate and evaporated and

the residue is distilled twice to give 3.2 g of crude 8,α - dimethyl - 1,2,3,4 - tetrahydro - 3 - dibenzofuranacetic acid ethyl ester of boiling point 95°—120°C/0.075 mm.

Example 12

Manufacture of racemic 8 - amino - α - methyldibenzofuran - 3 - acetic acid ethyl ester hydrochloride

A suspension of sodium p - acetamidophenoxide, prepared from 15.1 g of p - acetamidophenol and 5.4 g of sodium methylate, in 200 ml of benzene is stirred at room temperature in a nitrogen atmosphere while adding dropwise a solution of 2 - (3 - bromo - 4 - oxocyclohexyl)propionic acid ethyl ester in 150 ml of benzene. The mixture is heated at reflux for 50 hours, cooled and washed successively with two 100 ml portions of water, one 100 ml portion of saturated sodium bicarbonate solution and three 50 ml portions of water. The aqueous phases are extracted with two 250 ml portions of ethyl acetate and the combined organic layers are dried over sodium sulfate and evaporated to give 32.65 g of an oil which is dissolved in methylene chloride and filtered. Evaporation of the eluates yields 24 g of crude 2 - [3 - (4 - acetamidophenoxy) - 4 - oxocyclohexyl]propionic acid ethyl ester.

A mixture of 23 g of this ester and 230 g of polyphosphoric acid is stirred vigorously for 30 minutes at 20°C, decomposed with ice and water and extracted three times with ether (total volume of 1 litre). The organic layers are washed successively with one 250 ml portion of water, two 100 ml portions of 1-N sodium hydroxide and four 100 ml portions of water, dried over sodium sulfate and evaporated to give 12.8 g of an oil which is crystallised once from methylene chloride/ether/pentane and twice from methylene chloride/ether to yield 1.45 g of 8 - acetamido - α - methyl - 1,2,3,4 - tetrahydro - 3 - dibenzofuranacetic acid ethyl ester of melting point 140.5°—143°C.

The first recrystallisation mother liquor from the preceding step is evaporated and 7.7 g of the semicrystalline residue are dissolved in 200 ml of benzene, mixed with 11.2 g of 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone and heated at reflux for 17 hours in a nitrogen atmosphere. The cooled mixture is filtered and the residue washed with benzene and methylene chloride. The dark filtrate is evaporated and the residue chromatographed on 152 g of alumina, eluting successively with benzene, methylene chloride, ethyl acetate and acetone. The methylene chloride eluate is evaporated to give 1.58 g of a brown gum which is dissolved in 200 ml of ethanol saturated at 0°C with hydrogen chloride. The solution is stirred at 0°C for 1 hour, heated at reflux for 2 hours and permitted to stand at 20°C for 15 hours. Evaporation of the

solvent and drying of the residue by azeotropic distillation with benzene gives 1.45 g of a solid which is crystallised first from ethanol/ether and then from methanol/ether to yield 718 mg of 8 - amino - α - methylbenzofuran - 3 - acetic acid ethyl ester hydrochloride in the form of white crystals of melting point 192°—193°C.

Example 13

10 Manufacture of 8 - chloro - α - methylbenzofuran - 3 - acetamide

A solution of 2.75 g of 8 - chloro - α - methylbenzofuran - 3 - acetic acid in 100 ml of tetrahydrofuran is stirred for 16 hours at 20°C in a nitrogen atmosphere with 1.66 g of 1,1' - carbonyldiimidazole, cooled in an ice-water bath and saturated with ammonia. Evaporation of the mixture gives 4.32 g of solid which is digested several times with boiling ether. The insoluble material obtained by filtration is crystallised from tetrahydrofuran/ether to yield 1.63 g of white crystalline 8 - chloro - α - methylbenzofuran - 3 - acetamide of melting point 210°—211°C.

Example 14

25 Manufacture of 8 - chloro - α - methyl - 3 - dibenzofuranacetic acid 2 - dimethylaminoethyl ester hydrochloride

A solution of 1.1 g of 8 - chloro - α - methylbenzofuran - 3 - acetic acid in 25 ml of dimethylformamide is stirred for 85 minutes at 20°C in a nitrogen atmosphere with 1.22 g of anhydrous potassium carbonate and then treated over a 10—12 minute period with a suspension of 2 - chloro - N,N - dimethyl - ethylamine hydrochloride in 10 ml of dimethylformamide. The mixture is stirred first at 20°C for 69 hours and then at 100°C for 1 hour, cooled, poured on to 100 g of ice, diluted with water and extracted with three 200 ml portions of methylene chloride. The organic layers are washed with two 150 ml portions of water, dried over sodium sulfate and evaporated to give 1.7 g of an oil which is dissolved in methanol and acidified with 4.17-N ethanolic hydrogen chloride. Evaporation of the solvents and crystallisation of the residue twice from methanol/ether gives 953 mg of 8 - chloro - α - methyl - 3 - dibenzofuranacetic acid 2 - dimethylaminoethyl ester hydrochloride hemihydrate in the form of white crystals of melting point 178°—182°C.

Anhydrous 8 - chloro - α - methyl - 3 - dibenzofuranacetic acid 2 - dimethylaminoethyl ester hydrochloride is obtained by drying at 105°C/0.1 mm for 16 hours; melting point 177°—182°C.

Example 15

60 Manufacture of 8 - fluoro - α - methylbenzofuran - 3 - acetic acid

A solution of 7.8 g of 8 - fluoro - α -

methyl - 1,2,3,4 - tetrahydro - 3 - dibenzofuranacetic acid ethyl ester in 200 ml of benzene is heated for 16 hours at reflux with 12.8 g of 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone, cooled and filtered. The filtrate is washed once with water, once with 1-N sodium hydroxide and three times with saturated sodium chloride solution, dried over magnesium sulfate and evaporated. The residue is chromatographed on 60 g of alumina and eluted successively with benzene, methylene chloride, ethyl acetate and acetone. Evaporation of the benzene eluate yields 4.6 g of 8 - fluoro - α - methylbenzofuran - 3 - acetic acid ethyl ester.

A solution of 208 mg of 8 - fluoro - α - methylbenzofuran - 3 - acetic acid ethyl ester in 100 ml of ethanol is heated at reflux for 2.5—3 hours in a nitrogen atmosphere with 10 ml of 1-N sodium hydroxide and evaporated under reduced pressure. The residue is dissolved in hot water and the solution treated with charcoal and filtered. Acidification of the filtrate with concentrated hydrochloric acid yields a precipitate which is removed by filtration, washed with water and dissolved in acetone. This solution is evaporated and the residue dried by azeotropic distillation with benzene and sublimed at 135°—145°C/0.02 mm. The sublimate is crystallised twice from ether/pentane to give 28 mg of white crystalline 8 - fluoro - α - methylbenzofuran - 3 - acetic acid of melting point 153°—155°C.

The 8 - fluoro - α - methyl - 1,2,3,4 - tetrahydro - 3 - dibenzofuranacetic acid ethyl ester used as the starting material can be prepared as follows:

A solution of 27.7 g of 2 - (3 - bromo - 4 - oxocyclohexyl) - propionic acid ethyl ester in 25 ml of benzene is added gradually to a suspension of sodium 4 - fluorophenoxide, prepared from 11.2 g of 4 - fluorophenol and 5.4 g of sodium methylate, in 100 ml of benzene. The mixture is stirred for 16 hours at 20°C and for 1 hour at reflux and then cooled and washed successively with two 100 ml portions of water, one 100 ml portion of 1-N sodium hydroxide and three 100 ml portions of water. The aqueous layers are extracted with two 150 ml portions of benzene and the combined organic phases are dried over magnesium sulfate and evaporated. The residual oil is distilled to give 9.75 g of 2 - [3 - (4 - fluorophenoxy) - 4 - oxocyclohexyl]propionic acid ethyl ester of boiling point 120°—140°C/0.05 mm.

A mixture of the foregoing ester and 140 g of polyphosphoric acid is stirred at 20°C for 10 minutes, decomposed with ice and water and extracted with three 250 ml portions of ether. The organic layers are washed successively with one 150 ml portion of water, one 150 ml portion of 1-N sodium hydroxide and three 150 ml portions of water, dried over

magnesium sulfate and evaporated to give 7.8 g. of 8 - fluoro - α - methyl - 1,2,3,4 - tetrahydro - 3 - dibenzofuranacetic acid ethyl ester.

Example 16

Manufacture of (-) - 8 - chloro - α - methyl-dibenzofuran - 3 - acetic acid (+) - α - methylbenzylamine salt

A hot solution of 549 g. of racemic 8 - chloro - α - methyl-dibenzofuran - 3 - acetic acid in 30 ml of ethanol and 30 ml of acetonitrile is treated with 2.58 ml of d - (+) - α - methylbenzylamine and permitted to stand for 2 hours at 20°C. The precipitate is removed by filtration and washed with acetonitrile and ether to give 6.54 g of a white solid of melting point 172°—180°C (decomposition), $\alpha_D^{25.4} = +4.3^\circ$ (c=0.98% in methanol), which is crystallised successively from ethanol/acetonitrile, methanol/acetonitrile and ethanol to yield 574 mg of white crystalline (-) - 8 - chloro - α - methyl-dibenzofuran - 3 - acetic acid (+) - α - methylbenzylamine salt of melting point 184°—185°C; $\alpha_D^{25.4} = +14.2^\circ$ (c=0.99% in methanol).

Example 17

Manufacture of (-) - 8 - chloro - α - methyl-dibenzofuran - 3 - acetic acid

A mixture of 503 mg of (-) - 8 - chloro - α - methyl-dibenzofuran - 3 - acetic acid (+) - α - methylbenzylamine salt and 5 ml of 1-N sodium hydroxide is stirred until a clear solution forms. Dilution with 10 ml of water and acidification by the dropwise addition of 1 ml of concentrated hydrochloric acid yield a precipitate which is removed by filtration, washed with water and dissolved in acetone. Evaporation of the solvent and crystallisation of the residue from ether/pentane and then from methylene chloride/ether/pentane gives 236 mg of white crystalline (-) - 8 - chloro - α - methyl-dibenzofuran - 3 - acetic acid of melting point 156°—157°C; $\alpha_D^{25.1} = -44.4^\circ$ (c=0.99% in methanol).

Example 18

Manufacture of (+) - 8 - chloro - α - methyl-dibenzofuran - 3 - acetic acid (-) - α - methylbenzylamine salt

The reaction mother liquor and the first three recrystallisation mother liquors from the manufacture of (-) - 8 - chloro - α - methyl-dibenzofuran - 3 - acetic acid (+) - α - methylbenzylamine salt are combined and evaporated to give 3.27 g of residue which is treated with 25 ml of 1-N sodium hydroxide, diluted with water, warmed with charcoal and filtered. The clear filtrate is acidified with concentrated hydrochloric acid and the resulting precipitate removed by filtration, washed with water and dissolved in acetone. Evapora-

tion of the organic solvent and drying of the residue by azeotropic distillation with benzene give 3.17 g. of crude acid which is dissolved in 125 ml of hot ethanol and treated with 1.5 ml of 1 - (-) - α - methylbenzylamine. The resulting mixture is stirred at room temperature and the precipitate removed by filtration and washed with cold ethanol to yield 2.36 g of a solid of melting point 173°—182°C; $\alpha_D^{25.4} = -8.8^\circ$ (c=0.99% in methanol). Six crystallisations from ethanol gives 642 mg of white crystalline (+) - 8 - chloro - α - methyl-dibenzofuran - 3 - acetic acid (-) - α - methylbenzylamine salt of melting point 179°—180.5°C; $\alpha_D^{25} = -14.2^\circ$ (c=1.0% in methanol).

Example 19

Manufacture of (+) - 8 - chloro - α - methyl-dibenzofuran - 3 - acetic acid

A solution of 600 mg of (+) - 8 - chloro - α - methyl-dibenzofuran - 3 - acetic acid (-) - α - methylbenzylamine salt in 6 ml of 1-N sodium hydroxide is diluted with 15 ml of water, acidified with 1 ml of concentrated hydrochloric acid and stirred for 1 hour at 20°C. The precipitate is removed by filtration, washed with water and dissolved in acetone. Evaporation of this solution and drying of the residue by azeotropic distillation with benzene yield a solid which is crystallised twice from ether/pentane to give 253 mg of white crystalline (+) - 8 - chloro - α - methyl-dibenzofuran - 3 - acetic acid of melting point 155°—157°C; $\alpha_D^{25.1} = +43.7^\circ$ (c=1.0% in methanol).

Example 20

Manufacture of 3 - (8 - chloro - 3 - dibenzofuranyl)propionic acid ethyl ester

A solution of 3.07 g of 3 - (8 - chloro - 1,2,3,4 - tetrahydro - 3 - dibenzofuranyl)propionic acid ethyl ester in 250 ml of benzene is heated at reflux in a nitrogen atmosphere during the addition, over a 0.5 hour period, of a suspension of 4.8 g. of 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone in 300 ml of benzene. The mixture is heated at reflux for 66 hours and cooled, and the solid is removed by filtration and washed with benzene. Evaporation of the filtrate yields a semi-solid which is dissolved in methylene chloride and filtered. Evaporation of the eluates gives a brown oil which is dissolved in 150 ml of ether and washed successively with one 50 ml portion of 1-N sodium hydroxide and four 50 ml portions of water. The aqueous layers are extracted with two 150 ml portions of ether and the combined ether phases are dried over sodium sulfate and evaporated to give 2.02 g of oil which is distilled twice to yield 832 mg of 3 - (8 - chloro - 3 - dibenzofuranyl)propionic acid ethyl ester of boiling point 176°—181°C/0.15 mm.

The 3 - (8 - chloro - 1,2,3,4 - tetrahydro - 3 - dibenzofuranyl) - propionic acid ethyl ester used as the starting material can be prepared as follows:

5 A solution of 16.8 g of 3 - (4 - oxocyclohexyl)propionic acid ethyl ester in 200 ml of ether is stirred at -20°C during the dropwise addition, over a 10 minute period, of 4.36 ml of bromine. The mixture is then
10 stirred for an additional 40 minutes at 20°C and washed successively with three 100 ml portions of water, one 100 ml portion of saturated sodium bicarbonate solution and three 100 ml portions of water. The aqueous
15 phases are extracted with two 100 ml portions of ether and the combined ether layers are dried over magnesium sulfate and evaporated to give 23.6 g of 3 - (3 - bromo - 4 - oxocyclohexyl)propionic acid ethyl ester.

20 A mixture of 10.9 g of 4 - chlorophenol, 23.6 g of anhydrous potassium carbonate and 45 ml of dimethylformamide is stirred for 16 hours at 20°C and for 15 minutes at 100°C , cooled and treated with a solution of
25 23.6 g of 3 - (3 - bromo - 4 - oxocyclohexyl)propionic acid ethyl ester in 45 ml of dimethylformamide over a period of 1.25 hours. The resulting suspension is heated at 100°C for 1.5 hours, stirred at 20°C for 16 hours
30 and filtered. The filtrate is evaporated under reduced pressure below 40°C and the residue mixed with 200 ml of water and extracted with three 200 ml portions of ether. The ether phases are washed successively with one
35 200 ml portion of water, three 100 ml portions of 1-N sodium hydroxide and three 200 ml portions of water, dried over magnesium sulfate and evaporated to give 19 g of 3 - [3 - (4 - chlorophenoxy) - 4 - oxocyclohexyl]propionic acid ethyl ester.

40 A mixture of 15.8 g of 3 - [3 - (4 - chlorophenoxy) - 4 - oxocyclohexyl]propionic acid ethyl ester and 162 g of polyphosphoric acid is stirred at 20°C for 65 minutes and then
45 at $85^{\circ}\text{--}90^{\circ}\text{C}$ for 10 minutes, decomposed with ice and water and extracted three times with a total volume of 1 litre of ether. The organic layers are washed successively with one 150 ml portion of water, one 100 ml
50 portion of 1-N sodium hydroxide and four 150 ml portions of water, dried over sodium sulfate and evaporated to an oily residue which is dissolved in methylene chloride and filtered. Evaporation of the eluate yields 10.1 g of
55 3 - (8 - chloro - 1,2,3,4 - tetrahydro - 3 - dibenzofuranyl)propionic acid ethyl ester.

Example 21

Manufacture of 3 - (8 - chloro - 3 - dibenzofuranyl)propionic acid

60 A solution of 1.05 g of 3 - (8 - chloro - 3 - dibenzofuranyl)propionic acid ethyl ester in 50 ml of ethanol is heated at reflux for 1 hour with 25 ml of 1-N sodium hydroxide and then concentrated under reduced pressure.

The residual suspension is diluted with water, treated with 10 ml of concentrated hydrochloric acid and stirred for 16 hours at 20°C . The solid is removed by filtration, washed with water and dissolved in tetrahydrofuran. Evaporation and drying of the residue by azeotropic distillation with benzene gives a solid which is crystallised from acetone/methylene chloride/ether and sublimed at $160^{\circ}\text{C}/0.15\text{ mm}$ to yield white crystalline 3 - (8 - chloro - 3 - dibenzofuranyl)propionic acid of melting point $174^{\circ}\text{--}178^{\circ}\text{C}$.

Example 22

Manufacture of 8 - chloro - dibenzofuran - 3 - acetic acid

A mixture of 800 mg of methyl 8 - chloro - dibenzofuran - 3 - glyoxylate, 15 ml of diglyme, 5 ml of water and 200 mg of potassium hydroxide is stirred at 20°C for 18 hours. After the addition of 2 ml of hydrazine hydrate, the mixture is stirred for 5 hours at 20°C and then for 4 hours at 180°C . The mixture is cooled to 20°C and poured in 50 ml of water. The solids are filtered off and dissolved in 50 ml of p - dioxane. 10 ml of 1-N hydrochloric acid are added and the mixture is refluxed for 12 hours. The solvents are evaporated under reduced pressure. The residue is dissolved in chloroform, dried with brine and sodium sulfate and again evaporated. After crystallisation from chloroform/ether, 300 mg of 8 - chloro - dibenzofuran - 3 - acetic acid of melting point $220^{\circ}\text{--}223^{\circ}\text{C}$ are obtained.

The 8 - chloro - dibenzofuran - 3 - glyoxylate used as the starting material can be prepared as follows:

a) Preparation of methyl 6,7,8,9 - tetrahydro - dibenzofuran - 3 - glyoxylate

A solution of 18.9 g of 1,2,3,4 - tetrahydro - dibenzofuran in 300 ml of dichloromethane is cooled to $0^{\circ}\text{--}5^{\circ}\text{C}$. 10 ml of monomethyl oxalate chloride are added to this solution. While stirring vigorously, 32.2 g of finely powdered aluminium chloride are added in small portions at $0^{\circ}\text{--}5^{\circ}\text{C}$. The mixture is stirred for 6 hours at the same temperature and then poured on ice. The aqueous phase is extracted three times with 200 ml of dichloromethane. The organic phases are washed with a saturated sodium bicarbonate solution and with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residual oil is distilled to give 11.1 g of methyl 6,7,8,9 - tetrahydro - dibenzofuran - 3 - glyoxylate as a yellow oil of boiling point $180^{\circ}\text{--}185^{\circ}\text{C}/0.001\text{ mm}$.

b) Preparation of methyl dibenzofuran - 3 - glyoxylate

A mixture of 9 g of methyl 6,7,8,9 - tetrahydro - dibenzofuran - 3 - glyoxylate, 17.4

g of 2,3 - dichloro - 5,6 - dicyano - 1,4 - benzoquinone (DDQ) and 180 ml of toluene is refluxed for 14 hours, then cooled to 5°C and filtered. The filtrate is evaporated under reduced pressure. The remaining dark brown crystals are dissolved in a 1:1 mixture of toluene and ethyl acetate and filtered. The eluate is evaporated *in vacuo*. The dark red residue (11.1 g) is crystallised from ethyl acetate. 3.1 g of methyl dibenzofuran - 3 - glyoxylate of melting point 139°—140°C are isolated.

c) Preparation of methyl 8 - chloro - dibenzofuran - 3 - glyoxylate

Dry chlorine is passed at 55°C into a solution of 3 g of methyl dibenzofuran - 3 - glyoxylate in 300 ml of glacial acetic acid. After the starting material has been used up, the mixture is evaporated *in vacuo*. The residue is dissolved in chloroform and washed with 1-N sodium bicarbonate at 0°—2°C. The organic phase is dried with brine and anhydrous sodium sulfate and evaporated. After recrystallisation from benzene/methanol, 2.0 g of methyl 8 - chloro - dibenzofuran - 3 - glyoxylate of melting point 159°—161°C are obtained.

Example 23

Manufacture of 8 - chloro - 3 - dibenzofuran - acetic acid

A mixture of 4 g of methyl - 8 - chloro - dibenzofuran - 3 - ketone, 0.78 g of powdered sulfur and 2.2 g of morpholine is stirred and refluxed for 18 hours. The product is dissolved in chloroform and filtered. The filtrate is crystallised from methanol/chloroform to give 4 g of 8 - chloro - 3 - dibenzofuran - thioacetic acid morpholide of melting point 185°—187°C.

A mixture of 4 g of 8 - chloro - 3 - dibenzofuran - thioacetic acid morpholide, 200 ml of glacial acetic acid and 20 ml of concentrated hydrochloric acid is refluxed for 5 hours and then evaporated under reduced pressure. The residue is dissolved in 100 ml of chloroform/p - dioxan (5:1). The solution is dried with brine and sodium sulfate and evaporated. 2.4 g of 8 - chloro - 3 - dibenzofuran - acetic acid are obtained by recrystallisation from dioxane/cyclohexane; melting point 220°—225°C.

The 8 - chloro - dibenzofuran - 3 - ketone used as the starting material can be prepared as follows:

a) Preparation of 8 - chloro - dibenzofuran - 3 - carboxylic acid chloride

A solution of 4.9 g of 8 - chloro - dibenzofuran - 3 - carboxylic acid in 100 ml of dioxane is heated to 90°C and 10 g of thionyl chloride are added dropwise. The mixture is stirred at 90°C for 25 hours and then evaporated *in vacuo*. The residue is dissolved in benzene and evaporated under reduced

pressure and dried at 80°C/0.1 mm for 2 hours. The crude 8 - chloro - dibenzofuran - 3 - carboxylic acid chloride melts at 155°—158°C.

b) Preparation of diethyl 8 - chloro - dibenzofuran - 3 - carbonyl - malonate

1.44 g of zinc turnings and 12 ml of dry ethanol are heated at 78°C and a solution of 16.7 g of diethyl malonate in 12 ml of dry ethanol is dropped in slowly. The mixture is stirred at 78°C for 16 hours and then evaporated at 40°C/10 mm. The residue is dried at 100°C/0.01 mm for 6 hours and dissolved in 200 ml of dry ether to yield 158.7 g of a solution. 93.4 g of this solution are poured into the solution of the foregoing crude 8 - chloro - dibenzofuran - 3 - carboxylic acid chloride in 150 ml of dry benzene at 25°C. The solvents are distilled off at atmospheric pressure until the boiling point reaches 80°C. The mixture is held at this temperature for 16 hours, cooled and poured on ice. The organic phase is sequentially washed with 100 ml of cold 1-N hydrochloric acid, 100 ml of 1-N sodium bicarbonate and 50 ml of brine and then dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue is crystallised from dichloromethane/n - hexane to yield 7.5 g of diethyl 8 - chloro - dibenzofuran - 3 - carbonyl - malonate of melting point 101°—104°C.

c) Preparation of methyl 8 - chloro - 3 - dibenzofuran ketone

7.5 g of diethyl 8 - chloro - dibenzofuran - 3 - carbonyl - malonate are mixed with 70 ml of glacial acetic acid, 40 ml of water and 1 ml of sulfuric acid (96%). The mixture is heated in an oil-bath at 140°C for 4 hours and then evaporated *in vacuo* to about 50 g and dissolved in 100 ml of dichloromethane. The solution is washed with 50 ml of brine, 50 ml of 1-N sodium carbonate and again with 50 ml of brine, dried over sodium sulfate and evaporated. Recrystallisation from dichloromethane/n - hexane gives 3 g of methyl 8 - chloro - 3 - dibenzofuran ketone of melting point 155°—157°C.

Example 24

Manufacture of 8 - chloro - 3 - dibenzofuran - acetic acid methyl ester

A mixture of 2 g of 8 - chloro - 3 - dibenzofuran - acetic acid, 200 ml of methanol and 0.5 ml of sulfuric acid is refluxed for 8 hours and evaporated to about 20 ml under reduced pressure. The residue is poured on ice and the mixture extracted with 100 ml of dichloromethane. The organic phase is washed at 0°—5°C with 50 ml of brine and 50 ml of saturated sodium bicarbonate and then dried with 50 ml of brine and sodium sulfate. After evaporation and crystallisation from dichloromethane/n - hexane, 1.6 g of 8 - chloro -

3 - dibenzofuran - acetic acid methyl ester of melting point 122°—123°C are obtained.

Example 25

Manufacture of 2 - (8 - chloro - 3 - dibenzofuran)propionic acid methyl ester

A solution of 584 mg of 8 - chloro - 3 - dibenzofuran - acetic acid methyl ester in 15 ml of dry hexamethylphosphoric acid triamide is added dropwise in 10 minutes to a suspension of sodium amide in 50 ml of liquid ammonia, prepared from 48 mg of sodium. The mixture is stirred for 2 hours at reflux, then 312 mg of iodomethane are added, stirring is continued for 2.5 hours and 400 mg of ammonium chloride are added. After evaporation of the ammonia, the residue is dissolved in benzene and the solution washed at about 5°C with 20 ml of water, 20 ml of 1-N hydrochloric acid, 20 ml of 1-N sodium carbonate and 20 ml of a solution containing 10% of sodium thiosulfate. After drying with brine and sodium sulfate, the solution is evaporated under reduced pressure. A solution of the residue in dichloromethane is filtered and yields, after evaporation, 500 mg of crystalline material consisting of 87% of 2 - (8 - chloro - 3 - dibenzofuran)propionic acid methyl ester and of 11.5% of 2 - (8 - chloro - 3 - dibenzofuran)isobutyric acid methyl ester. This material is chromatographed on silicagel with diethyl ether/cyclohexane (1:1) as eluting agent to yield 360 mg of 2 - (8 - chloro - 3 - dibenzofuran)propionic acid methyl ester of melting point 68°C.

Example 26

Manufacture of 2 - (8 - chloro - 3 - dibenzofuran)propionic acid

360 mg of 2 - (8 - chloro - 3 - dibenzofuran)propionic acid methyl ester are dissolved in a mixture of 10 ml of methanol and 1 ml of 1-N sodium hydroxide and the mixture is left for 24 hours at 22°C. Then, 1 ml of 1-N sodium hydroxide is added and, after a further 24 hours at 22°C, the solution is evaporated *in vacuo*. The residue is dissolved in chloroform and washed with 1-N sodium hydroxide. The alkaline extract is acidified to pH 2 with concentrated hydrochloric acid and again extracted with chloroform. After drying with brine and sodium sulfate, evaporation and crystallisation from diethyl ether/n - hexane, there are obtained 200 mg of pure 2 - (8 - chloro - 3 - dibenzofuran)propionic acid of melting point 167°—169°C.

Example 27

Manufacture of 8 - chloro - 3 - hydroxymethyl - dibenzofuran

A solution of 12 g of 8 - chloro - 3 - dibenzofuran - carboxylic acid ethyl ester in 400 ml of dry ether is added under an atmosphere of nitrogen at 35°C to a suspension of 2 g of lithium aluminium hydride in 100 ml

of dry diethyl ether. The mixture is stirred at 35°C for 1 hour, then cooled and decomposed with ice and again stirred for 1 hour at 0°—5°C. 300 ml of 1-N hydrochloric acid are added. The ether solution is washed three times with 70 ml of brine, dried over sodium sulfate and evaporated. The residue is crystallised from chloroform/n - hexane. 8 g of 8 - chloro - 3 - hydroxymethyl - dibenzofuran of melting point 160°—163°C are isolated.

Example 28

Manufacture of 8 - chloro - 3 - dibenzofuran - acetonitrile

A solution of 6.2 g of 8 - chloro - 3 - chloromethyl - dibenzofuran in 50 ml of pure dimethyl sulfoxide is added at 60°C to a solution of 1.55 g of sodium cyanide in 80 ml of pure dimethyl sulfoxide. The mixture is stirred for 5 hours at 60°C and, after cooling, poured into a suspension of 100 g of ice in 200 ml of cold water. The solid material is filtered off, dissolved in 500 ml of chloroform and filtered. The solution is washed with 200 ml of 1-N hydrochloric acid and 200 ml of saturated sodium bicarbonate, then dried with brine and sodium sulfate and evaporated. The residue is crystallised from chloroform/ether to yield 4.5 g of 8 - chloro - 3 - dibenzofuran - acetonitrile of melting point 170°—174°C.

The 8 - chloro - 3 - chloromethyl - dibenzofuran used as the starting material can be prepared as follows:

A solution of 6 g of 8 - chloro - 3 - hydroxymethyl - dibenzofuran in 300 ml of dry benzene and 120 ml of dry p - dioxane is stirred at 50°C. 2.11 ml of dry pyridine and then 2.68 ml of thionyl chloride are slowly added. The mixture is stirred for 4 hours at 50°C and then extracted at 0°C with saturated sodium bicarbonate. After drying with brine and sodium sulfate, the solution is evaporated to 6.2 g of crystalline 8 - chloro - 3 - chloromethyl - dibenzofuran.

Example 29

Manufacture of 2 - (8 - chloro - 3 - dibenzofuran)propionitrile

A solution of 483 mg of 8 - chloro - 3 - dibenzofuran - acetonitrile in 15 ml of dry hexamethylphosphoric acid triamide is added dropwise to a suspension of sodium amide obtained from 50.6 mg of sodium in 50 ml of liquid ammonia. The mixture is stirred for 2 hours at reflux, then 313 mg of iodomethane are added and stirring is continued for 1 hour. 200 mg of ammonium chloride and 100 ml of diethyl ether are added. After evaporation of the ammonia, the solution is sequentially washed with 1-N hydrochloric acid, saturated sodium bicarbonate and 10% sodium thiosulfate, then dried with brine and sodium sulfate and evaporated. The residue is dissolved in diethyl ether/cyclohexane (1:2)

and filtered to yield 2 - (8 - chloro - 3 - dibenzofuran)propionitrile of melting point 113°—116°C.

Example 30

5 Manufacture of 8 - chloro - 3 - dibenzofuran-acetic acid

10 5 ml of 1-N sodium hydroxide are added to a solution of 300 mg of 8 - chloro - 3 - dibenzofuran - acetonitrile in a mixture of 15 ml of n - butanol and 5 ml of dioxane. The solution is stirred at reflux for 48 hours and evaporated under reduced pressure. The residue is extracted with hot water. The filtrate is adjusted to pH 1 with concentrated hydrochloric acid and the mixture cooled. The resulting solid is crystallised from chloroform/diethyl ether to give 120 mg of 8 - chloro - 3 - dibenzofuranacetic acid of melting point 220°—223°C.

20 Example 31

In an analogous manner to that described in Example 30, 2 - (8 - chloro - 3 - dibenzofuran)propionitrile is converted into 2 - (8 - chloro - 3 - dibenzofuran)propionic acid of melting point 159°—161°C.

Example 32

25 Manufacture of 8 - chloro - α - methyl dibenzofuran - 3 - acetaldehyde

30 5.48 g of 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid are refluxed with 15 ml of thionyl chloride for 5 hours. The mixture is then evaporated to dryness and the residue obtained distilled at 148°—155°C to yield 5.67 g of crystalline acid chloride of melting point 80°—83°C.

35 1.8 g of palladium/palladium oxide-barium sulfate 5% is suspended in 200 ml of o - xylene. The resulting suspension is pre-hydrogenated and then added to the aforementioned acid chloride. Hydrogenation is then carried out for 2 hours at 78°—80°C. The mixture is then evaporated and the resulting oily residue distilled at 209°—212°C to yield 5.67 g of 8 - chloro - α - methyl dibenzofuran - 3 - acetaldehyde of melting point 87°C.

40 The foregoing aldehyde may also be manufactured by oxidation of the corresponding alcohol, namely 2 - (8 - chloro - 3 - dibenzofuranyl)propanol, with activated manganese dioxide, or by reduction of ethyl 8 - chloro - α - methyl dibenzofuran - 3 - acetate with sodium - dimethoxyethoxy - aluminium hydride at -70°C to -50°C.

55 Example 33

Manufacture of the sodium salt of 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid

60 A solution of 0.23 g of sodium in 20 ml of methanol is added dropwise to a solution of 2.74 g of 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid in 150 ml of absolute

methanol. After 10 minutes, the mixture is evaporated to dryness under reduced pressure to yield 2.91 g of a white residue. After recrystallisation from methanol/ether, there is obtained 2.6 g of the desired sodium salt of melting point 302°—305°C.

Example 34

Manufacture of the aluminium salt of 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid

A solution of the sodium salt, obtained as described in the preceding Example from 0.23 g of sodium and 2.74 g of 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid, is mixed dropwise with a solution of 0.44 g of dry aluminium chloride in 100 ml of absolute methanol. After 10 minutes, the white precipitate formed is filtered off and then washed sequentially with water, methanol and ether to give 2 g of the aluminium salt of melting point 300°C.

Example 35

Manufacture of 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid

4.8 g of α - methyl dibenzofuran - 3 - acetic acid are suspended in 10 ml of acetic acid and mixed with 0.1 g of iron powder. 20 ml of an acetic acid solution containing 1.36 g of chlorine are then added dropwise at 20°C. The mixture is allowed to stand for 12 hours at 50°C and then 5 ml of an acetic acid solution containing 0.47 g of chlorine is added dropwise and the temperature is raised to 95°C. The mixture is left for 3 hours at this temperature. The mixture is then mixed with 50 ml of water at 20°C. The resulting precipitate is taken up in ether, the organic phase washed 3 times with 20 ml of water each time, dried over sodium sulfate and filtered. After evaporation, 5.7 g of a white residue are obtained. After refluxing this residue twice with 200 ml of n - heptane each time, 0.9 g of 2 - chloro - α - methyl dibenzofuran - 3 - acetic acid are obtained; melting point 180°—183°C. The filtrate is evaporated and subjected to a chromatographic separation, whereby 0.5 g of 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid are obtained; melting point 155°—157°C.

The α - methyl dibenzofuran - 3 - acetic acid used as the starting material can be prepared by methylation of dibenzofuran - 3 - acetic acid in a manner similar to that described in Examples 25 or 29.

Example 36

Alternative process for the manufacture of 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid

4.8 g of α - methyl dibenzofuran - 3 - acetic acid and 40 ml of nitrobenzene are heated to 120°C. With continuous stirring, 2.44 ml of sulfonyl chloride are added dropwise over 10

minutes. The mixture is then left to proceed further for 12 hours at 120°C. The mixture is reduced to dryness under a vacuum. The residue is washed with water and dissolved in 500 ml of ether. The resulting acid is displaced into the aqueous phase as the sodium salt by means of 2-N sodium hydroxide. The organic phase is separated. By acidification, the acid precipitates out once more. It is then taken up in ether and, after washing twice with water, dried. After evaporation, there are obtained 5 g of a crystalline product which is finally distilled at 170°—184°C. After recrystallisation from high-boiling petroleum ether and benzene, 1.1 g of 2 - chloro - α - methylidibenzofuran - 3 - acetic acid are obtained; melting point 180°—183°C. The reduced mother liquor (1.7 g) is subjected to chromatographic separation, whereby 680 mg of 8 - chloro - α - methylidibenzofuran - 3 - acetic acid of melting point 156°—159°C are obtained.

Example 37

Manufacture of ethyl (8 - chloro - α - methyl - 3 - dibenzofuran)acetate

6 g of ethyl (α - methyl - 3 - dibenzofuran)acetate are dissolved in 10 ml of acetic acid and 0.1 g of iron powder are added. Over 1.5 hours, 40 ml of an acetic acid solution containing 2.8 g of chlorine are added dropwise with continuous stirring. The mixture is then held at 50°C for 12 hours. After cooling, the mixture is evaporated and the residue taken up in 300 ml of ether. Then, with the addition of ice, the ethereal solution is extracted twice with water, twice with saturated sodium bicarbonate solution and again twice with water. After drying and evaporation, the oily residue (5.6 g) is distilled at 148°—165°C. By chromatographic separation, 1.1 g of ethyl (8 - chloro - α - methyl - 3 - dibenzofuran)acetate of melting point 43°—54°C are obtained.

The following Examples illustrate typical pharmaceutical preparations containing the benzofuran derivatives provided by the present invention:

Example A

Tablets of the following composition are prepared in a conventional manner:

	Per tablet
Racemic 8 - chloro - α - methylidibenzofuran - 3 - acetic acid	25 mg
Dicalcium phosphate dihydrate	175 mg
Corn starch	24 mg
Magnesium stearate	1 mg
Total weight	225 mg

Example B

Capsules containing the following in-

gredients are prepared in a conventional manner:

	Per capsule	
Racemic 8 - chloro - α - methylidibenzofuran - 3 - acetic acid	50 mg	65
Lactose	125 mg	
Corn starch	30 mg	
Talc	5 mg	
Total weight	210 mg	70

Example C

Tablets of the following composition are prepared in a conventional manner:

	Per tablet	
Racemic 8 - chloro - α - methylidibenzofuran - 3 - acetic acid	100 mg	75
Lactose	202 mg	
Corn starch	80 mg	
Prehydrolysed corn starch	20 mg	
Calcium stearate	8 mg	80
Total weight	410 mg	

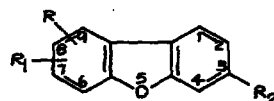
Example D

Suppositories of the following composition are prepared in a conventional manner:

	Per 1.3 g of suppository	
Racemic 8 - chloro - α - methylidibenzofuran - 3 - acetic acid	0.025 mg	90
Hydrogenated coconut oil	1.230 mg	
Carnauba wax	0.045 mg	

WHAT WE CLAIM IS:—

1) Compounds of the general formula



(I) 95

wherein R represents a hydrogen or halogen atom or a hydroxy, cyano, lower alkyl, hydroxy - (lower alkyl), lower alkoxy, acyl, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)-amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group, R₁ represents a halogen atom or a cyano, lower alkyl, hydroxy - (lower alkyl), lower alkoxy, acyl, acylamido, benzyloxy, lower alkylthio, trifluoromethyl, hydroxy, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl



* C L M S *

minutes. The mixture is then left to proceed further for 12 hours at 120°C. The mixture is reduced to dryness under a vacuum. The residue is washed with water and dissolved in 500 ml of ether. The resulting acid is displaced into the aqueous phase as the sodium salt by means of 2-N sodium hydroxide. The organic phase is separated. By acidification, the acid precipitates out once more. It is then taken up in ether and, after washing twice with water, dried. After evaporation, there are obtained 5 g of a crystalline product which is finally distilled at 170°—184°C. After recrystallisation from high-boiling petroleum ether and benzene, 1.1 g of 2 - chloro - α - methyl dibenzofuran - 3 - acetic acid are obtained; melting point 180°—183°C. The reduced mother liquor (1.7 g) is subjected to chromatographic separation, whereby 680 mg of 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid of melting point 156°—159°C are obtained.

Example 37

Manufacture of ethyl (8 - chloro - α - methyl - 3 - dibenzofuran)acetate

6 g of ethyl (α - methyl - 3 - dibenzofuran)acetate are dissolved in 10 ml of acetic acid and 0.1 g of iron powder are added. Over 1.5 hours, 40 ml of an acetic acid solution containing 2.8 g of chlorine are added dropwise with continuous stirring. The mixture is then held at 50°C for 12 hours. After cooling, the mixture is evaporated and the residue taken up in 300 ml of ether. Then, with the addition of ice, the ethereal solution is extracted twice with water, twice with saturated sodium bicarbonate solution and again twice with water. After drying and evaporation, the oily residue (5.6 g) is distilled at 148°—165°C. By chromatographic separation, 1.1 g of ethyl (8 - chloro - α - methyl - 3 - dibenzofuran)acetate of melting point 43°—54°C are obtained.

The following Examples illustrate typical pharmaceutical preparations containing the benzofuran derivatives provided by the present invention:

Example A

Tablets of the following composition are prepared in a conventional manner:

	Per tablet
Racemic 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid	25 mg
Dicalcium phosphate dihydrate	175 mg
Corn starch	24 mg
Magnesium stearate	1 mg
Total weight	225 mg

Example B

Capsules containing the following in-

gredients are prepared in a conventional manner:

	Per capsule
Racemic 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid	50 mg
Lactose	125 mg
Corn starch	30 mg
Talc	5 mg
Total weight	210 mg

Example C

Tablets of the following composition are prepared in a conventional manner:

	Per tablet
Racemic 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid	100 mg
Lactose	202 mg
Corn starch	80 mg
Prehydrolysed corn starch	20 mg
Calcium stearate	8 mg
Total weight	410 mg

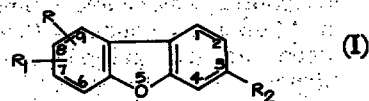
Example D

Suppositories of the following composition are prepared in a conventional manner:

	Per 1.3 g of suppository
Racemic 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid	0.025 mg
Hydrogenated coconut oil	1.230 mg
Carnauba wax	0.045 mg

WHAT WE CLAIM IS:—

1) Compounds of the general formula



wherein R represents a hydrogen or halogen atom or a hydroxy, cyano, lower alkyl, hydroxy - (lower alkyl), lower alkoxy, acyl, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)-amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group, R₁ represents a halogen atom or a cyano, lower alkyl, hydroxy - (lower alkyl), lower alkoxy, acyl, acylamido, benzyloxy, lower alkylthio, trifluoromethyl, hydroxy, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)-amino, sulfamoyl, di(lower alkyl)-sulfamoyl or difluoromethylsulfonyl

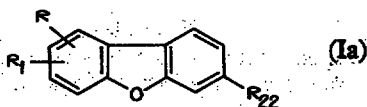
group, or R and R₁ on adjacent carbon atoms taken together represent a lower alkylendioxy group; and R₂ represents the grouping



in which A represents a cyano, hydroxy, lower alkoxy, amino - (lower alkoxy), mono(lower alkyl)amino - (lower alkoxy) or di(lower alkyl)amino - (lower alkoxy) group or the grouping $-\text{C}(\text{O})-\text{B}$, wherein B represents a hydrogen atom or a hydroxy, carboxy, lower alkoxy, amino, hydroxyamino, mono(lower alkyl)amino, di(lower alkyl)amino, amino - (lower alkoxy), mono(lower alkyl)amino - (lower alkoxy) or di(lower alkyl)amino - (lower alkoxy) group; X and Y each represent a hydrogen atom or a lower alkyl group and n stands for 1 to 7,

and salts thereof.

2) Compounds according to claim 1 of the general formula



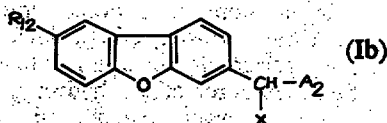
wherein R and R₁ have the significance given in claim 1 and R₂₂ represents the grouping



in which A represents a cyano, hydroxy, lower alkoxy, amino - (lower alkoxy), mono(lower alkyl)amino - (lower alkoxy) or di(lower alkyl)amino - (lower alkoxy) group or the grouping $-\text{C}(\text{O})-\text{B}$, wherein B represents a hydroxy, carboxy, lower alkoxy, amino, hydroxyamino, mono(lower alkyl)amino, di(lower alkyl)amino, amino - (lower alkoxy), mono(lower alkyl)amino - (lower alkoxy) or di(lower alkyl)amino - (lower alkoxy) group; and X, Y and n have the significance given in claim 1,

and salts thereof.

3) Compounds according to claim 1 of the general formula

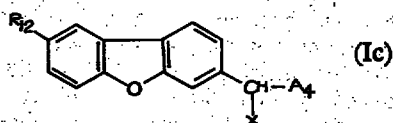


wherein R₁₂ represents a halogen atom or a hydroxy, lower alkyl, lower alkoxy, benzyloxy, nitro, amino, lower alkanoyl-

amido or trifluoromethyl group, A₂ represents a cyano, hydroxymethyl or hydroxy group or the grouping $-\text{C}(\text{O})-\text{B}$, wherein B represents a hydrogen atom or a hydroxy, lower alkoxy, amino, hydroxyamino, mono(lower alkyl)amino, di(lower alkyl)amino or di(lower alkyl)amino - (lower alkoxy) group and X represents a hydrogen atom or a lower alkyl group,

and salts thereof.

4) Compounds according to claim 1, claim 2 or claim 3 of the general formula

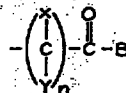


wherein R₁₂ and X have the significance given in claim 3 and A₄ represents a cyano or hydroxymethyl group or the grouping $-\text{C}(\text{O})-\text{B}$ in which B represents a hydroxy, lower alkoxy, amino, hydroxyamino, mono(lower alkyl)amino, di(lower alkyl)amino or di(lower alkyl)amino - (lower alkoxy) group,

and salts thereof.

5) Compounds according to any one of claims 1 to 4 inclusive and of formula I, wherein R represents a hydrogen atom and R₁ represents a halogen atom, and salts thereof.

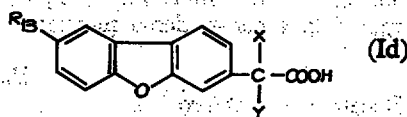
6) Compounds according to any one of claims 1 to 5 inclusive and of formula I, wherein R₂ represents the grouping



and salts thereof.

7) Compounds according to any one of claims 1 to 6 inclusive and of formula I, wherein B represents a hydroxy group, and salts thereof.

8) Compounds according to any one of claims 1 to 7 inclusive and of the general formula



wherein R₁₃ represents a halogen atom or a lower alkyl or lower alkoxy group and X and Y each represent a hydrogen atom or a lower alkyl group,

and salts thereof.

9) Racemic 8 - chloro - α - methylbenzofuran - 3 - acetic acid.

10) (+) - 8 - Chloro - α - methylbenzofuran - 3 - acetic acid.



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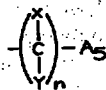
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11) (-) - 8 - Chloro - α - methyl dibenzofuran - 3 - acetic acid.

12) 8 - Chloro - dibenzofuran - 3 - acetic acid.

13) 8 - Chloro - dibenzofuran - 3 - acetamide.

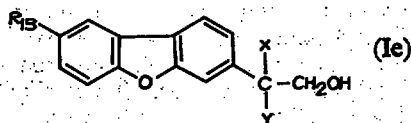
14) Compounds according to any one of claims 1 to 5 inclusive and of formula I, wherein R_2 represents the grouping



in which X, Y and n have the significance given in claim 1 and A_5 represents a cyano, hydroxy, lower alkoxy, amino - (lower alkoxy), mono(lower alkyl)amino - (lower alkoxy) or di(lower alkyl)amino - (lower alkoxy) group, and salts thereof.

15) Compounds according to any one of claims 1 to 5 inclusive and claim 14 and of formula I, wherein A represents a hydroxy group, and salts thereof.

16) Compounds according to any one of claims 1 to 5 inclusive, claim 14 and claim 15 and of the general formula



25) wherein R_{13} represents a halogen atom or a lower alkyl or lower alkoxy group and X and Y each represent a hydrogen atom or a lower alkyl group.

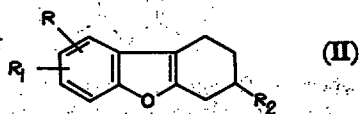
17) 2 - (8 - Chloro - 3 - dibenzofuranyl) - propanol.

18) 2 - (8 - Chloro - 3 - dibenzofuranyl) - ethanol.

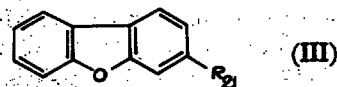
19) Compounds according to any one of claims 1 to 6 inclusive and of formula I, wherein B represents a hydrogen atom, and salts thereof.

20) 8 - Chloro - α - methyl dibenzofuran - 3 - acetaldehyde.

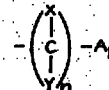
21) A process for the manufacture of the dibenzofuran derivatives claimed in claim 1, which process comprises reacting a compound of the general formula



45) wherein R, R_1 and R_2 have the significance given in claim 1, with an aromatising agent; or chlorinating or brominating a compound of the general formula

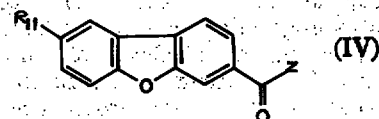


wherein R_{21} represents the grouping



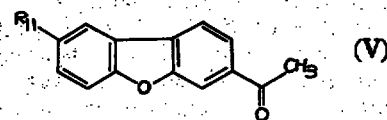
in which A_1 represents a cyano or lower alkoxy group or the grouping $-C(O)-B_1$, in which B_1 represents a hydroxy, lower alkoxy or di(lower alkyl)amino group, and n, X and Y have the significance given in claim 1,

to yield a corresponding compound of formula I in which R_1 represents a chlorine or bromine atom, R represents a hydrogen atom and R_2 has any of the values accorded to R_{21} ; or simultaneously reducing and saponifying a compound of the general formula



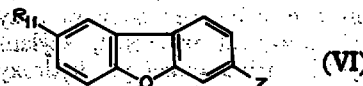
wherein R_{11} represents a chlorine or bromine atom and Z represents a carbonyl - (lower alkoxy) group,

to yield a corresponding compound of formula I in which R represents a hydrogen atom, R_1 has either of the values accorded to R_{11} and R_2 represents a carboxymethyl group; or reacting a compound of the general formula



wherein R_{11} has the significance given earlier in this claim,

with an amine having a boiling point in the range of from 100°C to 200°C, in the presence of sulfur and saponifying the resulting compound to yield a corresponding acid of formula I in which R represents a hydrogen atom, R_1 has either of the values accorded to R_{11} and R_2 represents a carboxymethyl group; or reducing a compound of the general formula



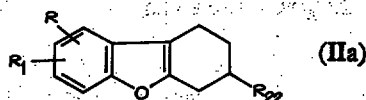
wherein R_{11} and Z have the significance given earlier in this claim,

to yield a corresponding alcohol of formula I in which R represents a hydrogen atom, R_1 has either of the values accorded to R_{11} and R_2 represents a hydroxymethyl group; for the manufacture of an acid of formula I in which B represents a hydroxy group, saponi-

fying an ester of formula I in which B represents a lower alkoxy group; if desired reducing an ester of formula I in which at least one of R, R₁ and —C(O)—B represents a carbo-
 5 (lower alkoxy) group to the corresponding alcohol in which the carbo - (lower alkoxy) group is replaced by a hydroxymethyl group; if desired, converting a hydroxy group denoted by B in an acid of formula I into an amino
 10 group; if desired, dehydrating an amide of formula I in which A represents a carbamoyl group to the corresponding nitrile; if desired, esterifying an acid of formula I in which B represents a hydroxy group, or a salt thereof with a base, or converting the group B in
 15 such an acid or salt thereof into an amino - (lower alkoxy), mono(lower alkyl)amino - (lower alkoxy) or di(lower alkyl)amino - (lower alkoxy) group; if desired, deacylating an acylamido group denoted by R₁ to an amino group; if desired, halogenating an acid of formula I in which B represents a hydroxy
 20 group to yield a corresponding acid halide and hydrogenating the resulting halide to yield a corresponding aldehyde of formula I in which B represents a hydrogen atom; if desired, converting the group denoted by A in an alcohol of formula I in which A represents a hydroxymethyl group or the group
 25 denoted by A in an ester of formula I in which A represents a carbo - (lower alkoxy) group into the formyl group; if desired, appropriately alkylating an amino group denoted by R or R₁ in a compound of formula I to yield a compound of formula I in which R or R₁ represents a di(lower alkyl)amino
 30 group; if desired, dealkylating a lower alkoxy group denoted by R, R₁ or A contained in an ether of formula I to a hydroxy group; if desired, transforming a hydroxy group denoted by A contained in an alcohol of formula I into a lower alkoxy, amino - (lower alkoxy), mono(lower alkyl)amino - (lower alkoxy) or di(lower alkyl)amino - (lower alkoxy) group; if desired, replacing the
 35 hydroxy group denoted by A in an alcohol of formula I in which R represents a hydrogen or halogen atom or a hydroxy, cyano, lower alkyl, lower alkoxy, acyl, lower alkylthio, trifluoromethyl, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group, R₁ represents a halogen atom or a cyano, lower alkyl, lower alkoxy, acyl, acylamido, lower alkylthio, trifluoromethyl, hydroxy, carboxy, carbo - (lower alkoxy), nitro, amino, mono-
 40 (lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group or R and R₁ on adjacent carbon atoms together represent a lower alkylenedioxy group, by a halogen atom and reacting the compound obtained with an alkali metal cyanide to yield a corresponding
 45 compound of formula I in which A represents

a cyano group; if desired, saponifying a nitrile of formula I in which R represents a hydrogen or halogen atom or a hydroxy, cyano, lower alkyl, hydroxy - (lower alkyl), lower alkoxy, acyl, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino or difluoromethylsulfonyl group, R₁ represents a halogen atom or a cyano, lower alkyl, hydroxy - (lower alkyl), lower alkoxy, acyl, acylamido, benzyloxy, lower alkylthio, trifluoromethyl, hydroxy, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino or difluoromethylsulfonyl group or R and R₁ on adjacent carbon atoms together represent a lower alkylenedioxy group with the proviso that at least one of A, R and R₁ represents a cyano group, to the corresponding acid in which a cyano group is replaced by a carboxy group; if desired, appropriately alkylating a compound of formula I in which R represents a hydrogen or halogen atom or a hydroxy, cyano, lower alkyl, lower alkoxy, acyl, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group, R₁ represents a halogen atom or a cyano, lower alkyl, lower alkoxy, acyl, acylamido, benzyloxy, lower alkylthio, trifluoromethyl, hydroxy, carboxy, carbo - (lower alkoxy), nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, sulfamoyl, di(lower alkyl)sulfamoyl or difluoromethylsulfonyl group or R and R₁ on adjacent carbon atoms together represent a lower alkylenedioxy group, n stands for 1, A represents a cyano group or the grouping —C(O)—B in which B represents a hydrogen atom or a lower alkoxy group and at least one of X and Y represents a hydrogen atom, to yield a corresponding compound in which at least one of X and Y represents a lower alkyl group; if desired, converting an acid or base of formula I into a salt; and, also if desired, resolving a racemate obtained into its optically active isomers and isolating the desired isomer.

22) A process according to claim 21 for the manufacture of the dibenzofuran derivatives claimed in claim 2, wherein a compound of the general formula



wherein R and R₁ have the significance given in claim 1 and R₂₂ has the significance given in claim 2,
 is reacted with an aromatising agent; for the manufacture of an acid of formula Ia in which B₂ represents a hydroxy group, an ester of formula Ia in which B₂ represents a lower alkoxy group is saponified; if desired, an ester



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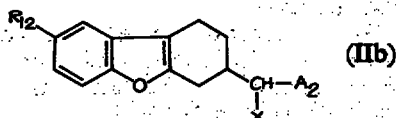
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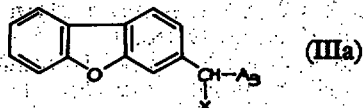
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of formula Ia in which at least one of R, R₁ and —C(O)—B₂ represents a carbo - (lower alkoxy) group is reduced to the corresponding alcohol in which the carbo - (lower alkoxy) group is replaced by a hydroxymethyl group; if desired, an acid of formula Ia in which B₂ represents a hydroxy group, or a salt thereof with a base, is esterified or the group B₂ in such an acid or salt thereof is converted into an amino - (lower alkoxy), mono(lower alkyl)-amino - (lower alkoxy) or di(lower alkyl)-amino - (lower alkoxy) group; if desired, an acylamido group denoted by R₁ is deacylated to an amino group; if desired, an amino group denoted by R or R₁ in a compound of formula Ia is appropriately alkylated to yield a corresponding compound of formula Ia in which R or R₁ represents a di(lower alkyl)amino group; if desired, a lower alkoxy group denoted by R, R₁ or A contained in an ether of formula Ia is dealkylated to a hydroxy group; if desired, a hydroxy group denoted by A contained in an alcohol of formula Ia is transformed into a lower alkoxy, amino - (lower alkoxy), mono(lower alkyl)amino - (lower alkoxy) or di(lower alkyl)amino - (lower alkoxy) group; if desired, an acid or base of formula Ia is converted into a salt and, also if desired, a racemate obtained is resolved into its optically active isomers and the desired isomer isolated.

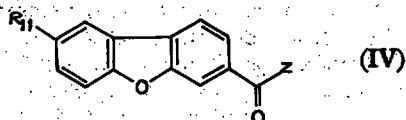
23) A process according to claim 1 for the manufacture of the dibenzofuran derivatives claimed in claim 3, wherein a compound of the general formula



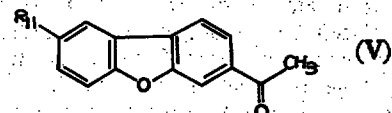
wherein R₁₂, X and A₂ have the significance given in claim 3, is reacted with an aromatising agent; or a compound of the general formula



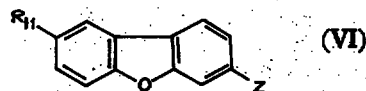
wherein A₃ represents a cyano group or the grouping —C(O)—B₄ in which B₄ represents a hydroxy, lower alkoxy or di(lower alkyl)amino group and X has the significance given in claim 3, is chlorinated or brominated to yield a corresponding compound of formula Ib in which R₁₂ represents a chlorine or bromine atom and A₂ has any of the values accorded to A₃; or a compound of the general formula



wherein R₁₁ represents a chlorine or bromine atom and Z represents a carbo - (lower alkoxy) group, is simultaneously reduced and saponified to yield a corresponding compound of formula Ib in which X represents a hydrogen atom, R₁₂ has either of the values accorded to R₁₁ and A₂ represents a carboxy group; or a compound of the general formula



wherein R₁₁ has the significance given earlier in this claim, is reacted with an amine having a boiling point in the range of from 100°C to 200°C, in the presence of sulfur and the resulting compound saponified to yield a corresponding acid of formula Ib in which X represents a hydrogen atom and A₂ represents a carboxy group; or a compound of the general formula

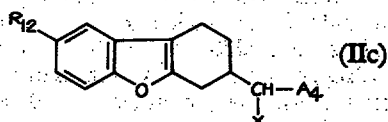


wherein R₁₁ and Z have the significance given earlier in this claim, is reduced to the corresponding alcohol of formula Ib in which R₁₂ has either of the values accorded to R₁₁, X represents a hydrogen atom and A₂ represents a hydroxy group; for the manufacture of an acid of formula Ib in which B₂ represents a hydroxy group, an ester of formula Ib in which B₂ represents a lower alkoxy group is saponified; if desired, the group denoted by A₂ in an ester of formula Ib in which A₂ represents a carbo - (lower alkoxy) group is reduced to a hydroxymethyl group; if desired, a hydroxy group denoted by B₂ in an acid of formula Ib is converted into an amino group; if desired, an amide of formula Ib in which A₂ represents a carbamoyl group is dehydrated to the corresponding nitrile; if desired, an acid of formula Ib in which B₂ represents a hydroxy group, or a salt thereof with a base, is esterified or the group B₂ in such an acid or salt thereof is converted into a di(lower alkyl)amino - (lower alkoxy) group; if desired, a lower alkanoylamido group denoted by R₁₂ is deacylated to an amino group; if desired, an acid of formula Ib in which B₂ represents a hydroxy group is halogenated to the corresponding acid halide and this acid halide is hydrogenated to yield a corresponding aldehyde of formula Ib in which B₂ represents a hydrogen atom; if desired, the group denoted by A₂ in an alcohol of formula Ib in which A₂ represents a hydroxymethyl group or the group denoted by A₂ in an ester of formula



Ib in which A_2 represents a carbo - (lower alkoxy) group is converted into the formyl group; if desired, a lower alkoxy group denoted by R_{12} contained in an ether of formula Ib is dealkylated to a hydroxy group; if desired, the hydroxy group denoted by A_2 in an alcohol of formula Ib in which R_{12} represents a halogen atom or a hydroxy, lower alkyl, lower alkoxy, nitro, amino, lower alkanoylamido or trifluoromethyl group, is replaced by a halogen atom and the resulting compound is reacted with an alkali metal cyanide to yield a corresponding compound of formula Ib in which A_2 represents a cyano group; if desired, a compound of formula Ib in which A_2 represents a cyano group is saponified to a corresponding acid; if desired, a compound of formula Ib in which A_2 represents a cyano group or the grouping $-C(O)-B_3$ in which B_3 represents a hydroxy atom or a lower alkoxy group and X represents a hydrogen atom is alkylated to a corresponding compound in which X represents a lower alkyl group; if desired, an acid or base of formula Ib is converted into a salt; and, also if desired, a racemate obtained is resolved into its optically active isomers and the desired isomer isolated.

24) A process according to claim 21, claim 22 or claim 23 for the manufacture of a dibenzofuran derivative claimed in claim 4, wherein a compound of the general formula



wherein R_{12} , X and A_4 have the significance given in claim 4, is reacted with an aromatising agent; for the manufacture of an acid of formula Ic in which B_5 represents a hydroxy group, an ester of formula Ic in which B_5 represents a lower alkoxy group is saponified; if desired, the group denoted by A_4 in an ester of formula Ic in which A_4 represents a carbo - (lower alkoxy) group is reduced to a hydroxymethyl group; if desired, an acid of formula Ic in which B_5 represents a hydroxy group, or a salt thereof with a base, is esterified or the group B_5 in such an acid or salt thereof is converted into a di(lower alkyl)amino - (lower alkoxy) group; if desired, a lower alkanoylamido group denoted by R_{12} is deacylated to an amino group; if desired, a lower alkoxy group denoted by R_{12} contained in an ether of formula Ic is dealkylated to a hydroxy group; if desired, an acid or base of formula Ic is converted into a salt and, also if desired, a racemate obtained is resolved into its optically active isomers and the desired isomer isolated.

25) A process according to any one of claims 21-24 inclusive, wherein a dibenzo-

furan derivative as claimed in claim 5 is manufactured.

26) A process according to any one of claims 21 to 25 inclusive, wherein a dibenzofuran derivative as claimed in claim 6 is manufactured.

27) A process according to any one of claims 21 to 26 inclusive, wherein a dibenzofuran derivative as claimed in claim 7 is manufactured.

28) A process according to any one of claims 21 to 27 inclusive, wherein a dibenzofuran derivative as claimed in claim 8 is manufactured.

29) A process according to any one of claims 21 to 28 inclusive, wherein racemic 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid is manufactured.

30) A process according to any one of claims 21 to 28 inclusive, wherein (+) - 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid is manufactured.

31) A process according to any one of claims 21 to 28 inclusive, where (-) - 8 - chloro - α - methyl dibenzofuran - 3 - acetic acid is manufactured.

32) A process according to any one of claims 21 to 28 inclusive, wherein 8 - chloro - dibenzofuran - 3 - acetic acid is manufactured.

33) A process according to any one of claims 21 to 26 inclusive, wherein 8 - chloro - dibenzofuran - 3 - acetamide is manufactured.

34) A process according to any one of claims 21 to 25 inclusive, wherein a dibenzofuran derivative as claimed in claim 14 is manufactured.

35) A process according to any one of claims 21 to 25 inclusive and claim 34, wherein a dibenzofuran derivative as claimed in claim 15 is manufactured.

36) A process according to any one of claims 21 to 25 inclusive, claim 34 or claim 35, wherein a dibenzofuran derivative as claimed in claim 16 is manufactured.

37) A process according to any one of claims 21 to 25 inclusive, claim 34, claim 35 and claim 36, wherein 2 - (8 - chloro - 3 - dibenzofuranyl)propanol is manufactured.

38) A process according to any one of claims 21 to 25 inclusive, claim 34, claim 35 and claim 36, wherein 2 - (8 - chloro - 3 - dibenzofuranyl)ethanol is manufactured.

39) A process according to any one of claims 21 to 26 inclusive, wherein a dibenzofuran derivative as claimed in claim 19 is manufactured.

40) A process according to any one of claims 21 to 26 inclusive and claim 39, wherein 8 - chloro - α - methyl dibenzofuran - 3 - acetaldehyde is manufactured.

41) A process for the manufacture of the dibenzofuran derivatives claimed in claim 1, substantially as hereinbefore described with reference to any one of Examples 1 to 37.

42) Dibenzofuran derivatives as set forth



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in claim 1, when manufactured by the process claimed in any one of claims 21 to 41 inclusive.

43) A pharmaceutical preparation containing a compound claimed in any one of claims 1 to 20 inclusive or a pharmaceutically acceptable salt thereof in association with a compatible pharmaceutical carrier.

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