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3,784,602

ARYLOXY- AND ARYLTHIOALKANOIC ACIDS AND ESTERS AND SALTS THEREOF

Jorg Frei, Binningen, Basel, Charles J. Morel, Arlesheim, Basel, and Oskar Wacker, Basel, Switzerland, assignors to Ciba-Geigy Corporation, Ardsley, N.Y.

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13 Claims

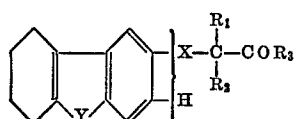
ABSTRACT OF THE DISCLOSURE

Compounds of the class of substituted 6,7,8,9-tetrahydrodibenzofuranyloxy-, 6,7,8,9 - tetrahydrodibenzothiophenyloxy-, and the corresponding furanylthio- and thiophenylthioacetic acids, lower alkyl esters thereof and alkali and alkaline earth metal salts thereof have hypolipaeamic activity; they are active ingredients of pharmaceutical compositions and are useful for treating hyperlipaemic conditions in warm-blooded animals.

DETAILED DESCRIPTION

The present invention relates to new aryloxy- and arylthioalkanoic acids, their salts and functional derivatives, to processes for the production of the new compounds, to medicaments containing the new compounds, and to the use thereof.

More particular the present invention relates to compounds of the Formula I



(I)

wherein

R₁ represents an alkyl group having at most 14 carbon atoms, or a cycloalkyl group having 5–7 carbon atoms,

R₂ represents hydrogen or the methyl group,

R₃ represents the hydroxyl group, wherein the hydrogen atom can be replaced by an alkali metal atom or an alkaline-earth metal atom, an alkyloxy group having at most 3 carbon atoms, or the amino group, and

X and Y represent, independently of each other, oxygen or sulphur.

The compounds of the General Formula I such as, e.g.

2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid,

2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-dodecanoic acid,

2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octanoic acid,

2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-dodecanoic acid,

2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanoic acid,

2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-dodecanoic acid,

2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid,

2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-octanoic acid,

2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-octanoic acid, and

2-(6,7,8,9-tetrahydrodibenzothiophen-2-yl)-octanoic acid

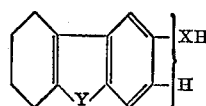
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possess valuable pharmacological properties and have a high therapeutic index. In the case of oral administration they have, in particular, hypolipaeamic activity, which can be shown, e.g. by the lowering of the level of cholesterol and triglyceride in the blood and liver on repeated administration, in dosages of 2 times 10 mg./kg. per day to male rats, according to standard methods. The total cholesterol is determined according to R. Richterich and K. Lauber [cp. Klin. Wochenschrift 40, 1252–1256 (1962)] direct in the serum. Furthermore, serum- as well as liver-lipids are extracted according to J. Folch et al. [cp. J. Biol. Chem. 226, 497 (1957)], and triglycerides and total cholesterol determined with the autoanalyzer, according to G. Kessler and H. Lederer [cp. Automation in der Analytischen Chemie (1965), Technicon G.m.b.H., Frankfurt/Main, pp. 863–872, and W. D. Block et al., ibid. pp. 970–971].

The new compounds are distinguished by a, in comparison with the hypolipaeamic activity, only slight hepatomegal activity.

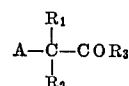
As an alkyl group having at most 14 carbon atoms in the compounds of the General Formula I, R₁ is, e.g. the methyl, ethyl, propyl, butyl, isobutyl, pentyl, isopentyl, 2,2-dimethylpropyl, hexyl, isohexyl, 3,3-dimethylbutyl, heptyl, nonyl, decyl, undecyl, dodecyl, tridecyl or tetradecyl group; and as a cycloalkyl group having 5–7 carbon atoms R₁ is, e.g. the cyclopentyl, cyclohexyl, or cycloheptyl group.

The new compounds of the General Formula I are produced according to the invention by reacting an alkali metal salt of a phenol or thiophenol of the General Formula II:



(II)

wherein X and Y have the meaning given under the General Formula I with a compound of the General Formula III:



(III)

wherein R₁, R₂ and R₃ have the meaning given under the General Formula I, and A represents halogen, an alkylsulphonyloxy group or an arylsulphonyloxy group. The reaction is preferably performed in a solvent or diluent. Such solvents or diluents are, e.g. lower alkanols such as ethanol, or solvents free of hydroxyl groups, such as N,N-dimethylformamide, N,N-dimethylacetamide, or N,N,N',N',N'',N''-hexamethylphosphoric acid triamide.

The reaction temperatures are between 50 and 150°, preferably at the boiling point of the applied solvent. The boiling temperature of the solvent attainable under normal conditions can, if required, be raised by the reaction being performed in a closed vessel. The formation of the alkali salts of phenols or thiophenols of the General Formula II which are used as starting material, and of the alkali salts of the carboxylic acids embraced by the General Formula III, is preferably effected in situ, e.g. with the aid of an alkali metal alcoholate, alkali metal hydroxide, or alkali metal hydride, depending on whether an anhydrous alkanol or a solvent free of hydroxyl groups is used as the reaction medium. Instead of an alkali metal hydride, it is also possible to use a corresponding amide, e.g. sodium amide.

The phenols or thiophenols of the General Formula II to be used according to the invention as starting materials, namely:

6,7,8,9-tetrahydrodibenzofuran-2-ol,
6,7,8,9-tetrahydrodibenzofuran-3-ol,
6,7,8,9-tetrahydrodibenzofuran-2-thiol,
6,7,8,9-tetrahydrodibenzofuran-3-thiol,
6,7,8,9-tetrahydrodibenzothiophen-2-ol,
6,7,8,9-tetrahydrodibenzothiophen-3-ol,
6,7,8,9-tetrahydrodibenzothiophene-2-thiol, and
6,7,8,9-tetrahydrodibenzothiophene-3-thiol,

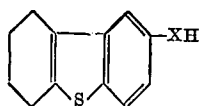
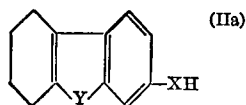
can be obtained using various methods. For example, 6,7,8,9-tetrahydrodibenzofuran-2-ol can be produced in a simple manner by reaction of 1-morpholinocyclohexene (1) and p-benzoquinone at room temperature in methylene chloride, and splitting the initially obtained 5a,6,7,8,9,9a-hexahydro-5a-morpholinodibenzofuran-2-ol by boiling in aqueous hydrochloric acid to give 6,7,8,9-tetrahydrodibenzofuran-2-ol and morpholine hydrochloride [cp. G. Domschke, J. Prakt. Chem. 32, 144-157 (1966)].

A further possibility for the production of 6,7,8,9-tetrahydrodibenzofuran-2-ol, which includes at the same time the production of 6,7,8,9-tetrahydrodibenzofuran-3-ol, consists in reacting 2-chlorocyclohexanone or 2-bromocyclohexanone with an alkali metal salt of hydroquinone-monomethyl ether or resorcinmonomethyl ether, and then converting the firstly obtained 2-(4-methoxyphenoxy)cyclohexanone or 2-(3-methoxyphenoxy)-cyclohexanone in the presence of an acid catalyst such as, e.g. phosphoric acid or sulphuric acid, into 2-methoxy-6,7,8,9-tetrahydro- or 3-methoxy-6,7,8,9-tetrahydrodibenzofuran, and subsequently splitting off the methyl group. The methyl group can be split off, e.g. by boiling the substance in a mixture of concentrated hydrobromic acid and glacial acetic acid, or by heating with pyridine hydrochloride.

6,7,8,9-tetrahydrodibenzofuran-2-thiol, as well as 6,7,8,9-tetrahydrodibenzofuran-3-thiol, can be obtained in a simple manner, starting with the corresponding 2- or 3-hydroxy compounds, by reacting these with an N,N-dialkylthiocarbamic acid chloride, and rearranging the N,N-dialkylthiocarbamoyloxy group present in the 2- or 3-position to give the N,N-dialkylthiocarbamoylthio group, and subsequently hydrolyzing this. The rearrangement is advantageously effected by the substance being heated for several hours to temperatures of 250-300° [cp. also M. S. Newman and H. A. Karnes, J. Org. Chem. 31, 3980-3984 (1966)].

6,7,8,9-tetrahydrodibenzothiophen-2-ol and 6,7,8,9-tetrahydrodibenzothiophen-3-ol are produced by reacting e.g. 2-chloro or 2-bromocyclohexanone with an alkali salt of 4-methoxy- and 3-methoxythiophenol to give 2-(4-methoxyphenylthio)-cyclohexanone and 2-(3-methoxyphenylthio)-cyclohexanone, respectively, and converting these compounds by subsequent ring closure with phosphoric acid, and ether-splitting with pyridine hydrochloride, into 6,7,8,9-tetrahydrodibenzothiophen-2-ol or -3-ol. From these compounds it is possible to finally obtain: 6,7,8,9-tetrahydrodibenzothiophene-2-thiol and 6,7,8,9-tetrahydrodibenzothiophene-3-thiol again by reaction with N,N-dialkylthiocarbamic acid chloride, rearrangement of the N,N-dialkylthiocarbamoyloxy group present in the 2- or 3-position to give the N,N-dialkylthiocarbamoylthio group, and subsequent hydrolysis [cp. M. S. Newman and H. S. Karnes, J. Org. Chem. 31, 3980-3984 (1966)].

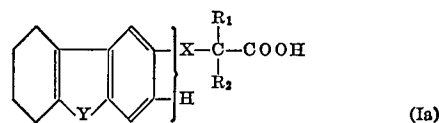
The phenols and thiophenols (required as starting materials and likewise embraced by the General Formula II) of the General Formula IIa and IIb:



wherein X and Y have the meaning given under the General Formula I, as well as 6,7,8,9-tetrahydrodibenzofuran-2-thiol, have hitherto not been known.

The starting materials of the General Formula III which embraces chlorides and bromides derived from 2-hydroxyalkanoic acids, -alkanoic acid esters and -alkanoic acid amides can be produced in a manner analogous to that for producing 2-bromopropionic acid ethyl ester [cp. Ann. 197, 13 (1879)]. The alkyl- or arylsulphonic acid esters likewise embraced by the General Formula III can be obtained, starting with the thus produced bromides, by reaction with corresponding sulphonic acid salts, or by reaction of 2-hydroxyalkanoic acids, -esters or -amides with an alkyl- or arylsulphonic acid chloride in the presence of alkali. α -Halogenocarboxylic acids can moreover be produced by the generally known α -halogenation of carboxylic acids. Starting with these, the corresponding lower alkyl esters, and the amides likewise embraced by the General Formula III are readily accessible in a manner known per se.

The aryloxy- or arylthioalkanoic acids (also embraced by the General Formula I) of the General Formula Ia:

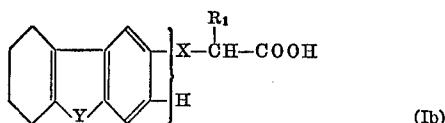


wherein R₁, R₂, X and Y have the meanings given under the General Formula I, and their salts with alkali metals and alkaline-earth metals, can be produced using a second process according to the invention by hydrolyzing a functional derivative of such an acid.

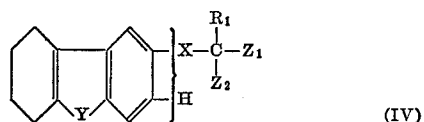
Suitable functional derivatives of aryloxy- and arylthioalkanoic acids of the General Formula Ia are esters thereof, e.g. lower alkyl esters, or the cyclohexyl, phenyl or benzyl ester, as well as nitriles, amides and lower imidoalkyl esters. These functional derivatives or carboxylic acids of the General Formula Ia can be hydrolyzed by heating in an aqueous mineral acid, e.g. by boiling in 60-70% sulphuric acid, or in a mixture of, e.g. 6-n. hydrochloric acid and glacial acetic acid. The free carboxylic acids of the General Formula Ia obtained by this procedure can optionally be converted into an alkali metal salt or alkaline-earth metal salt. On account of the starting materials being difficultly soluble in water it is necessary to add, in carrying out the process with dilute mineral acids, a solubility-promoting agent. Suitable as such are water-miscible organic solvents such as, e.g. lower alkanols, tetrahydrofuran or, as already mentioned, glacial acetic acid. The hydrolysis may, however, also be carried out in an alkaline medium, e.g. by heating in alkanolic or aqueous-alkanolic alkali hydroxide solutions to temperatures between about 50° and the boiling temperature of the applied reaction medium. From the alkali metal salts obtained direct with this procedure it is possible to obtain, if required, the free acids of the General Formula Ia by dissolving for example, the alkali salts in water and adding mineral acid. The functional derivatives of alkanolic acids of the General Formula Ia required as starting materials can be obtained analogously to the first process by reacting an alkali metal salt of a phenol or thiophenol of the General Formula II with corresponding 2-bromoalkanoic acid esters, -amides and -nitriles. Starting with the nitriles obtained in this manner it is moreover possible to produce the imidoalkyl esters likewise usable as starting materials by reaction with an alkanol in the presence of hydrogen chloride. A further method of production of functional derivatives of carboxylic acids of the General Formula Ia consists in decarboxylating monoesters or monoamides of corresponding substituted aryloxy- or arylthiomalonic acids, or corresponding substituted aryloxy- or arylthiocyanoacetic acids.

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Obtained using a third process according to the invention are aryloxy- or arylthioalkanoic acids of the General Formula Ib:



wherein R_1 , X and Y have the meanings given under the General Formula I, and their salts with alkali metals or alkaline-earth metals, by heating under hydrolyzing conditions compounds of the General Formula IV:



wherein R_1 , X and Y have the meanings given under the General Formula I, and Z_1 and Z_2 represent, independently of each other, lower alkoxy carbonyl groups or nitrile groups, until one of the groups Z_1 or Z_2 is completely hydrolyzed and hydrogen is present in place of the other.

Applying one embodiment of this process according to the invention, compounds of the General Formula IV are heated in an aqueous mineral acid, e.g. in 60-70% sulphuric acid or conc. hydrochloric acid, and, optionally, the obtained carboxylic acid of the General Formula Ib is converted into an alkali metal salt or alkaline-earth metal salt. If necessary, the reaction is performed in the presence of an inert, water-miscible organic solvent which serves as solubility-promoting agent for the starting materials difficultly soluble in water. As such solvents, it is possible to use, e.g. lower alkanols, tetrahydrofuran, glacial acetic acid, etc.

Using a further embodiment of this process according to the invention, compounds of the General Formula IV are heated with alkanolic alkali hydroxide, e.g. with methanolic potassium hydroxide solution, or in aqueous-alkalolic alkali hydroxide, and the alkali metal salts of carboxylic acids of the General Formula Ib obtained in this manner are optionally converted into the free acids. In carrying out the process in an alkaline medium, mixtures are occasionally obtained in which are present, in addition to the desired end product, still incompletely saponified and incompletely decarboxylated intermediates. These can be converted by subsequent heating with an aqueous mineral acid, optionally in the presence of a water-miscible organic solvent—corresponding to the first embodiment of the process—into homogeneous aryloxy- or arylthioalkanoic acids of the General Formula Ib. For carrying out the process, substituted malonic acid dialkyl esters of the General Formula IV are refluxed for several hours in the stated reaction media. The malonic acid dinitriles likewise embraced by the General Formula IV and the corresponding cyanocetic esters are reacted analogously; they require however, as a rule, more energetic reaction conditions and longer reaction times. In this case, the reaction according to the invention may be performed, if required, in a closed reaction vessel under pressure.

The following compounds embraced by the general Formula IV are, for their part, new compounds:

6,7,8,9-tetrahydrodibenzofuran-2-yloxy,
6,7,8,9-tetrahydrodibenzofuran-3-yloxy-
6,7,8,9-tetrahydrodibenzofuran-2-ylthio-
6,7,8,9-tetrahydrodibenzofuran-3-ylthio-
6,7,8,9-tetrahydrodibenzothiophen-2-yloxy-
6,7,8,9-tetrahydrodibenzothiophen-3-yloxy-
6,7,8,9-tetrahydrodibenzothiophen-2-ylthio- and
6,7,8,9-tetrahydrodibenzothiophen-3-ylthiomalonic acid
esters,
-malonic acid nitriles and
-cyanoacetic acid alkyl esters.

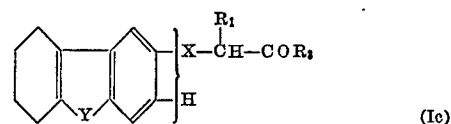
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They can be obtained, for example, by reaction of alkali metal salts of

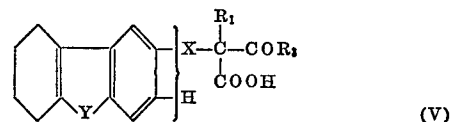
6,7,8,9-tetrahydrodibenzofuran-2-ol,
6,7,8,9-tetrahydrodibenzofuran-3-ol,
6,7,8,9-tetrahydrodibenzofuran-2-thiol,
6,7,8,9-tetrahydrodibenzofuran-3-thiol,
6,7,8,9-tetrahydrodibenzothiophen-2-ol,
6,7,8,9-tetrahydrodibenzothiophen-3-ol,
6,7,8,9-tetrahydrodibenzothiophene-2-thiol or
6,7,8,9-tetrahydrodibenzothiophene-3-thiol

with R_1 -substituted bromomalonic acid dialkyl esters, bromocyanoacetic acid alkyl esters, or bromomalonic acid nitriles. Of the stated bromine compounds some are known, e.g. bromopropylmalonic acid diethyl ester [cp. A. W. Dox. and L. Joder, J. Am. Chem. Soc. 44, 1578-1581 (1922)]. Further compounds of this type can be produced analogously.

Using a fourth process according to the invention, aryloxy- or arylthioalkanoic acids embraced by the General Formula I, their salts with alkali metals and alkaline-earth metals, their lower alkyl esters and amides of the General Formula Ic:



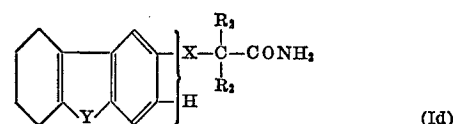
wherein R_1 , R_3 , X and Y have the meanings given under the General Formula I can be obtained by heating a compound of the General Formula V:



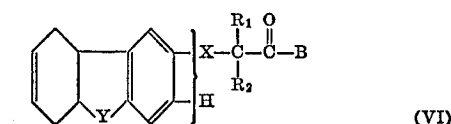
wherein R_1 , R_3 , X and Y have the meanings given under the General Formula I until the equimolar amount of carbon dioxide is split off.

For the splitting off of carbon dioxide, the compounds of the General Formula V can be heated either in substance or in an inert solvent, e.g. toluene or xylene, to temperatures of 100-150°. The compounds of the General Formula V can, for example, be produced by completely or partially saponifying esters of malonic acid or of malonamic acid. Malonamic acid can be obtained by addition of water to the nitrile group of the corresponding cyanoacetic acid esters and, immediately afterwards, saponification of the ester group. Alkali metal salts of carboxylic acids of the General Formula Ic are preferably produced by starting with acid salts of the malonic acids embraced by the General Formula V, heating these until the equimolar amount of carbon dioxide is split off and, optionally, liberating from the obtained salt the carboxylic acid embraced by the General Formula Ic.

The aryloxy- or arylthioalkanoic acid amides (embraced by the General Formula I) of the General Formula Id:



wherein R_1 , R_2 , X and Y have the meanings given under the General Formula I can be produced using a fifth process according to the invention by reacting an aryloxy- or arylthioalkanoic acid derivative of the General Formula VI:

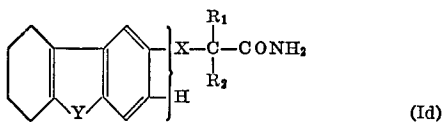


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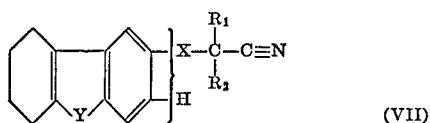
wherein R_1 , R_2 , X and Y have the meanings given under the General Formula I, and B represents halogen or an alkoxy group, with ammonia. The reaction according to the invention is preferably performed by dissolving a compound of the General Formula VI in an inert solvent, and then introducing ammonia. The acid halides thereby react already at room temperature, whereas aminolysis of the esters requires, as a rule, higher temperatures. Suitable as solvents for the reaction of the acid halides embraced by the General Formula VI with ammonia are ethereal liquids such as, e.g. diethyl ether, tetrahydrofuran, or hydrocarbons such as, e.g. benzene, toluene, and so forth, or chlorinated hydrocarbons such as chloroform and methylene chloride. Suitable as solvent for the reaction of the esters likewise embraced by the General Formula VI with ammonia are, besides the already stated higher ethers and hydrocarbons, also lower alkanols such as, e.g. methanol or ethanol. The reaction is performed, e.g. by refluxing the ammonia-saturated solutions of the esters in the stated solvents, or, if necessary, it is performed under pressure in a closed vessel.

The acid halides of the General Formula VI which are used as starting materials can be obtained, starting with the corresponding carboxylic acids, by reaction with thionyl chloride or phosphorus pentachloride, phosphorus trichloride or phosphorus oxychloride. The free carboxylic acids forming the basis of the compounds of the General Formula VI, as well as the esters embraced by this formula, can be produced, for their part, analogously to the first process by reaction of alkali metal salts of the corresponding phenols or thiophenols with α -halides of corresponding alkanolic acids or their lower alkyl esters.

The aryloxy- or arylthioalkanoic acid amides (embraced by the General Formula I) of the General Formula Id:



wherein R_1 , R_2 , X and Y have the meanings given under the General Formula I can be obtained using a sixth process according to the invention by adding water to a nitrile of the General Formula VII:

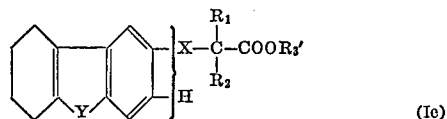


wherein R_1 , R_2 , X and Y have the meanings given under the General Formula I. This process can be carried out by dissolving the nitrile of the General Formula VII used as starting material in a strong mineral acid, e.g. sulphuric acid, containing an amount of water sufficient for the formation of the amide, and subsequently stirring the solution for half an hour to one hour at temperatures between 20 and 60°. Optionally, this reaction may also be carried out in the presence of a solvent, e.g. ether or tetrahydrofuran. A further possibility of carrying out the reaction according to the invention consists in dissolving a nitrile of the General Formula VII in hydrous ether and feeding in gaseous hydrogen chloride. According to a further embodiment of the process according to the invention, a nitrile of the General Formula VII is reacted in an alkaline medium in the presence of hydrogen peroxide. The reaction is performed in aqueous medium, whereby it is necessary to ensure, of course, that the medium contains a sufficient amount of water-miscible organic solvent, e.g. a lower alkanol, which will render certain the solubility of a nitrile of the General Formula VII. According to a further modification of the process according to the invention, a nitrile of the General Formula VII is first converted, by dissolving in an anhydrous lower

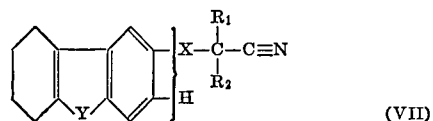
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alkanol and feeding in hydrogen chloride, into the imido-alkyl ester hydrochloride, and subsequently splitting this, by heating to temperatures of 80–130°, preferably to 90–100°, into an amide of the General Formula Id and alkyl chloride.

The aryloxy- or arylthioalkanoic acid esters (embraced by the General Formula I) of the General Formula Ie:



wherein R_1 , R_2 , X and Y have the meanings given under the General Formula I, and R_3' represents a lower alkyl radical having 1–3 carbon atoms can be produced according to the invention by reacting a nitrile of the General Formula VII:

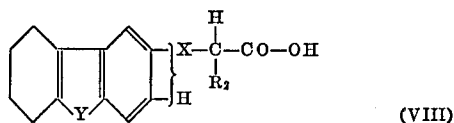


wherein R_1 , R_2 , X and Y have the meanings given under the General Formula I, in the presence of water and mineral acid, with a lower alkanol. Several embodiments are possible for the carrying out of the process according to the invention. The nitrile of the General Formula VII can, for example, be refluxed, in the presence of the equimolar amount of sulphuric acid and water, with an excess of lower alkanol. The isolation of the final product is performed by dilution of the reaction mixture with water, whereby the ester of the General Formula Ie which is difficultly soluble in this medium precipitates as crude product.

According to a further embodiment of the process covered by the invention, the nitrile of the General Formula VII can be firstly converted into the imido ester hydrochloride by reaction with a lower alkanol in the presence of hydrogen chloride, and the imido ester hydrochloride then hydrolyzed to an ester of the General Formula Ie. The conversion of the nitrile into the imido ester hydrochloride is advantageously performed in a solvent. As the solvent it is possible to use, e.g. excess alkanol, ether or chloroform. Finally, it is also possible to firstly add water to a nitrile of the General Formula VII, and to subject the obtained amide, in the presence of a mineral acid, to alcoholysis. The water-addition to the nitrile is advantageously carried out in 80–95% sulphuric acid, and to the obtained solution of the amide in sulphuric acid is added an excess of alkanol, and the mixture refluxed. In this case too, the isolation of the final product is performed most simply by dilution of the reaction mixture with water, whereby the desired ester precipitates as crude product.

The nitrile of the General Formula VII used as starting material can likewise be produced analogously to the first process by reaction of an alkali metal salt of a corresponding phenol or thiophenol with an α -halogenalkanoic acid nitrile.

The aryloxy- and arylthioalkanoic acids (likewise embraced by the General Formula I) of the above given General Formula Ia wherein R_1 , R_2 , X and Y have the meanings given under the General Formula I, and their salts with alkali metals and alkaline-earth metals, are produced according to an eighth process by reacting a bis-alkali metal compound or bis-halogenmagnesium compound of a carboxylic acid of the General Formula VIII:



wherein X, Y and R₂ have the meanings given under Formula I with the essentially equimolar amount of a compound of the General Formula IX:

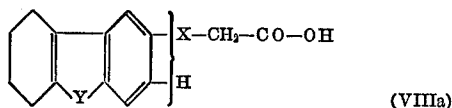


wherein R₁ has the meaning given under Formula I, and A represents halogen, an alkylsulphonyloxy group or an arylsulphonyloxy group; optionally liberating from the obtained salt of a carboxylic acid of the General Formula Ia the carboxylic acid and, optionally, again converting it into an alkali metal salt or alkaline-earth metal salt. Suitable bis-alkali metal compounds are, in particular, the bis-lithium compounds, also bis-sodium compounds. For example, the lithium-diisopropylamide is initially formed at ca. -10° to 0° from diisopropylamine and butyllithium in a tetrahydrofuranhexane mixture, the carboxylic acid of the General Formula VIII is subsequently added, then an, at least, equimolar amount of hexamethylphosphoric acid triamide, and finally the compound of the General Formula IX; and the reaction is completed at room temperature. The addition of hexamethylphosphoric acid triamide may optionally be omitted, especially with the use of starting materials having a methyl group as R₂. According to a further embodiment of the process are formed from sodium amide suspensions in liquid ammonia (which, for their part, have been obtained in situ from solutions of sodium in ammonia by addition of catalytic amounts of iron(III)-nitrate and stirring until the blue color of the metal solution has disappeared) and carboxylic acids of the General Formula VIII the bis-sodium compounds of the latter, and these then reacted with compounds of the General Formula IX, which are added dissolved in ether or tetrahydrofuran.

Bis-halogenmagnesium compounds of carboxylic acids of the General Formula VIII are obtained, e.g. by reaction of these acids with the double-molar amount of isopropyl magnesium bromide or isopropyl magnesium chloride in ethereal solution at room temperature and a reaction duration of ca. 4-15 hours. The reaction is subsequently performed with the compounds of the General Formula IX likewise in ether, or in another ethereal solvent such as, e.g. tetrahydrofuran, at room temperature to boiling temperature of the reaction medium.

The carboxylic acids, required as starting materials, of the General Formula VIII wherein R₂ is a methyl group are new materials which are embraced by the General Formula I and producible according to the above mentioned processes, preferably according to the first and second process.

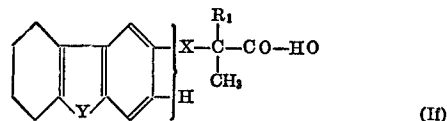
The carboxylic acids (likewise embraced by the General Formula VIII and required as starting materials) of the General Formula VIIIa:



wherein X and Y have the meaning given under Formula I are likewise new materials. They are produced by reacting, e.g. analogously to the first process, an alkali metal salt of a compound of the General Formula II with a halogenated acetic acid, or a lower halogenated acetic acid alkyl ester; and hydrolyzing the alkyl ester firstly obtained in the last-mentioned case, analogously to the second process.

As halogen in the compounds of the General Formula IX, A is preferably bromine, but also iodine or chlorine, as an alkylsulphonyloxy group A is, e.g. the methanesulphonyloxy group, and as an arylsulphonyloxy group A is, e.g. the p-toluenesulphonyloxy group.

According to a ninth process, the aryloxy- and arylthio-alkanoic acids of the General Formula II:



wherein X, Y and R₁ have the meaning given under Formula I, and their salts with alkali metals and alkaline-earth metals, are produced by reacting a compound of the previously given General Formula II wherein X and Y have the meaning given there with a methane tri- or tetra-substituted by chlorine and/or bromine, and a ketone of the General Formula X:



wherein R₁ has the meaning given under Formula I, or with the reaction product of the last two mentioned components, i.e. a compound of the General Formula XI:



wherein R₁ has the meaning given under Formula I, and Hal represents chlorine or bromine, in the presence of the, at least, fourfold molar amount of a strong base; optionally liberating from the obtained salt of a carboxylic acid of the General Formula II, the carboxylic acid and, optionally, converting this again into an alkali metal salt or alkaline-earth metal salt. The reaction is preferably in an excess of ketone of the General Formula X as the reaction medium. Also with the use of starting materials of the General Formula XI, the corresponding ketone is preferably used as solvent. The reaction temperature is preferably between 0° and the boiling temperature of the applied ketone. The last-mentioned is preferably acetone, whereas a suitable halogen-substituted methane derivative is preferably chloroform, a suitable compound of Formula XI is preferably 1,1,1-trichloro-2-methyl-2-propanol, and a suitable strong base is an alkali metal hydroxide such as sodium or potassium hydroxide. Since, in the presence of these strong bases, acetone and other methylketones react, as is known, with chloroform, as also with further tri- and tetrahalogen-methanes such as bromoform, carbon tetrachloride and carbon tetrabromide, to form compounds of the General Formula XI, it is after all, in the case of both embodiments of the process, the same reaction which occurs.

Suitable alkali metal salts and alkaline-earth metal salts of carboxylic acids embraced by the General Formula I are, e.g. their sodium, potassium, lithium, magnesium, and calcium salts. These salts are produced, e.g. by the combining of acid and base in a suitable solvent such as, e.g. methanol, ethanol, or acetone/water. Formed salts which are relatively difficultly soluble can be isolated by filtration, and readily soluble salts by concentration by evaporation of the solvent. Furthermore, salts which are relatively difficultly soluble in the applied solvent may also be produced by double reaction of another salt of the acid with the base or with a suitable salt thereof.

The compounds of the General Formula I and the alkali salts and alkaline-earth metal salts of the free carboxylic acids embraced by this formula are administered, as previously mentioned, orally or parenterally. The daily dosages vary between 0.5 and 10 mg./kg. for warm-blooded animals. Suitable dosage units such as dragées, tablets, suppositories, and capsules preferably contain as active substance 10-250 mg., e.g. 50 or 100 mg. of a compound of the General Formula I, or of an alkali metal salt or alkaline-earth metal salt of one of the free carboxylic acids embraced by the General Formula I.

Dosage units for oral administration contain as active substance preferably between 10 and 90% of a compound of the General Formula I. The said dosage units are pro-

duced by a combination of the active substance, e.g. with solid pulverulent carriers such as lactose, saccharose, sorbitol, mannitol; starches such as potato starch, maize starch or amylopectin, also laminaria powder or citrus pulp powder; cellulose derivatives or gelatine, optionally with the addition of lubricants such as magnesium or calcium stearate, or polyethylene glycols, to form tablets or dragée cores. The dragée cores are coated, e.g. with concentrated sugar solutions which can also contain, e.g. gum arabic, talcum and/or titanium dioxide; or they are coated with a lacquer dissolved in readily volatile organic solvents or mixtures of solvents. Dyestuffs may be added to these coatings, e.g. for identification of the various dosages of active substance.

Further suitable dosage units for oral administration are hard gelatine capsules, as well as as soft closed capsules made from gelatine and a softener such as glycerin. The hard capsules contain the active substance preferably as a granulate, e.g. in admixture with fillers such as maize starch, and/or lubricants such as talcum or magnesium stearate, and optionally stabilizers such as sodium metadisulphite ($\text{Na}_2\text{S}_2\text{O}_5$) or ascorbic acid. In soft capsules the active substance is preferably dissolved or suspended in suitable liquids, such as liquid polyethylene glycols.

The following prescriptions are to further illustrate the production of tablets, dragées, suppositories and capsules:

(a) An amount of 1000 g. of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid or of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-dodecanoic acid is mixed with 550 g. of lactose and 292 g. of potato starch; the mixture is moistened with analcoholic solution of 8 g. of gelatine, and then granulated through a sieve. After the granulate has dried, 60 g. of potato starch, 60 g. of talcum, 10 g. of magnesium stearate and 20 g. of highly dispersed silicon dioxide are mixed in; the mixture is then pressed to form 10,000 tablets each weighing 200 mg. and each containing 100 mg. of active substance. If required, the tablets can be provided with grooves to effect a more precise adjustment of the dosage amount.

(b) An amount of 100 g. of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid or of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-dodecanoic acid is well mixed with 16 g. of maize starch and 6 g. of highly-dispersed silicon dioxide. The mixture is moistened with a solution of 2 g. of stearic acid, 6 g. of ethyl cellulose, and 6 g. of stearin in ca. 70 ml. of isopropyl alcohol; it is afterwards granulated through a sieve III (Ph. Helv. V). The granulate is dried for about 14 hours, and is then put through a sieve II-IIIa. The granulate is thereupon mixed together with 16 g. of maize starch, 16 g. of talcum and 2 g. of magnesium stearate; the obtained mixture is then pressed to form 1000 dragée cores. These are coated with a concentrated syrup of 2 g. of lacca, 7.5 g. of gum arabic, 0.15 g. of dyestuffs, 2 g. of highly-dispersed silicon dioxide, 25 g. of talcum and 53.35 g. of sugar; the coated dragée cores are then dried. The obtained dragées each weigh 260 mg. and each contain 100 mg. of active substance.

(c) To produce 1000 capsules each containing 75 mg. of active substance, 75 g. of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid or 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid are mixed with 198.0 g. of lactose; the mixture is evenly moistened with an aqueous solution of 20 g. of gelatine, and then granulated through a suitable sieve (e.g. sieve III according to Ph. Helv. V.). The granulate is mixed with 10.0 g. of dried maize starch and 15.0 g. of talcum; the obtained mixture is evenly filled into 1000 hard gelatine capsules, size 1.

The following examples further illustrate the production of compounds of the General Formula I and of salts thereof; the examples, however, in no way limit the scope of the invention. The temperatures are given in degrees centigrade. With regard to the nomenclature for the produced compounds, alkyl radicals which deviate from the normal unbranched chain are indicated by designa-

tions such as sec-, tetra- or iso-alkyl. Where these designations do not appear, then the normal unbranched radical is always meant. The expression mMol denotes millimol=0.001 mol.

Example 1

In a round-bottomed flask fitted with reflux condenser, dropping funnel, stirrer, gas-inlet tube, and drying-tube containing potassium hydroxide, 4.0 g. (21.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol are added, under nitrogen, to a solution of 0.48 g. (21.0 mMol) of sodium in 50 ml. of absolute ethanol. To the thus obtained solution of sodium-6,7,8,9-tetrahydrodibenzofuran-2-olate are added dropwise, with stirring, 4.98 g. (21.0 mMol) of 2-bromoheptanoic acid ethyl ester, and the whole is then refluxed for 4 hours. After cooling, the reaction mixture is concentrated in vacuo, and the residue distributed between water and ether. After being washed with water until the pH-value is 7 and dried with magnesium sulphate, the ether solution is concentrated by evaporation, whereby a light-yellow oil is obtained. The crude, 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid ethyl ester, which is still contaminated with 6,7,8,9-tetrahydrodibenzofuran-2-ol is purified by column chromatography (neutral silica gel 0.05-0.2 mm., Merck, solvent: benzene). The benzene fractions containing the desired ester are combined and concentrated by evaporation. After drying in high vacuum, is obtained pure 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid ethyl ester, a slightly yellowish oil; n_D^{25} : 1.5248.

Analogously are obtained

from 4.0 g. (21.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 3.8 g. (21.0 mMol) of 2-bromopropionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-propionic acid ethyl ester; n_D^{20} : 1.5408;
from 1.88 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 1.95 g. (10.0 mMol) of 2-bromo-2-methylpropionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-methylpropionic acid ethyl ester; n_D^{25} : 1.5361.
from 3.76 g. (20.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 4.18 g. (20.0 mMol) of 2-bromopentanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-pentanoic acid ethyl ester; n_D^{20} : 1.5324;
from 1.88 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 2.23 g. (10.0 mMol) of 2-bromoheptanoic acid methyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid methyl ester; n_D^{20} : 1.5320;
from 1.88 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 2.60 g. (10.0 mMol) of 2-bromoheptanoic acid propyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid propyl ester; n_D^{20} : 1.5220;
from 1.88 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 2.37 g. (10.0 mMol) of 2-bromoisoheptanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-isoheptanoic acid ethyl ester; n_D^{20} : 1.5241;
from 3.76 g. (20.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 5.02 g. (20.0 mMol) of 2-bromooctanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid ethyl ester; n_D^{20} : 1.5219;
from 1.88 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 2.79 g. (10.0 mMol) of 2-bromodecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-decanoic acid ethyl ester; n_D^{20} : 1.5262;
from 3.0 g. (16.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 4.91 g. (16.0 mMol) of 2-bromododecanoic acid ethyl ester: 8-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-dodecanoic acid ethyl ester; n_D^{22} : 1.5133;
from 1.88 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 3.35 g. (10.0 mMol) of 2-bromotetradec-

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anoic acid ethyl ester: 2-(6,7,8,9 - tetrahydrodibenzofuran-2-yloxy)-tetradecanoic acid ethyl ester; n_D^{20} : 1.5098;

from 1.88 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 3.63 g. (10.0 mMol) of 2-bromohexadecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-hexadecanoic acid ethyl ester; n_D^{20} : 1.5062;

from 1.88 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 2.35 g. (10.0 mMol) of α -bromocyclopentaneacetic acid ethyl ester: α -(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-cyclopentaneacetic acid ethyl ester; n_D^{20} : 1.5423;

from 1.88 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 2.49 (10.0 mMol) of α -bromocyclohexaneacetic acid ethyl ester: α -(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-cyclohexaneacetic acid ethyl ester; n_D^{20} : 1.5422;

from 1.88 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 1.95 g. (10.0 mMol) of 2-bromobutyric acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-butyric acid ethyl ester; n_D^{20} : 1.5372.

The 6,7,8,9-tetrahydrodibenzofuran-2-ol used as starting material can be produced as follows:

(a) In a three-necked, round-bottomed flask fitted with thermometer, stirrer, and reflux condenser, an addition is made in portions of 36.7 g. (0.25 mol) of the sodium salt of hydroquinone-monomethyl ether to a solution of 46.6 g. (0.264 mol) of 2-bromocyclohexanone in 130 ml. of absolute toluene, whereby the temperature rises from 25° to 50°. The thus obtained yellow slurry is then refluxed for 2 hours, whereby the sodium salt of hydroquinone-monomethyl ether gradually dissolves, and sodium bromide simultaneously precipitates. After cooling, this is taken up in 700 ml. of ether, and the ethereal solution washed four times with, in all, 200 ml. of 15% potassium hydroxide solution and water, dried over magnesium sulphate, and concentrated in vacuo. In this manner is obtained crude 2-(4-methoxyphenoxy)-cyclohexanone as yellow oil. After recrystallization twice from ether/hexane, pure 2-(4-methoxyphenoxy)-cyclohexanone is obtained in the form of pale yellow needles, M.P. 77-79°.

(b) In a round-bottomed flask with stirrer, 4.0 g. (18.0 mMol) of 2-(4-methoxyphenoxy)-cyclohexanone are added in portions to 40 ml. of phosphoric acid ($d=1.71$), whereby a green solution is formed, which is subsequently heated for 2½ hours to 105°. The color of the solution thereby changes from green to red-brown, and there simultaneously precipitates an almost colorless oil. After cooling, the reaction mixture is poured onto ice, and extracted twice with 200 ml. of ether in all. The ethereal solution is washed with 1-n. sodium hydroxide solution and water. Thus obtained is crude 2-methoxy-6,7,8,9-tetrahydrodibenzofuran as brown oil, which is distilled twice in a bulb tube at 0.005 torr between 80 and 100°. The thus obtained pure 2-methoxy-6,7,8,9-tetrahydrodibenzofuran is a colorless oil; n_D^{20} : 1.5783.

(c) In a round-bottomed flask fitted with reflux-condenser and drying tube containing potassium hydroxide, 3.0 g. (14.85 mMol) of 2-methoxy-6,7,8,9-tetrahydrodibenzofuran are heated for 2¾ hours, whilst stirring is maintained, with 20.0 g. of pyridine hydrochloride to 170°. The still hot reaction mixture is then poured onto a mixture of 200 g. of ice and 100 ml. of 1-n. hydrochloric acid, and the whole stirred for a further half an hour.

The 6,7,8,9 - tetrahydrodibenzofuran-2-ol precipitating in the form of white crystals is filtered off under suction, and washed with cold water until the washing water is neutral. After drying in high vacuum is obtained pure 6,7,8,9-tetrahydrodibenzofuran-2-ol as white powder, M.P. 106-107°.

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Example 2

In a round-bottomed flask fitted with reflux condenser, dropping funnel, stirrer, gas-inlet tube, and drying tube containing potassium hydroxide, 3.76 g. (20.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol are added under nitrogen to a solution of 0.46 g. (20.0 mMol) of sodium in 80 ml. of absolute ethanol. To the thus obtained solution of sodium - 6,7,8,9 - tetrahydrodibenzofuran-3-olate are added dropwise, with stirring, 5.02 g. (200 mMol) of 2-bromooctanoic acid ethyl ester, and refluxing is carried out for 3 hours. After cooling, the reaction mixture is concentrated in vacuo, and the residue is distributed between water and ether. The ether phase is separated and, after being washed with water to give pH=7 and dried with magnesium sulphate, concentrated in vacuo, whereby a light-yellow oil is obtained. The crude 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid ethyl ester, which is still contaminated with 6,7,8,9-tetrahydrodibenzofuran-3-ol, is purified by column chromatography (neutral silica gel 0.05-0.2 mm. Merck, solvent: benzene). The benzene fractions containing the desired ester are combined and concentrated in vacuo. After drying in high vacuum is obtained the pure 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octanoic acid ethyl ester, a slightly yellowish oil; n_D^{20} : 1.5233.

Analogously are obtained

from 2.82 g. (15.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 2.80 g. (15.0 mMol) of 2-bromopropionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-propionic acid ethyl ester; n_D^{20} : 1.5426;

from 1.88 (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 1.95 g. (10.0 mMol) of 2-bromobutyric acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-butyric acid ethyl ester; n_D^{20} : 1.5376;

from 2.82 g. (15.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 2.92 g. (15.0 mMol) of 2-bromo-2-methylpropionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran - 3 - yloxy)-2-methyl-propionic acid ethyl ester; n_D^{20} : 1.5366;

from 2.82 g. (15.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 3.56 g. (15.0 mMol) of 2-bromoisoheptanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-isoheptanoic acid ethyl ester; n_D^{20} : 1.5260;

from 3.76 g. (20.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 6.14 g. (20.0 mMol) of 2-bromododecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-dodecanoic acid ethyl ester; n_D^{20} : 1.5155;

from 2.82 g. (15.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 5.45 g. (15.0 mMol) of 2-bromohexadecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-hexadecanoic acid ethyl ester; n_D^{20} : 1.5075;

from 3.76 g. (20.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 4.99 g. (20.0 mMol) of α -bromocyclohexaneacetic acid ethyl ester: α -(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-cyclohexaneacetic acid ethyl ester; n_D^{20} : 1.5445.

The 6,7,8,9 - tetrahydrodibenzofuran-3-ol used as starting material can be produced as follows:

(a) In a three-necked round-bottomed flask fitted with thermometer, stirrer, and reflux condenser, 300.0 g. (2.05 mol) of the sodium salt of resorcinolmonomethyl ether are added in portions to a solution of 382.0 g. (2.16 mol) of 2-bromocyclohexanone in 825 ml. of absolute toluene, whereby the temperature rises from 25° to 60°. The thus obtained yellow slurry is then refluxed for 2 hours, whereby the sodium salt of the resorcinolmonomethyl ether gradually dissolves, and sodium bromide simultaneously precipitates. After cooling, the reaction mixture is distributed between ether and water, the ether phase is separated and washed four times with, in all, 2.0 litres of 15% potassium hydroxide solution and water;

it is then dried over magnesium sulphate and concentrated in vacuo. In this manner is obtained the crude 2-(3-methoxy-phenoxy)-cyclohexanone as yellow oil. After recrystallization twice from ether/hexane is obtained the pure 2-(3-methoxy-phenoxy)-cyclohexanone in the form of pale yellow crystals, M.P. 72.5–73°. The non-crystallizing mother liquors can likewise be further processed according to (b).

(b) In a round-bottomed flask fitted with stirrer, 134.0 g. (0.61 mol) of 2-(3-methoxy-phenoxy)-cyclohexanone are added in portions to 1340 ml. of phosphoric acid ($d_r=1.71$), whereby a green solution is formed, which is subsequently heated for 2 hours to 105°. After cooling, the reaction mixture is poured on to ice, and extracted with ether. The ethereal solution is washed with 1-n. sodium hydroxide solution and water, dried over magnesium sulphate, and concentrated in vacuo. Thus obtained is a mixture of 3- and 1-methoxy-6,7,8,9-tetrahydrodibenzofuran in the form of a brown oil, which is distilled at 0.005 torr between 99 and 108°. In this manner is obtained a colorless oil which contains, in addition to 3-methoxy-6,7,8,9-tetrahydrodibenzofuran, according to the NMR-spectrum, ca. 8% of 1-methoxy-6,7,8,9-tetrahydrodibenzofuran, and can be further processed without further purification.

(c) In a round-bottomed flask fitted with reflux condenser and a drying tube containing potassium hydroxide, 129.1 g. (0.64 mol) of a mixture, obtained according to (b), of 3- and 1-methoxy-6,7,8,9-tetrahydrodibenzofuran are heated for 2¾ hours, with stirring, with 401.1 g. of pyridine hydrochloride to 170°. The still hot reaction mixture is then poured on to a mixture of 800 g. of ice and 400 ml. of 1-n. hydrochloric acid, and stirred for a further ½ hour. The precipitated oil is extracted with ether, and the ethereal solution concentrated, whereby crystallises, on cooling, the crude 6,7,8,9-tetrahydrodibenzofuran-3-ol. It is filtered off under suction, and further crystallized twice from ether-benzene. Thus obtained is pure 6,7,8,9-tetrahydrodibenzofuran-3-ol in the form of light-yellow crystals, M.P. 105–106°, whilst 6,7,8,9-tetrahydrodibenzofuran-1-ol remains in the mother liquors.

Example 3

In a round-bottomed flask fitted with reflux condenser, dropping funnel, stirrer, gas-inlet tube, and drying tube containing potassium hydroxide, 1.0 g. (4.9 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-thiol is added, under nitrogen, to a solution of 0.112 g. (4.9 mMol) of sodium in 10 ml. of absolute ethanol.

To the thus obtained solution of sodium-6,7,8,9-tetrahydrodibenzofuran-2-thiolate are added dropwise, with stirring, 1.23 g. (4.9 mMol) of 2-bromooctanoic acid ethyl ester, and the whole is refluxed for 3 hours, whereby nitrogen is continuously passed through the solution. After cooling, the reaction mixture is concentrated in vacuo, and the residue distributed between water and ether. After washing with water until the pH-value is 7, and drying with magnesium sulphate, the ether solution is concentrated by evaporation, whereby a yellow oil is obtained. The crude 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid ethyl ester, which is still contaminated with 6,7,8,9-tetrahydrodibenzofuran-2-thiol, is purified by column chromatography (neutral silica gel 0.05–0.2 mm., Merck, solvent: benzene). The benzene fractions containing the desired ester are combined and concentrated by evaporation. After drying in high vacuum, pure 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid ethyl ester is obtained as a colorless oil; n_D^{20} : 1.5465.

Analogously are obtained

from 1.43 g. (7.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-thiol and 1.27 g. (7.0 mMol) of 2-bromo-

propionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-propionic acid ethyl ester; n_D^{20} : 1.5699;

from 2.0 g. (9.78 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-thiol and 1.92 g. (9.78 mMol) of 2-bromo-2-methylpropionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-2-methylpropionic acid ethyl ester; n_D^{20} : 1.5663;

from 1.43 g. (7.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-thiol and 1.66 g. (7.0 mMol) of 2-bromoisoheptanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-isoheptanoic acid ethyl ester; n_D^{20} : 1.5503;

from 0.7 g. (3.42 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-thiol and 1.24 g. (3.42 mMol) of 2-bromohexadecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-hexadecanoic acid ethyl ester; n_D^{20} : 1.5245.

The 6,7,8,9-tetrahydrodibenzofuran-2-thiol used as starting material can be produced as follows:

(a) In a round-bottomed flask fitted with reflux condenser, stirrer, thermometer, gas-inlet tube, and drying tube containing potassium hydroxide, 0.48 g. (10 mMol) of 50% sodium hydride dispersion are added in small portions, under nitrogen, to a solution of 1.88 g. (10 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol in 10 ml. of dimethylformamide. The evolution of hydrogen has ceased after half an hour. The formed dark-brown suspension is now cooled to 10° and then are added, all at once, 1.65 g. (13.0 mMol) of dimethylthiocarbamic acid chloride. The temperature thereby rises immediately to 18°; the whole is subsequently heated, with stirring, for a further hour to 80°, whereby sodium chloride precipitates in the now light-brown colored solution. After cooling, the solution is concentrated in vacuo, and the brown oil remaining behind distributed between ether and water. The ether phase is repeatedly washed with cold dilute sodium hydroxide solution and water, dried over magnesium sulphate, and concentrated by evaporation, whereby crude dimethylthiocarbamic acid-O-(6,7,8,9-tetrahydrodibenzofuran-2-yl)-ester remains behind as yellow-brown oil, which is then purified by column-chromatography [silica-gel 0.05–0.2 mm., Merck, solvent: benzene/ethyl acetate (9:1)]. After concentration by evaporation of the pure fractions, these are recrystallized twice from aqueous methanol with the addition of active charcoal. Thus obtained is pure dimethylthiocarbamic acid-O-(6,7,8,9-tetrahydrodibenzofuran-2-yl)-ester, M.P. 129–131°.

(b) In a round-bottomed flask fitted with magnetic stirrer and gas-inlet tube, 9.6 g. (35 mMol) of dimethylthiocarbamic acid-O-(6,7,8,9-tetrahydrodibenzofuran-2-yl)-ester are heated under nitrogen, with stirring, for 3½ hours at 280–295°. The thus formed dark-brown oil can be directly processed according to (c). Optionally it is purified by column-chromatography [silica gel 0.05–0.2 mm., Merck, solvent: benzene/ethyl acetate (9:1)]. The pure fractions are combined and concentrated by evaporation. After recrystallization twice from aqueous methanol, pure dimethylthiocarbamic acid-S-(6,7,8,9-tetrahydrodibenzofuran-2-yl)-ester, M.P. 73–74°, is obtained.

(c) In a round-bottomed flask fitted with reflux condenser, stirrer, gas-inlet tube, and drying tube containing potassium hydroxide, a solution of 3.0 g. (11.0 mMol) of dimethylthiocarbamic acid-S-(6,7,8,9-tetrahydrodibenzofuran-2-yl)-ester (crude product) in 18.8 ml. of 10% sodium hydroxide solution and 60 ml. of methanol is refluxed, under nitrogen, for 3½ hours. After cooling, the methanol is evaporated off in vacuo, the residue acidified with 2-n. hydrochloric acid, and extracted with ether. After washing of the ethereal solution with water until the pH-value is 7, and drying over magnesium sulphate, concentration by evaporation is again performed. In this manner is obtained crude 6,7,8,9-tetrahydrodibenzofuran-2-thiol as yellow oil, which is purified by column-chroma-

tography [silica gel 0.05–0.2 mm., Merck, solvent: benzene/ethyl acetate (9:1)]. The pure fractions are combined and concentrated by evaporation. After recrystallization from aqueous ethanol, pure 6,7,8,9-tetrahydrodibenzofuran-2-thiol is obtained in the form of pale yellow crystals, M.P. 44.5–46°.

Example 4

In a round-bottomed flask provided with reflux condenser, dropping funnel, stirrer, gas-inlet tube, and drying tube containing potassium hydroxide, 4.08 g. (20 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-thiol are added under nitrogen to a solution of 0.46 g. (20 mMol) of sodium in 100 ml. of absolute ethanol.

To the thus obtained solution of sodium-6,7,8,9-tetrahydrodibenzofuran-3-thiolate are added, with stirring, 5.02 g. (20 mMol) of 2-bromooctanoic acid ethyl ester, and refluxing is carried out for 3 hours, whereby nitrogen is continuously passed through the solution. After cooling, the reaction mixture is concentrated in vacuo, and the residue distributed between water and ether. After washing with water until the pH-value is 7 and drying with magnesium sulphate, the ether solution is concentrated by evaporation. The obtained crude (6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanoic acid ethyl ester, which is still contaminated with 6,7,8,9-tetrahydrodibenzofuran-3-thiol, is purified by column chromatography (neutral silica gel 0.05–0.2 mm., Merck, solvent: benzene). The benzene fractions containing the desired ester are combined and concentrated by evaporation. After drying in high vacuum is obtained the pure 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanoic acid ethyl ester, a yellowish oil; n_D^{20} : 1.5517.

Analogously are obtained

from 2.04 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-thiol and 1.81 g. (10.0 mMol) of 2-bromopropionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-propionic acid ethyl ester; n_D^{20} : 1.5768;
from 3.06 g. (15 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-thiol and 4.6 g. (15 mMol) of 2-bromododecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-dodecanoic acid ethyl ester; n_D^{20} : 1.5392;
from 1.70 g. (8.35 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-thiol and 3.03 g. (8.35 mMol) of 2-bromohexadecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-hexadecanoic acid ethyl ester; n_D^{20} : 1.5296;
from 2.04 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-thiol and 1.95 g. (10.0 mMol) of 2-bromo-2-methylpropionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-2-methyl-propionic acid ethyl ester.

The 6,7,8,9-tetrahydrodibenzofuran-3-thiol used as starting material can be produced as follows:

(a) Analogously to Example 3(a) is obtained

from 22.6 g. (0.12 mol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 19.8 g. (0.16 mol) of dimethylthiocarbamic acid chloride: dimethylthiocarbamic acid-O-(6,7,8,9-tetrahydrodibenzofuran-3-yl)-ester, M.P. 158–159° (from ethyl acetate);

(b) Analogously to Example 3(b) is obtained

from 19.0 g. (69.0 mMol) of dimethylthiocarbamic acid-O-(6,7,8,9-tetrahydrodibenzofuran-3-yl)-ester: dimethylthiocarbamic acid-S-(6,7,8,9-tetrahydrodibenzofuran-3-yl)-ester, M.P. 102–103° (from ethanol/water).

(c) Analogously to Example 3(c) is obtained

from 11.75 g. (42.0 mMol) of dimethylthiocarbamic acid-S-(6,7,8,9-tetrahydrodibenzofuran-3-yl)-ester: 6,7,8,9-tetrahydrodibenzofuran-3-thiol, M.P. 73–74° (from methanol/water).

Example 5

To a solution of 0.23 g. (10.0 mMol) of sodium in 23 ml. of absolute ethanol are added 2.043 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-2-ol. To the solution are added dropwise, whilst nitrogen is being passed through, 2.51 g. (10.0 mMol) of 2-bromooctanoic acid ethyl ester, and the reaction mixture is refluxed for 2 hours. After the mixture has cooled, the alcohol is evaporated off in vacuo, and the residue distributed between water and ether. The ether extract, washed until neutral with water, is dried over sodium sulphate, and then concentrated in vacuo. Purification of the crude product is carried out by column-chromatography on silica gel (Merck, 0.05–0.2 mm., elution with benzene). Thus obtained is 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-octanoic acid ethyl ester in the form of colorless oil; n_D^{20} : 1.5498. [With benzene/ethyl acetate (9:1) is further eluted a small amount of starting phenol.]

In an analogous manner are obtained

from 1.40 g. (6.85 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-2-ol and 2.12 g. (6.85 mMol) of 2-bromododecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-dodecanoic acid ethyl ester; n_D^{20} : 1.5323;
from 2.50 g. (12.24 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-2-ol and 4.45 g. (12.2 mMol) of 2-bromohexadecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-hexadecanoic acid ethyl ester; n_D^{20} : 1.5271;
from 2.50 g. (12.24 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-2-ol and 2.21 g. (12.2 mMol) of 2-bromopropionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-propionic acid ethyl ester, M.P. 71–72° (from hexane);
from 2.50 g. (12.24 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-2-ol and 2.38 g. (12.2 mMol) of 2-bromo-2-methylpropionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-2-methylpropionic acid ethyl ester, M.P. 62–63.5° (from hexane);
from 2.50 g. (12.24 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-2-ol and 2.56 g. (12.2 mMol) of 2-bromo-3-methylbutyric acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-3-methylbutyric acid ethyl ester, M.P. 59–60° (from hexane).

The 6,7,8,9-tetrahydrodibenzothiophen-2-ol used as starting material can be produced as follows:

(a) An amount of 12 g. (50.78 mMol) of 2-(4-methoxyphenylmercapto)-cyclohexanone is added, with stirring and whilst nitrogen is being passed through, to 120 ml. of conc. phosphoric acid ($d_4 = 1.71$). The reaction mixture is heated to 85°, and is stirred at this temperature for 14 hours. After cooling to room temperature, it is poured onto ice, and extracted with ether. The combined ether phases are washed with 2-n. sodium hydroxide solution and water, dried over sodium sulphate, and concentrated in vacuo. Purification of the crystalline crude product obtained is performed by column-chromatography on silica gel, 0.05–0.2 mm., Merck, elution with benzene/hexane [3:2].

Thus obtained is pure 2-methoxy-6,7,8,9-tetrahydrodibenzothiophene, M.P. 85° (hexane).

(b) To 3.5 g. (16.03 mMol) of 2-methoxy-6,7,8,9-tetrahydrodibenzothiophene are added 28 g. (0.24 mol) of melted pyridine hydrochloride. The reaction mixture, under nitrogen, is stirred for 2 hours at 160–165° and, after cooling, distributed between 2-n. hydrochloric acid and ether. The combined ether extracts are washed until neutral, dried over sodium sulphate, and concentrated in vacuo. The obtained crystalline crude product is purified by chromatography on silica gel, 0.02–0.5 mm., Merck [elution with benzene and benzene/ethyl acetate (9:1)]. The fractions containing the desired product are concentrated by evaporation, and recrystallised from meth-

ylene chloride/hexane. The obtained 6,7,8,9-tetrahydrobenzothiophen-2-ol melts at 113–114°.

Example 6

Analogously to Example 5 are obtained

from 4.08 g. (20.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-3-ol and 5.02 g. (20.0 mMol) of 2-bromooctanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-octanoic acid ethyl ester; n_D^{20} : 1.5482;

from 2.04 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-3-ol and 1.81 g. (10.0 mMol) of 2-bromopropionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-propionic acid ethyl ester, M.P. 41–43° (from hexane);

from 1.02 g. (5.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-3-ol and 1.82 g. (5.0 mMol) of 2-bromohexadecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-hexadecanoic acid ethyl ester, M.P. 34–37° (from hexane);

from 2.04 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-3-ol and 1.95 g. (10.0 mMol) of 2-bromo-2-methylpropionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-2-methylpropionic acid ethyl ester;

The 6,7,8,9-tetrahydrodibenzothiophen-3-ol used as starting material is produced as follows:

(a) To a solution of 23.0 g. (1.0 mol) of sodium in 700 ml. of absolute ethanol are added, with stirring and the introduction of nitrogen, 140.2 g. (1.0 mol) of *m*-methoxythiophenol. In the course of 15 minutes are then added dropwise 177.0 g. (1.0 mol) of 2-bromocyclohexanone, whereby the reaction mixture heats up. It is subsequently refluxed for a further 1½ hours. The ethanol is then evaporated off in vacuo, and the residue distributed between water and ether. The ether extract, washed neutral with water and dried over sodium sulphate, is concentrated by evaporation. To effect purification, the crude product is fractionated under high vacuum (20 cm. Vigreux-column). Thus obtained is 2-[*m*-methoxyphenylthio]-cyclohexanone, B.P. 146–147°/0.15 torr, in the form of a yellow colored oil, n_D^{20} : 1.5786.

(b) An amount of 118.5 g. (0.5 mol) of 2-[*m*-methoxyphenylthio]-cyclohexanone is added, with stirring and the introduction of nitrogen, to 1200 ml. of concentrated phosphoric acid ($d=1.71$). The reaction mixture is heated to 105°, and stirred for 5 hours at this temperature. After cooling to room temperature, it is poured onto ice, and extracted with ether. The combined ether phases are washed with 2-n. sodium hydroxide solution and water, dried over sodium sulphate, and concentrated in vacuo. Purification of the crude product is effected by chromatography on silica gel [Merck, 0.05–0.2 mm., elution with benzene/hexane (1:3)]. Thus obtained is 3-methoxy-6,7,8,9-tetrahydrodibenzothiophene, M.P. 46–46.5° (from methanol).

As by-product is further isolated 1-methoxy-6,7,8,9-tetrahydrodibenzothiophene, M.P. 57–58° (from methanol).

(c) An amount of 54.57 g. (0.25 mol) of 3-methoxy-6,7,8,9-tetrahydrodibenzothiophene is added, with stirring and the introduction of nitrogen, to a melt of 150 g. (0.77 mol) of freshly distilled pyridine hydrochloride. The mixture is heated for 1.25 hours to 220°, and the melt is then added to a mixture of 400 ml. of 2-n. hydrochloric acid and 200 g. of ice. The crystalline crude product, obtained after extraction with ether/methylene chloride (3:1), washing of the organic phase with water, drying over sodium sulphate, and concentration in vacuo, is filtered through silica gel [Merck, 0.05–0.2 mm., elution with benzene/ethyl acetate (9:1)], and recrystallized from methylene chloride/hexane. Thus ob-

tained is 6,7,8,9-tetrahydrodibenzothiophen-3-ol, M.P. 117–118° (from methanol).

Example 7

To a solution of 0.11 g. (4.78 mMol) of sodium in 20 ml. of absolute ethanol is added 1.0 g. (4.54 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-2-thiol. With stirring and whilst nitrogen is being introduced, 0.86 g. (4.78 mMol) of 2-bromopropionic acid ethyl ester are rapidly added dropwise to the above solution. The reaction mixture is refluxed for 3 hours. After cooling, the ethanol is evaporated off in vacuo, and the residue distributed between water and ether. The ether extract, washed neutral with water and dried over sodium sulphate, is concentrated in vacuo, and the yellow colored oil remaining behind is then purified by column chromatography through silica gel (Merck), elution with benzene/hexane (2:1). Thus obtained is 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-propionic acid ethyl ester in the form of a colorless oil; n_D^{20} : 1.6023.

Analogously are obtained

from 1.40 g. (6.36 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-2-thiol and 1.64 g. (6.53 mMol) of 2-bromooctanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-octanoic acid ethyl ester; n_D^{20} : 1.5728;

from 1.0 g. (4.54 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-2-thiol and 1.47 g. (4.80 mMol) of 2-bromododecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-dodecanoic acid ethyl ester; n_D^{20} : 1.5561;

from 1.0 g. (4.54 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-2-thiol and 1.73 g. (4.78 mMol) of 2-bromohexadecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-hexadecanoic acid ethyl ester; n_D^{20} : 1.5439;

from 1.0 g. (4.54 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-2-thiol and 0.94 g. (4.82 mMol) of 2-bromo-2-methylpropionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-2-methylpropionic acid ethyl ester.

The 6,7,8,9-tetrahydrodibenzothiophene-2-thiol used as starting material can be produced as follows:

(a) To the solution, cooled to ca. 5°, of 10.0 g. (49.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-2-ol in 50 ml. of absolute dimethylformamide are added in portions, with stirring and the introduction of nitrogen, 2.35 g. (49.0 mMol) of 50% sodium hydride dispersion. The evolution of hydrogen has finished after stirring has been performed for ½ hour at room temperature and 5 minutes at 80°. At 5–10° are now added dropwise, within ca. 2 minutes, 8.07 g. (65.4 mMol) of dimethylthiocarbamic acid chloride in 10 ml. of absolute dimethylformamide, and the reaction mixture is stirred for a further 2 hours at 80°. After cooling, it is concentrated in vacuo, the residue taken up in water, and thoroughly extracted with ether and chloroform. The combined organic phases are washed with water, dried over magnesium sulphate, concentrated by evaporation, and the residue purified by column chromatography on silica gel 0.05–0.2 mm. (Merck), elution with benzene/ethyl acetate [9:1].

Thus obtained is the dimethylthiocarbamic acid-O-(6,7,8,9-tetrahydrodibenzothiophen-2-yl)-ester, M.P. 154–155° (methanol or ethyl acetate).

(b) In a nitrogen atmosphere, 9.0 g. (30.9 mMol) of dimethylthiocarbamic acid-O-(6,7,8,9-tetrahydrodibenzothiophen-2-yl)-ester are melted at 250°, and subsequently heated for 3 minutes at 350°. After cooling (by means of air stream), the yellow colored residue is purified by column chromatography on silica gel (Merck) [elution with benzene/ethyl acetate (19:1)]. The fractions containing the desired product are combined, and recrystallized from methanol. Thus obtained is dimethylthiocarbamic acid-S-

(6,7,8,9-tetrahydrodibenzothiophen-2-yl)-ester, M.P. 98–99° (from methanol).

(c) With stirring and whilst nitrogen is being introduced, 5.1 g. (17.5 mMol) of dimethylthiocarbamic acid-S-(6,7,8,9-tetrahydrodibenzothiophen-2-yl)-ester are refluxed in 100 ml. of methanol and 80 ml. of 10% sodium hydroxide solution for 3 hours. The organic solvent is then evaporated off in vacuo, the residue acidified with 1-n. hydrochloric acid, and extracted with ether. The ether phase, washed with water and dried over magnesium sulphate, is concentrated in vacuo, and the residue chromatographed on silica gel (Merck), elution with benzene and benzene/ethyl acetate (19:1). After recrystallization from methylene chloride/hexane is obtained 6,7,8,9-tetrahydrodibenzothiophene-2-thiol, M.P. 64–65°.

Example 8

Analogously to Example 7 are obtained

from 1.30 g. (5.90 mMol) of 6,7,8,9-tetrahydrodibenzothiophene-3-thiol and 1.48 g. (5.90 mMol) of 2-bromooctanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-octanoic acid ethyl ester, n_D^{20} : 1.5754;

from 2.20 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophene-3-thiol and 3.07 g. (10.0 mMol) of 2-bromododecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-dodecanoic acid ethyl ester, n_D^{20} : 1.5594;

from 2.20 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophene-3-thiol and 1.81 g. (10.0 mMol) of 2-bromopropionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-propionic acid ethyl ester;

from 2.20 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophene-3-thiol and 1.95 g. (10.0 mMol) of 2-bromo-2-methylpropionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-2-methylpropionic acid ethyl ester.

The 6,7,8,9-tetrahydrodibenzothiophene-3-thiol used as starting material can be produced by a reaction sequence analogous to that described in Examples 7(a), (b) and (c):

(a) Analogously to Example 7(a) is obtained from 16.0 g. (78.3 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-3-ol and 12.95 g. (104.9 mMol) of dimethylthiocarbamic acid chloride: dimethylthiocarbamic acid-O-(6,7,8,9-tetrahydrodibenzothiophen-3-yl)-ester, M.P. 139.5–140° (from methanol).

(b) Analogously to Example 7(b), but with a reaction temperature of 260° and a reaction duration of 5 hours, is obtained from 12.10 g. (41.5 mMol) of dimethylthiocarbamic acid-O-(6,7,8,9-tetrahydrodibenzothiophen-3-yl)-ester: dimethylthiocarbamic acid-S-(6,7,8,9-tetrahydrodibenzothiophen-3-yl)-ester, M.P. 98–99° (from methanol).

(c) Analogously to Example 7(c) is obtained from 8.74 g. (30.0 mMol) of dimethylthiocarbamic acid-S-(6,7,8,9-tetrahydrodibenzothiophen-3-yl)-ester: 6,7,8,9-tetrahydrodibenzothiophene-3-thiol, M.P. 36–36.5° (from hexane).

Example 9

In a round-bottomed flask fitted with reflux condenser, dropping funnel, stirrer, gas-inlet tube, and drying tube containing potassium hydroxide, 2.82 g. (15 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol are added, under nitrogen, to a solution of 0.345 g. (15 mMol) of sodium in 25 ml. of absolute ethanol. To the thus obtained solution of sodium-6,7,8,9-tetrahydrodibenzofuran-2-olate is added, with stirring, an ethanolic solution (prepared in the same manner) of the sodium salt of 2-bromoheptanoic acid [from 3.14 g. (15 mMol) of 2-bromoheptanoic acid, 0.345 g. (15 mMol) of sodium, 60 ml. of absolute ethanol], and refluxing is carried out for 8 hours. After cooling, the reaction mixture is concentrated in vacuo, the

residue remaining behind suspended in water, and acidified with concentrated hydrochloric acid. The oil thereby precipitating is taken up in ether. The ethereal solution is washed with water, dried with magnesium sulphate, and the solvent evaporated off in vacuo. The crude 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid remaining behind as oil and which is still mainly contaminated with 6,7,8,9-tetrahydrodibenzofuran-2-ol is then chromatographically purified through a column of silica gel 0.05–0.2 mm. Merck), elution with benzene/glacial acetic acid (85:15). The solid residue, obtained after concentration by evaporation of the pure fractions, is recrystallized twice from methanol/water. Thus obtained is the pure 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid, M.P. 123–124°.

Analogously are obtained:

from 2.82 g. (15 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 2.30 g. (15 mMol) of 2-bromopropionic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-propionic acid, M.P. 128–129° (from methanol/water);

from 2.82 g. (15 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 3.34 g. (15 mMol) of 2-bromooctanoic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid, M.P. 99–100° (from methanol/water);

from 2.82 g. (15 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 4.19 g. (15 mMol) of 2-bromododecanoic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-dodecanoic acid, M.P. 65–66° (from pentane);

from 2.82 g. (15 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 3.35 g. (15 mMol) of 2-bromooctanoic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octanoic acid, M.P. 78–79° (from hexane);

from 2.82 g. (15 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 4.19 g. (15 mMol) of 2-bromododecanoic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-dodecanoic acid, M.P. 87–87.5° (from hexane);

from 3.06 g. (15 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-thiol and 3.35 g. (15 mMol) of 2-bromooctanoic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid, M.P. 86.5–88° (from hexane);

from 6.12 g. (30 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-thiol and 6.69 g. (30 mMol) of 2-bromooctanoic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanoic acid, M.P. 62–63° (from hexane);

from 6.12 g. (30 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-thiol and 8.37 g. (30 mMol) of 2-bromododecanoic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-dodecanoic acid, M.P. 73.5–74.5° (from hexane).

Example 10

To a solution of 2.3 g. (100 mMol) of sodium in 100 ml. of absolute ethanol are added 10.20 g. (50 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-2-ol. With stirring and whilst nitrogen is being introduced, a solution of 11.15 g. (50 mMol) of 2-bromooctanoic acid in 60 ml. of absolute ethanol is quickly added dropwise. The reaction mixture is refluxed for 4 hours, then concentrated in vacuo, and the residue taken up in water. After acidification with concentrated hydrochloric acid, extraction is performed with ether. The extract, washed neutral with water and dried over sodium, is concentrated in vacuo, and the yellow colored oil remaining behind purified by column chromatography on silica gel 0.05–0.2 mm. (Merck), elution with benzene/ethyl acetate (9:1) and benzene/glacial acetic acid (19:1). After recrystallization from hexane of the pure fractions is obtained 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-octanoic acid, M.P. 90–91°.

Analogously are obtained:

from 10.20 g. (50 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-3-ol and 11.15 g. (50 mMol) of 2-bromooctanoic acid: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-octanoic acid, M.P. 106–107° (from hexane);

from 11.0 g. (50 mMol) of 6,7,8,9-tetrahydrodibenzothiophene-2-thiol and 10.45 g. (50 mMol) of 2-bromoheptanoic acid: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-heptanoic acid, M.P. 101° (from hexane);
 from 11.0 g. (50 mMol) of 6,7,8,9-tetrahydrodibenzothiophene-2-thiol and 11.15 g. (50 mMol) of 2-bromooctanoic acid: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-octanoic acid, M.P. 91–92° (from hexane);
 from 11.0 g. (50 mMol) of 6,7,8,9-tetrahydrodibenzothiophene-3-thiol and 11.15 g. (50 mMol) of 2-bromooctanoic acid: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-octanoic acid, n_D^{20} : 1.5848, after purification by chromatography on silica gel, Merck 0.05–0.2 mm.; elution with benzene and benzene/glacial acetic acid (49:1).

Example 11

In a round-bottomed flask fitted with reflux condenser, dropping funnel, stirrer, gas-inlet tube, and drying tube containing potassium hydroxide, 4.0 g. (21 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol are added, under nitrogen, to a solution of 0.48 g. (21 mMol) of sodium in 50 ml. of absolute ethanol. To the thus obtained solution of sodium-6,7,8,9-tetrahydrodibenzofuran-2-olate is added, with stirring, a solution of 3.43 g. (21 mMol) of 2-chloroheptanamide in 50 ml. of absolute ethanol, and refluxing is carried out for 6 hours. After cooling, the reaction mixture is concentrated in vacuo, and the residue is distributed between water and ether. After washing with water until the pH-value is 7 and drying with magnesium sulphate, the ether solution is evaporated off in vacuo, and the residue crystallized twice from ethanol. Thus obtained is the pure 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanamide, M.P. 145–146°.

Analogously are obtained:

from 4.0 g. (21 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 3.72 g. (21 mMol) of 2-chlorooctanamide: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanamide, M.P. 130–131° (from ethanol/water);
 from 4.0 g. (21 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 2.25 g. (21 mMol) of 2-chloropropionamide: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-propionamide;
 from 4.0 g. (21 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 4.90 g. (21 mMol) of 2-chlorododecanamide: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-dodecanamide, M.P. 112–112.5° (from ethanol);
 from 4.0 g. (21 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 3.72 g. (21 mMol) of 2-chlorooctanamide: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octanamide, M.P. 140–141° (from ethanol);
 from 4.0 g. (21 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 4.90 g. (21 mMol) of 2-chlorododecanamide: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-dodecanamide, M.P. 131.5–132.5° (from ethyl acetate);
 from 4.34 g. (21 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-thiol and 3.72 g. (21 mMol) of 2-chlorooctanamide: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanamide, M.P. 135–136° (from ethanol);
 from 4.34 g. (21 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-thiol and 3.72 g. (21 mMol) of 2-chlorooctanamide: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanamide, M.P. 107.5–109° (from ethanol/water);
 from 4.34 g. (21 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-2-ol and 3.72 g. (21 mMol) of 2-chlorooctanamide: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-octanamide, M.P. 142–143° (from acetone/hexane);
 from 4.34 g. of (21 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-3-ol and 3.72 g. (21 mMol) of 2-chlorooctanamide: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-octanamide, M.P. 116–117° (from methanol);

from 4.68 g. (21 mMol) of 6,7,8,9-tetrahydrodibenzothiophene-2-thiol and 3.43 g. (21 mMol) of 2-chloroheptanamide: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-heptanamide, M.P. 150–150.5° (from methanol);
 from 4.68 g. (21 mMol) of 6,7,8,9-tetrahydrodibenzothiophene-3-thiol and 3.72 g. (21 mMol) of 2-chlorooctanamide: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)octanamide.

Example 12

In a round-bottomed flask fitted with reflux condenser, 6.2 g. (18 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid ethyl ester are refluxed in a solution of 2.02 g. (36 mMol) of potassium hydroxide, 60 ml. of methanol and 6 ml. of water for 4 hours. After cooling, the reaction mixture is concentrated in vacuo, the residue distributed between dilute hydrochloric acid and ether, and extracted with ether. The combined ether solutions are washed until neutral with water, dried over magnesium sulphate, and again concentrated by evaporation. Thus obtained is crude 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid as colorless oil. From aqueous methanol crystallizes pure 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid, M.P. 123–124°.

Analogously and in the same quality is obtained 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid methyl or -propyl ester.

Analogously are obtained:

from 4.6 g. (16 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-propionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-propionic acid, M.P. 128–129° (from methanol/water);
 from 1.25 g. (4 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-methylpropionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-methylpropionic acid, M.P. 136.5–138° (from methanol/water);
 from 4.0 g. (13 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-pentanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-pentanoic acid, M.P. 98–100° (from pentane);
 from 3.0 g. (9 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-isheptanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-isheptanoic acid, M.P. 66–69° (from hexane);
 from 11.6 g. (35 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid, M.P. 99–100° (from hexane);
 from 2.3 g. (6 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-decanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-decanoic acid; M.P. 70–71° (from hexane);
 from 4.0 g. (10 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-dodecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-dodecanoic acid, M.P. 65–66° (from pentane);
 from 2.5 g. (6 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-tetradecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-tetradecanoic acid, M.P. 52.5–55° (from hexane);
 from 2.8 g. (6 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-hexadecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-hexadecanoic acid, M.P. 55–56° (from hexane);
 from 1.0 g. (3 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-cyclopentanecetic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-cyclopentanecetic acid, M.P. 103–104° (from hexane);
 from 1.7 g. (5 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-cyclohexanecetic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-

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cyclohexanecetic acid, M.P. 133–134° (from methanol/water);
 from 1.51 g. (5 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy) - butyric acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran - 2 - yloxy) - butyric acid, M.P. 95.5–97°.

Example 13

In a round-bottomed flask fitted with reflux condenser, 5.7 g. (16 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid ethyl ester are refluxed in a solution of 2.0 g. (35 mMol) of potassium hydroxide in 50 ml. of methanol and 5 ml. of water for 3 hours. After cooling, the reaction mixture is concentrated in vacuo, the residue distributed between dilute hydrochloric acid and ether, and extracted with ether. The combined ether solutions are washed until neutral with water, dried over magnesium sulphate, and again concentrated by evaporation, whereby crude 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octanoic acid remains behind as yellow oil. After crystallization twice from hexane is obtained pure 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octanoic acid in the form of pale yellow crystals, M.P. 78–79°.

Analogously are obtained:

from 3.1 g. (10.7 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-propionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-propionic acid, M.P. 144° (from benzene/hexane);
 from 2.1 g. (7 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-butyric acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-butyric acid, M.P. 106–107° (from hexane);
 from 2.4 g. (8 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-2-methylpropionic acid ethyl ester: 2-(6,7,8,9 - tetrahydrodibenzofuran - 3-yloxy)-2-methylpropionic acid, M.P. 78–80° (from hexane);
 from 3.9 g. (11.3 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-isoheptanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran - 3-yloxy)-isoheptanoic acid, M.P. 104–105° (from hexane);
 from 6.0 g. (14.5 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-dodecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-dodecanoic acid, M.P. 87–87.5° (from hexane);
 from 5.6 g. (12.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-hexadecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran - 3-yloxy) - hexadecanoic acid, M.P. 77.5–78.5° (from methanol/water);
 from 2.8 g. (7.8 mMol) of α -(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-cyclohexanecetic acid ethyl ester: α -(6,7,8,9-tetrahydrodibenzofuran - 3 - yloxy) - cyclohexanecetic acid, M.P. 118–120° (from hexane).

Example 14

In a round-bottomed flask provided with a reflux condenser, 1.4 g. (3.73 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid ethyl ester are refluxed in a solution of 0.414 g. (7.4 mMol) of potassium hydroxide in 20 ml. of methanol and 1 ml. of water for 5½ hours. After cooling, the reaction mixture is concentrated in vacuo, the residue distributed between water and ether, the aqueous phase acidified with 2-n. hydrochloric acid, and extracted with ether. The combined ether solutions are washed with water until neutral, dried over magnesium sulphate and again concentrated by evaporation. Thus obtained is crude 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid as colorless oil. From hexane crystallizes pure 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid in the form of white crystals, M.P. 92–93°.

Analogously are obtained:

from 1.6 g. (5.2 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-propionic acid ethyl ester: 2-(6,7,8,9-

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tetrahydrodibenzofuran-2-ylthio)-propionic acid, M.P. 95° (from hexane);
 from 2.7 g. (8.47 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-2-methylpropionic acid ethyl ester: 2-(6,7,8,9 - tetrahydrodibenzofuran - 2-ylthio)-2-methylpropionic acid, M.P. 146–147° (from ether/hexane);
 from 2.1 g. (5.8 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-isoheptanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-isoheptanoic acid, M.P. 71.5–73° (from hexane);
 from 0.8 g. (1.645 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-hexadecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran - 2 - ylthio)-hexadecanoic acid, M.P. 72–74° (from pentane).

Example 15

In a round-bottomed flask fitted with reflux condenser, 6.35 g. (17 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanoic acid ethyl ester are refluxed in a solution of 2.6 g. (46 mMol) of potassium hydroxide in 60 ml. of ethanol and 6 ml. of water for 4 hours. After cooling, the reaction mixture is concentrated in vacuo, the oily residue suspended in water, the suspension acidified with dilute hydrochloric acid, and repeatedly extracted with ether. The ether extracts are washed with water until neutral, dried over magnesium sulphate, and again concentrated by evaporation. By crystallization of the oily residue from hexane is obtained 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanoic acid in the form of white crystals, M.P. 62–63°.

Analogously are obtained:

from 2.1 g. (6.9 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-propionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-propionic acid, M.P. 133–134° (from methanol/water);
 from 5.45 g. (12.7 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-dodecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-dodecanoic acid, M.P. 73.5–74.5° (from hexane);
 from 3.6 g. (7.4 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-hexadecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-hexadecanoic acid, M.P. 69–70° (from methanol).

Example 16

To a solution of 2.1 g. (5.607 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-octanoic acid ethyl ester in 25 ml. of methanol is added a solution of 0.65 g. (9.96 mMol) of potassium hydroxide (86%) in 5 ml. of water. The mixture is refluxed for 1½ hours, and is then concentrated in vacuo. The residue is distributed between dilute hydrochloric acid and ether, and the crude precipitated carboxylic acid extracted with ether. The ether extract, washed until neutral with water, is dried over sodium sulphate, and concentrated in vacuo. After recrystallization of the crude product from methylene chloride/hexane is obtained 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-octanoic acid, M.P. 90–91°.

Analogously are obtained:

from 1.92 g. (4.46 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-dodecanoic acid ethyl ester: 2-(6,7,8,9 - tetrahydrodibenzothiophen-2-yloxy)-dodecanoic acid, M.P. 74–76° (from methylene chloride/hexane);
 from 2.56 g. (8.42 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-propionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen - 2 - yloxy)-propionic acid, M.P. 156–157° (from methylene chloride/hexane);
 from 1.76 g. (5.53 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen - 2 - yloxy)-2-methylpropionic acid ethyl ester: 2 - (6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-2-methylpropionic acid, M.P. 121–122° (from methylene chloride /hexane);

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from 1.80 g. (5.42 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-3-methylbutyric acid ethyl ester: 2-(6,7,8,9 - tetrahydrodibenzothiophen - 2 - yloxy)-3-methylbutyric acid, M.P. 91–93° (from methylene chloride/hexane);

from 1.94 g. (3.99 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-hexadecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen - 2 - yloxy)-hexadecanoic acid, M.P. 89–91° (from methanol).

Example 17

Analogously to Example 16 are obtained:

from 3.10 g. (8.28 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-octanoic acid ethyl ester: 2-(6,7,8,9 - tetrahydrodibenzothiophen-3-yloxy)-octanoic acid, M.P. 106–107° (hexane);

from 3.04 g. (10.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-propionic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-propionic acid, M.P. 146–147° (hexane);

from 2.43 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-hexadecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen - 3 - yloxy)-hexadecanoic acid, M.P. 71–72° (hexane).

Example 18

An amount of 1.0 g. (3.12 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-propionic acid ethyl ester is dissolved in 20 ml. of methanol; to the solution are added 0.75 g. of potassium hydroxide and 2 ml. of water, and the whole is refluxed, whilst nitrogen is fed in, for 1½ hours. After cooling, the reaction mixture is concentrated in vacuo, and the residue distributed between dilute hydrochloric acid and ether. The ether phase is separated, washed with water until neutral, dried over sodium sulphate, and concentrated by evaporation. The thereby obtained crude acid is recrystallized from methylene chloride/hexane. Thus obtained is 2-(6,7,8,9-tetrahydrodibenzothiophen - 2 - ylthio)-propionic acid, M.P. 106–107°.

Analogously are obtained:

from 2.15 g. (5.51 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-octanoic acid ethyl ester: 2-(6,7,8,9-dibenzothiophen - 2 - ylthio)-octanoic acid, M.P. 91–92° (from hexane);

from 1.65 g. (3.70 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-dodecanoic acid ethyl ester: 2-(6,7,8,9 - tetrahydrodibenzothiophen - 2 - ylthio)-dodecanoic acid, M.P. 57–58° (hexane);

from 1.92 g. (3.83 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen - 2 - ylthio)-hexadecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen - 2 - ylthio)-hexadecanoic acid, M.P. 68–70° (hexane);

from 1.20 g. (3.07 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-octanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-octanoic acid as oil, n_D^{20} : 1.5848;

from 3.20 g. (7.17 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen - 3 - ylthio)-dodecanoic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen - 3 - ylthio)-dodecanoic acid as oil, n_D^{20} : 1.5718.

Purification of the two last-mentioned non-crystallizing acids can be performed by chromatography on silica gel, Merck 0.05–0.2 mm., elution with benzene and benzene/glacial acetic acid (49:1).

Example 19

In a round-bottomed flask fitted with reflux condenser, 3.15 g. (10 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptaneamide are refluxed in a solution of 3 g. (50 mMol) of potassium hydroxide in 70 ml. of ethanol and 7 ml. of water for 20 hours. After cooling, the reaction mixture is acidified with 2-n. hydrochloric acid, the ethanol evaporated off in vacuo, the aqueous phase re-

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maining behind extracted with ether, and the ether solution washed twice with water. After drying with sodium sulphate, the ether phase is evaporated off. The crude 2-(6,7,8,9-tetrahydrodibenzofuran - 2 - yloxy)-heptanoic acid remaining behind is recrystallized twice from methanol/water. M.P. of the pure acid=123–124°.

Analogously are obtained:

from 3.28 g. (10 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octaneamide: 2 - (6,7,8,9-tetrahydrodibenzofuran - 2 - yloxy)-octanoic acid, M.P. 99–100° (from hexane);

from 3.44 g. of 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octaneamide: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanoic acid, M.P. 62–63° (from hexane).

Example 20

An amount of 1.60 g. (4.60 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen - 2 - ylthio)-heptaneamide is dissolved in 40 ml. of ethanol; to this solution is then added a solution of 2.3 g. (41 mMol) of potassium hydroxide in 40 ml. of water, and the reaction mixture refluxed for 45 hours. After the ethanol has been evaporated off in vacuo, the residue is distributed between 1-n. hydrochloric acid and ether. The ether phase, after being separated, washed with water and dried over sodium sulphate, is concentrated by evaporation, and the crude product recrystallized from hexane. Thus obtained is 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-heptanoic acid, M.P. 101°.

Analogously are obtained

from 1.38 g. (4.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen - 2 - yloxy)octaneamide: 2-(6,7,8,9-tetrahydrodibenzothiophen - 2 - yloxy)-octanoic acid, M.P. 90–91° (from hexane);

from 1.38 g. (4.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen - 3 - yloxy)-octaneamide: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-octanoic acid, M.P. 106–107° (from hexane).

Example 21

In a round-bottomed flask fitted with reflux condenser and stirrer, 2.4 g. (7 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octaneamide are refluxed in a mixture of 30 ml. of 6-n. hydrochloric acid and 50 ml. of glacial acetic acid for 5 hours. After cooling, the reaction mixture is concentrated in vacuo, and the residue remaining taken up in ether. The ethereal solution is firstly washed with water; it is then extracted with 2-n. sodium hydroxide solution, the alkaline extract separated, and washed with ether.

The alkaline solution is then acidified with conc. hydrochloric acid (pH=1) and the precipitating oil taken up in ether. The thus obtained ethereal solution is washed with water until neutral, dried over magnesium sulphate, and concentrated in vacuo, whereby crude 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid is obtained as a yellow oil. After recrystallization twice from hexane, the pure acid is obtained in the form of white crystals, M.P. 99–100°.

Example 22

In a round-bottomed flask fitted with reflux condenser, 0.3 g. (1 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid nitrile are refluxed in a solution of 0.3 g. (5 mMol) of potassium hydroxide in 20 ml. of ethanol and 2 ml. of water for 20 hours. After cooling, the reaction solution is acidified with 2-n. hydrochloric acid, the ethanol evaporated off in vacuo, the aqueous phase remaining behind extracted with ether, and the ether solution washed twice with water. After being dried with sodium sulphate, the ether phase is concentrated by evaporation. The crude 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid remaining behind is recrystallized from methanol/water, whereby the pure acid, M.P. 123–124°, is obtained.

Analogously are obtained

from 3.12 g. (10 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid, M.P. 99–100° (from hexane);

from 3.12 g. (10 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octanoic acid, M.P. 78–79° (from hexane);

from 3.28 g. (10 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid, M.P. 86.5–88° (from hexane);

from 3.28 g. (10 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanoic acid, M.P. 62–63° (from hexane).

The 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid nitrile used as starting material can be produced as follows:

(a) In a round-bottomed flask provided with reflux condenser, dropping funnel, stirrer, gas-inlet tube, and drying tube containing potassium hydroxide, 3.76 g. (20 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol are added, under nitrogen, to a solution of 0.46 g. (20 mMol) of sodium in 30 ml. of absolute ethanol. To the thus obtained solution of sodium-6,7,8,9-tetrahydrodibenzofuran-2-olate are added dropwise, with stirring, 3.8 g. (20 mMol) of 2-bromoheptanoic acid nitrile, and refluxing is performed for 3 hours. After cooling, the reaction mixture is concentrated in vacuo, and the residue distributed between water and ether. After being washed with water until the pH-value is 7 and dried with magnesium sulphate, the ether solution is concentrated by evaporation, whereby 6.0 g. of a brown oil are obtained. The crude 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)heptanoic acid nitrile, which is still mainly contaminated with 6,7,8,9-tetrahydrodibenzofuran-2-ol, is purified by column chromatography (neutral silica gel 0.05–0.2 mm., Merck, elution with benzene). The benzene fractions containing the desired nitrile are combined and concentrated by evaporation. After drying under high vacuum is obtained pure 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid nitrile, a yellow oil, n_D^{20} : 1.5395.

Analogously are obtained

from 15.1 g. (80 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 16.32 g. (80 mMol) of 2-bromooctanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid nitrile, n_D^{20} : 1.5355;

from 7.52 g. (40 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 8.16 g. (40 mMol) of 2-bromooctanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octanoic acid nitrile, n_D^{20} : 1.5366;

from 6.92 g. (33.8 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-thiol and 6.9 g. (33.8 mMol) of 2-bromooctanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid nitrile, n_D^{20} : 1.5645;

from 4.08 g. (20 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-thiol and 4.1 g. (20 mMol) of 2-bromooctanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanoic acid nitrile, n_D^{20} : 1.5704.

Example 23

To 3.28 g. (10 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-octanoic acid nitrile in 70 ml. of ethanol is added a solution of 5.0 g. (89 mMol) of potassium hydroxide in 15 ml. of water, and the mixture is refluxed for 24 hours. The ethanol is then evaporated off in vacuo, the residue acidified with 2-n. hydrochloric acid, and extracted with ether. The extract, washed with water until neutral and dried over sodium sulphate, is concentrated in vacuo. The crude hydrolysis product remaining behind is recrystallized from hexane. Thus obtained is 2-(6,7,8,9-

tetrahydrodibenzothiophen-2-yloxy)-octanoic acid, M.P. 90–91°.

Analogously are obtained

from 3.28 g. (10.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-octanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-octanoic acid, M.P. 105–107° (from hexane);

from 3.30 g. (10.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-heptanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)heptanoic acid, M.P. 101° (from hexane);

from 3.44 g. (10.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-octanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-octanoic acid in the form of oil, n_D^{20} : 1.5848; after chromatographic purification on silica gel, eluting with benzene and benzene/glacial acetic acid (49:1).

The 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-octanoic acid nitrile used as starting material can be produced as follows:

(a) To a solution of 1.47 g. (63.7 mMol) of sodium in 120 ml. of absolute ethanol are added 13.0 g. (63.7 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-2-ol. With stirring and whilst nitrogen is being introduced, 13.0 g. (63.7 mMol) of 2-bromooctanoic acid nitrile in 50 ml. of absolute ethanol are quickly added dropwise. The reaction mixture is refluxed for 5 hours, and then concentrated in vacuo. The residue is taken up in water and then extracted with ether. The ether phase is washed with water until neutral, dried over sodium sulphate, and concentrated in vacuo. To effect purification, the crude product is chromatographed on silica gel, Merck 0.05–0.2 mm., elution with benzene/hexane (2:1). Thus obtained is 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-octanoic acid nitrile as a slightly yellow colored oil, n_D^{20} : 1.5657.

Analogously is obtained

from 6.13 g. (30.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-3-ol and 6.13 g. (30.0 mMol) of 2-bromooctanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-octanoic acid nitrile, n_D^{20} : 1.5657;

from 2.20 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophene-2-thiol and 1.90 g. (10.0 mMol) of 2-bromooctanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-heptanoic acid nitrile, n_D^{20} : 1.6017;

from 2.20 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophene-3-thiol and 2.04 g. (10.0 mMol) of 2-bromooctanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-octanoic acid nitrile, n_D^{20} : 1.5972.

Example 24

A solution of 3.11 g. (10.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid nitrile in 50 ml. of absolute chloroform and 5 ml. of absolute ethanol is saturated at 0° to 5° with dry hydrogen chloride gas; the solution is then stirred for 20 hours at room temperature, and subsequently concentrated in vacuo at 30°. The crude 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid imidoethyl ester hydrochloride is refluxed with a solution of 2.0 g. (ca. 30 mMol) of potassium hydroxide in 40 ml. of ethanol and 5 ml. of water for 24 hours. The reaction mixture is firstly concentrated by evaporation; water is then added, and the residual ethanol evaporated off in vacuo. The obtained alkaline-aqueous solution is shaken with ether, and then acidified with 2-n. hydrochloric acid. The precipitated crude acid is taken up in ether, the ether solution washed with water, dried over magnesium sulphate, and concentrated by evaporation. By crystallization of the residue from hexane is obtained 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid, M.P. 99–100°.

Example 25

In a round-bottomed flask fitted with reflux condenser and stirrer, 4.0 g. (9.3 mMol) of 2-(6,7,8,9-tetrahydrodi-

benzofuran-2-yloxy)-2-hexylmalonic acid diethyl ester are refluxed in a mixture of 10 ml. of 5-n. sulphuric acid and 50 ml. of glacial acetic acid for 20 hours. After cooling, the reaction mixture is concentrated in vacuo, and the oily residue remaining is distributed between ether and water. After the ether phase has been separated, it is first washed with water and then extracted with 100 ml. of 2% potassium hydroxide solution.

The alkaline solution is acidified with concentrated hydrochloric acid (pH=1), and the thereby precipitating oil taken up in ether. The thus obtained ethereal solution is washed with water until neutral, dried with magnesium sulphate, and concentrated in vacuo, whereby crude 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid is obtained as yellow oil. After recrystallization twice from hexane is obtained the pure acid in the form of white crystals, M.P. 99–100°.

Analogously are obtained

from 1.80 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-methylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-propionic acid, M.P. 128–129° (from methanol/water);

from 2.71 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-tetradecylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-hexadecanoic acid, M.P. 55–56° (from hexane);

from 0.8 g. (2.2 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-2-methylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-propionic acid, M.P. 144° (from benzene/hexane);

from 1.0 g. (2.33 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-2-hexylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octanoic acid, M.P. 78–79° (from hexane);

from 2.16 g. (6 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-2-tetradecylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-hexadecanoic acid, M.P. 77.5–78.5° (from methanol/water);

from 1.34 g. (3.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-2-hexylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid, M.P. 92–93° (from hexane);

from 2.26 g. (6.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-2-methylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-propionic acid, M.P. 133–134° (from methanol/water);

from 3.57 g. (8.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-2-hexylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanoic acid, M.P. 62–63° (from hexane);

from 3.02 g. (6.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-2-decylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-dodecanoic acid, M.P. 73.5–74.5° (from hexane);

from 3.35 g. (6.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-2-tetradecylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-hexadecanoic acid, M.P. 69–70° (from methanol).

The 2-bromo-2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-hexylmalonic acid diethyl ester used as starting material can be produced, starting with 2-hexylmalonic acid diethyl ester, as follows:

(a) From 152.7 g. (0.6 mol) of 2-hexylmalonic acid diethyl ester is obtained, by bromination with 96.0 g. (1.2 mol) of bromine: 2-bromo-2-hexylmalonic acid diethyl ester as colorless oil, B.P._{0.3}=107.5–108°; n_D^{20} : 1.4552.

Produced analogously are 2-bromo-2-methylmalonic acid diethyl ester; 2-bromo-2-decylmalonic acid diethyl ester; and 2-bromo-2-tetradecylmalonic acid diethyl ester.

(b) In a round-bottomed flask fitted with reflux condenser, dropping funnel, stirrer, gas-inlet tube, and drying tube containing potassium hydroxide, 18.83 g. (0.1 mol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol are added, under nitrogen, to a solution of 2.3 g. (0.1 mol) of sodium in

200 ml. of absolute ethanol. To the thus obtained light-brown solution of sodium phenolate are added dropwise, with stirring, 32.3 g. (0.1 mol) of 2-bromo-2-hexylmalonic acid diethyl ester, and refluxing is carried out for 12 hours. After cooling, the precipitated sodium bromide is filtered off under suction, and the filtrate is concentrated in vacuo. The thus obtained oily brown residue is taken up in ether, the ethereal solution washed with water until neutral, dried with magnesium sulphate, and again concentrated by evaporation, whereby a yellow oil is obtained. This oil is purified by column chromatography (silica gel 0.05–0.2 mm., Merck, elution with benzene). The fractions containing the desired ester are combined and concentrated by evaporation. After drying under high vacuum is obtained pure 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-hexylmalonic acid diethyl ester as a pale yellow oil; n_D^{22} : 1.5114.

Analogously are obtained:

from 1.88 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 2.53 g. (10.0 mMol) of 2-bromo-2-methylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-methylmalonic acid diethyl ester; n_D^{20} : 1.5285;

from 1.88 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 4.35 g. (10.0 mMol) of 2-bromo-2-tetradecylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-tetradecylmalonic acid diethyl ester; n_D^{20} : 1.5033;

from 1.88 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 2.53 g. (10.0 mMol) of 2-bromo-2-methylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-2-methylmalonic acid diethyl ester; n_D^{20} : 1.5310;

from 3.76 g. (20.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 6.46 g. (20.0 mMol) of 2-bromo-2-hexylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-2-hexylmalonic acid diethyl ester; n_D^{20} : 1.5181;

from 1.88 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 4.35 g. (10.0 mMol) of 2-bromo-2-tetradecylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-2-tetradecylmalonic acid diethyl ester; n_D^{20} : 1.5053;

from 1.02 g. (5.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-thiol and 1.61 g. (5.0 mMol) of 2-bromo-2-hexylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-2-hexylmalonic acid diethyl ester; n_D^{20} : 1.5359;

from 2.04 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-thiol and 2.53 g. (10.0 mMol) of 2-bromo-2-methylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-2-methylmalonic acid diethyl ester; n_D^{20} : 1.5592;

from 2.04 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-thiol and 3.22 g. (10.0 mMol) of 2-bromo-2-hexylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-2-hexylmalonic acid diethyl ester; n_D^{20} : 1.5412;

from 2.04 g. (10 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-thiol and 3.79 g. (10 mMol) of 2-bromo-2-decylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-2-decylmalonic acid diethyl ester;

from 2.04 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-thiol and 4.35 g. (10.0 mMol) of 2-bromo-2-tetradecylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-2-tetradecylmalonic acid diethyl ester; n_D^{20} : 1.5240.

Example 26

In a round-bottomed flask fitted with reflux condenser and stirrer, 3.0 g. (6.9 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-hexylmalonic acid diethyl ester are refluxed in 30 ml. of 1-n. sodium hydroxide solution

for 20 hours. After cooling, the reaction mixture is acidified with 1-n. hydrochloric acid, and extracted with ether. The ethereal solution is washed with water until neutral, dried over magnesium sulphate, and concentrated by evaporation.

From the thus obtained oily residue is derived the desired 2-(6,7,8,9-tetrahydrodibenzofuran - 2 - yloxy)-octanoic acid by crystallization from hexane. The pure (6,7,8,9 - tetrahydrodibenzofuran - 2 - yloxy) - octanoic acid melts at 99–100°.

Example 27

To a solution of 1.34 g. (3.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-2-hexylmalonic acid diethyl ester in 15 ml. of glacial acetic acid are added 3 ml. of 5-n. sulphuric acid, and the whole is then refluxed for 24 hours in a nitrogen atmosphere. The reaction mixture is afterwards concentrated in vacuo, and the oily residue distributed between water and ether. After washing of the ether phase with water, drying over sodium sulphate, and concentration in vacuo, a brown colored oil is obtained, which is subsequently purified by column chromatography on silica gel, Merck [elution with benzene and benzene/glacial acetic acid (20:1)]. The fractions containing the desired product are combined and recrystallized from hexane. Thus obtained is 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy) - octanoic acid, M.P. 90–91°.

Analogously are obtained

from 2.68 g. (60 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-2-hexylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy) - octanoic acid, M.P. 105–106°;

from 1.30 g. (2.81 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio) - 2 - hexylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-2 - ylthio)-octanoic acid, M.P. 91–92° (from hexane);

from 1.85 g. (4.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio) - 2 - hexylmalonic acid diethyl ester: 2 - (6,7,8,9 - tetrahydrodibenzothiophen - 3 - ylthio)-octanoic acid; n_D^{20} : 1.5848, after chromatographic purification on silica gel, elution with benzene and benzene/glacial acetic acid (49:1).

The 2-(6,7,8,9-tetrahydrodibenzothiophen - 2 - yloxy)-2-hexylmalonic acid diethyl ester used as starting material is produced as follows:

(a) To a solution of 0.258 g. (11.2 mMol) of sodium in 15 ml. of absolute ethanol are added 2.29 g. (11.2 mMol) of 6,7,8,9-tetrahydrodibenzothiophen - 2 - ol. To this solution are then added dropwise, with stirring and while nitrogen is being fed in, 3.62 g. (11.2 mMol) of 2-bromo-2-hexylmalonic acid diethyl ester in 15 ml. of absolute ethanol; the reaction mixture is subsequently refluxed for 4 hours. After cooling, the ethanol is evaporated off in vacuo, and the residue distributed between water and ether. The ether phase is separated, washed with water, dried over magnesium sulphate, and concentrated by evaporation. Purification of the crude products is effected by column chromatography on silica gel [elution with benzene/hexane (2:1)]. Thus obtained is 2-(6,7,8,9-tetrahydrodibenzothiophen - 2 - yloxy)-2-hexylmalonic acid diethyl ester; n_D^{20} : 1.5383.

Analogously are obtained

from 2.04 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-3-ol and 3.23 g. (10.0 mMol) of 2-bromo-2-hexylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-2-hexylmalonic acid diethyl ester; n_D^{20} : 1.5361;

from 1.0 g. (4.54 mMol) of 6,7,8,9-tetrahydrodibenzothiophene-2-thiol and 1.47 g. (4.54 mMol) of 2-bromo-2-hexylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-2-hexylmalonic acid diethyl ester; n_D^{20} : 1.5598;

from 2.20 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophene-3-thiol and 3.23 g. (10.0 mMol) of 2-bromo-2-hexylmalonic acid diethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-2-hexylmalonic acid diethyl ester; n_D^{20} : 1.5601.

Example 28

To 2.68 g. (6.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-2-hexylmalonic acid diethyl ester in 20 ml. of methanol is added a solution of 0.92 g. of potassium hydroxide in 3 ml. of water. With stirring and while nitrogen is being fed in, the mixture is then refluxed for 24 hours. After the solvent has been evaporated off, the residue is distributed between ether and 1-n. hydrochloric acid. The ether phase is washed with water, dried over sodium sulphate, and concentrated in vacuo. The thereby obtained crude mixture is purified by column chromatography on silica gel [elution with benzene and benzene/glacial acetic acid (50:1)]. Thus obtained is 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-octanoic acid, M.P. 90–91° (from hexane) with, in addition, a small amount of 2-(6,7,8,9-tetrahydrodibenzothiophen - 2 - yloxy)-2-hexylmalonic acid (commencing decomposition at 119°).

Example 29

In a round-bottomed flask fitted with reflux condenser and stirrer, 3.0 g. (7.8 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran - 2 - yloxy)-2-hexylcyanoacetic acid ethyl ester are refluxed in a solution of 50 ml. of glacial acetic acid and 10 ml. of 5-n. sulphuric acid for 20 hours. After cooling, the reaction mixture is concentrated in vacuo, and the residue remaining distributed between ether and water. The ether phase is separated, washed with water until neutral, dried with magnesium sulphate, and then concentrated in vacuo. The thus obtained crude 2-(6,7,8,9-tetrahydrodibenzofuran - 2 - yloxy)-octanoic acid is purified by column chromatography (silica gel, 0.05–0.2 mm., Merck, elution with benzene/glacial acetic acid 85:15). The fractions containing the desired acid are combined, concentrated in vacuo, and the thus obtained oily residue crystallized twice from hexane, whereby pure 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid, M.P. 99–100°, is obtained.

Analogously are obtained

from 1.15 g. (3.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-2-hexylcyanoacetic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran - 3 - yloxy)-octanoic acid, M.P. 78–79° (from hexane);

from 1.20 g. (3.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-2-hexylcyanoacetic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran - 2 - ylthio)-octanoic acid, M.P. 92–93° (from hexane);

from 4.00 g. (10.0 mMol) of 2-(6,7,8,9 - tetrahydrodibenzofuran-3-ylthio) - 2 - hexylcyanoacetic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran - 3 - ylthio)-octanoic acid, M.P. 62–63° (from hexane).

The 2-(6,7,8,9-tetrahydrodibenzofuran - 2 - yloxy)-2-hexylcyanoacetic acid ethyl ester used as starting material can be produced as follows:

(a) In a round-bottomed flask with reflux condenser, dropping funnel, stirrer, gas-inlet tube, and drying tube containing potassium hydroxide, 18.8 g. (0.1 mol) of 6,7,8,9-tetrahydrodibenzofuran - 2 - ol are added, under nitrogen, to a solution of 2.3 g. (0.1 mol) of sodium in 80 ml. of absolute ethanol. To the thus obtained brown solution of sodium phenolate are added dropwise, with stirring, 27.6 g. (0.1 mol) of 2-bromo-2-hexylcyanoacetic acid ethyl ester; the solution is then heated for one hour at 40°, one hour at 50° and for one hour at 70°. The reaction mixture is then concentrated in vacuo to dryness. The residue is distributed between water and ether, the ether phase separated, and washed with water. The ethereal phase is dried with magnesium sulphate and again concentrated in vacuo. The oily residue is purified

by column chromatography (silica gel 0.05–0.2 mm., Merck, solvent: benzene). The benzene fractions containing the desired ester are combined and concentrated by evaporation. Thus obtained is pure 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-hexylcyanoacetic acid ethyl ester as a hygroscopic yellow oil.

Analogously are obtained

from 1.88 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 2.76 g. (10.0 mMol) of 2-bromo-2-hexylcyanoacetic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-2-hexylcyanoacetic acid ethyl ester; n_D^{20} : 1.5245;

from 6.12 g. (30.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-thiol and 8.28 g. (30.0 mMol) of 2-bromo-2-hexylcyanoacetic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-2-hexylcyanoacetic acid ethyl ester; n_D^{20} : 1.5505;

from 6.12 g. (30.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-thio and 8.28 g. (30.0 mMol) of 2-bromo-2-hexylcyanoacetic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-2-hexylcyanoacetic acid ethyl ester; n_D^{20} : 1.5553.

Example 30

In a round-bottomed flask fitted with reflux condenser and stirrer, 2.11 g. (5 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-hexylcyanoacetic acid ethyl ester are refluxed in a solution of 1.0 g. of potassium hydroxide in 25 ml. of ethanol and 2.5 ml. of water for 20 hours. After cooling, the reaction mixture is concentrated in vacuo, the residue suspended in ca. 30 ml. of water, acidified with concentrated hydrochloric acid, and the thereby precipitating solid substance exhaustively extracted with ether, whereby only a small part goes into solution. The ether extracts are combined, washed with water until neutral, dried over magnesium sulphate, and concentrated by evaporation. The thus obtained solid residue (1.6 g.) is purified by column chromatography (neutral silica gel, 0.05–0.2 mm., Merck, solvent: benzene/glacial acetic acid 85:15). The fractions containing the desired acid are combined and concentrated by evaporation. After recrystallization twice from hexane is obtained pure 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid, M.P. 99–100°.

Example 31

In a round-bottomed flask fitted with reflux condenser and stirrer, 1.0 g. (2.6 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-hexylcyanoacetic acid ethyl ester is refluxed in 20 ml. of 1-n. sodium hydroxide solution for 22 hours. After cooling, the reaction mixture is acidified with concentrated hydrochloric acid, and extracted with ether. The ethereal solutions are washed with water until neutral, dried over magnesium sulphate, and concentrated by evaporation. The thus obtained solid residue contains only very little 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid. The residue is extracted with hot hexane, whereby only a small part of the residue goes into solution. After concentration by evaporation of the hexane extract, the thereby obtained residue is recrystallized from hexane. Thus obtained is pure 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid, M.P. 99–100°.

Example 32

With stirring and while nitrogen is being fed in, 2.31 g. (6.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-2-pentylcyanoacetic acid ethyl ester are refluxed in a solution of 35 ml. of glacial acetic acid and 7 ml. of 5-n. sulphuric acid for 48 hours. The reaction mixture is then concentrated by evaporation in vacuo, and the residue distributed between water and ether. The ether phase, washed with water and dried over sodium sulphate, is again concentrated by evaporation, and the crude

product purified by column chromatography on silica gel [elution with benzene/glacial acetic acid (19:1)]. After recrystallization of the pure fractions from hexane is obtained 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-heptanoic acid, M.P. 84–84.5°.

Analogously is obtained

from 1.80 g. (4.51 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-2-hexylcyanoacetic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-octanoic acid, M.P. 90–91° (from hexane).

The 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-2-pentylcyanoacetic acid ethyl ester used as starting material is produced as follows:

(a) With stirring and the introduction of nitrogen, 0.588 g. (12.25 mMol) of sodium hydride (50%, in mineral oil) are added to a solution of 2.50 g. (12.25 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-3-ol in 40 ml. of absolute dimethylformamide. After the evolution of hydrogen has ceased, the reaction medium is heated for a further 5 minutes to 90°; it is then cooled to room temperature and to it is quickly added dropwise a solution of 3.21 g. (12.25 mMol) of 2-bromo-2-pentylcyanoacetic acid ethyl ester. The reaction mixture is refluxed for 2½ hours; it is then cooled, concentrated in vacuo, and the residue distributed between water and ether. The ether phase, washed with water and dried over sodium sulphate, is again concentrated by evaporation. The crude product remaining behind is purified by chromatography on silica gel [elution with benzene/hexane (2:1)], whereby pure 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-2-pentylcyanoacetic acid ethyl ester, n_D^{20} : 1.5504, is obtained.

Analogously is obtained

from 2.04 g. (10.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-2-ol and 2.62 g. (10.0 mMol) of 2-bromo-2-hexylcyanoacetic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-2-hexylcyanoacetic acid ethyl ester.

Example 33

An amount of 3.4 g. (9.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-hexylmalonic acid is refluxed in 34 ml. of xylene for half an hour. After cooling, the reaction mixture is completely concentrated in vacuo. The thus obtained oily residue is recrystallized twice from hexane. Thus obtained is pure 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid in the form of white needles, M.P. 99–100°.

Analogously are obtained

from 1.20 g. (ca. 4.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-methylmalonic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-propionic acid, M.P. 128–129° (from methanol/water);

from 1.45 g. (ca. 3.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-tetradecylmalonic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-hexadecanoic acid, M.P. 55–56° (from hexane);

from 2.25 g. (6.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-6-hexylmalonic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octanoic acid, M.P. 78–79° (from hexane);

from 1.95 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-2-hexylmalonic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid, M.P. 92–93° (from hexane);

from 1.95 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-2-hexylmalonic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanoic acid, M.P. 62–63° (from hexane);

from 2.23 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-2-decylmalonic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-dodecanoic acid, M.P. 73.5–74.5° (from hexane).

The 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-2-hexylmalonic acid used as starting material can be obtained as follows:

(a) An amount of 4.0 g. (9.3 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-hexylmalonic acid diethyl ester is refluxed in a solution of 2.5 g. of potassium hydroxide in 10 ml. of methanol and 1 ml. of water for 20 hours. The reaction mixture is then diluted with 100 ml. of water, washed twice with a little ether, the aqueous phase acidified with ice-cold concentrated hydrochloric acid, and the thereby precipitating oil extracted with ether. The thus obtained ethereal solution is washed with water until neutral, dried over magnesium sulphate, and carefully concentrated in vacuo. After drying in high vacuum is obtained crude 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-hexylmalonic acid, which is contaminated with a very little (ca. 2%) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid. The malonic acid is obtained as viscous yellow oil that does not crystallize and is reacted without further purification.

In an analogous manner are obtained from the corresponding diethyl esters

2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-methylmalonic acid,
2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-2-tetradecylmalonic acid,
2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-2-hexylmalonic acid,
2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-2-hexylmalonic acid,
2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-2-hexylmalonic acid, and
2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-2-decylmalonic acid,

which can be further used as crude products.

Example 34

Analogously to Example 33 are obtained

from 0.80 g. (ca. 2 mMol) of crude 2-(6,7,8,9-tetrahydrodibenzothiofuran-2-ylthio)-2-hexylmalonic acid: 2-(6,7,8,9-tetrahydrodibenzothiofuran-2-ylthio)-octanoic acid, M.P. 91–92° (from hexane);
from 1.20 g. (ca. 3 mMol) of crude 2-(6,7,8,9-tetrahydrodibenzothiofuran-3-ylthio)-2-hexylmalonic acid: 2-(6,7,8,9-tetrahydrodibenzothiofuran-3-ylthio)-octanoic acid; n_D^{20} : 1.5718, after chromatographic purification on silica gel, elution with benzene and benzene/glacial acetic acid (49:1).

The starting materials are obtained analogously to Example 33(a), but with only two hours' boiling, from

0.924 g. (2.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiofuran-2-ylthio)-2-hexylmalonic acid diethyl ester, or 1.386 g. (3.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiofuran-3-ylthio)-2-hexylmalonic acid diethyl ester.

Example 35

An amount of 0.78 g. (ca. 2 mMol) of crude 2-(6,7,8,9-tetrahydrodibenzothiofuran-2-yloxy)-2-hexylmalonic acid is heated under nitrogen for half an hour at 150°. The decarboxylated crude product is purified by chromatography on silica gel [elution with benzene and benzene/glacial acetic acid (19:1)]. After recrystallization of the pure fractions from hexane is obtained 2-(6,7,8,9-tetrahydrodibenzothiofuran-2-yloxy)-octanoic acid, M.P. 90–91°.

From 0.78 g. (ca. 2 mMol) of crude 2-(6,7,8,9-tetrahydrodibenzothiofuran-3-yloxy)-2-hexylmalonic acid is obtained, by heating to 240–250° for 5 minutes and processing as above, 2-(6,7,8,9-tetrahydrodibenzothiofuran-3-yloxy)-octanoic acid, M.P. 106–107° (from hexane).

The starting materials are obtained analogously to Example 33(a), but with only two hours' boiling, from 0.892 g. (2.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothio-

phen-2-yloxy)-2-hexylmalonic acid diethyl ester, or 0.892 g. (2.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiofuran-3-yloxy)-2-hexylmalonic acid diethyl ester.

Example 36

In a round-bottomed flask fitted with reflux condenser, stirrer, gas-inlet tube, and drying tube containing potassium hydroxide are placed 100 ml. of absolute benzene, 12.0 g. (99 mMol) of thionyl chloride and 0.5 ml. of dimethylformamide; to these are then added 9.4 g. (28 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid. After all acid is dissolved, refluxing is carried out for a further 2 hours. After cooling, the clear yellow solution is concentrated in vacuo, and the oily residue remaining behind repeatedly evaporated off with benzene. The thus obtained crude 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid chloride is taken up in 150 ml. of abs. ether, and the thus obtained ethereal solution added dropwise to 500 ml. of ether saturated with ammonia, whereby a thick slurry is formed. Ammonia gas is fed into the reaction mixture for a further 3 minutes; stirring then proceeds for a further 10 minutes, and the reaction mixture is afterwards washed with water until neutral. The ether phase is dried with magnesium sulphate, and concentrated by evaporation, whereby is obtained in solid form crude 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octaneamide. From ethanol/water crystallizes the pure amide, M.P. 130–131°.

Analogously to the above described procedure are obtained

from 1.38 g. (3.5 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-dodecanoic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-dodecaneamide, M.P. 112–112.5° (from ethanol);
from 1.04 g. (4.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-propionic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-propionamide;
from 1.57 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptaneamide, M.P. 145–146° (from ethanol);
from 1.65 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octanoic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octaneamide, M.P. 140–141° (from ethanol);
from 1.93 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-dodecanoic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-dodecaneamide, M.P. 131.5–132.5° (from ethyl acetate);
from 1.73 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octaneamide, M.P. 135–136° (from ethanol);
from 2.77 g. (8.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanoic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octaneamide, M.P. 107.5–109° (from ethanol/water).

Example 37

A solution of 3 g. (7.24 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-dodecanoic acid ethyl ester in 10 ml. of ethanol is heated with 20 g. of ammonia, at a maximum pressure of 45 bar, for 40 hours to 100°. After concentration by evaporation and recrystallization of the thus obtained residue is obtained pure 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-dodecaneamide, M.P. 131.5–132.5°.

Example 38

While stirring is maintained, 1.19 g. (10.0 mMol) of thionyl chloride are added dropwise to a solution of 1.73 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiofuran-3-yloxy)-octanoic acid in 25 ml. of absolute benzene and 0.1 ml. of dimethylformamide. The reaction mixture is refluxed for 1½ hours, and subsequently concentrated in vacuo. Excess thionyl chloride is removed by repeated addition of absolute benzene, and concentration in vacuo.

The oily residue, crude 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-octanoic acid chloride, is taken up in 100 ml. of absolute ether, and the ethereal solution saturated with ammonia gas. Stirring proceeds for a further 20 minutes, and the reaction mixture is then washed with water. After drying of the ether phase over magnesium sulphate and concentration in vacuo, the crystalline crude product is recrystallized from acetone/hexane. Thus obtained is 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-octaneamide, M.P. 142–143°.

Analogously are obtained

from 1.73 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-octanoic acid: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-octaneamide, M.P. 116–117° (from methanol);

from 1.74 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-heptanoic acid: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-heptaneamide, M.P. 150–150.5° (from methanol);

from 1.81 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-octanoic acid: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-octaneamide, M.P. 106–109° (from methanol).

Example 39

In a round-bottomed flask fitted with stirrer, gas-inlet tube, thermometer, and drying tube containing potassium hydroxide, a solution of 1.1 g. (4.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid nitrile in 40 ml. of absolute chloroform and 2 ml. of absolute methanol is saturated at 5–8°, with stirring, for 10 minutes with dry hydrogen chloride, and subsequently stirred for 4 hours at room temperature. The reaction mixture is afterwards concentrated in vacuo, and the oily residue remaining behind heated, to remove the formed methyl chloride, for ca. 3 minutes in vacuo to 90°. The thus obtained solid residue is recrystallized twice from ethanol with the addition of active charcoal. In this manner is obtained pure 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptaneamide in the form of white needles, M.P. 145–146°.

Analogously are obtained

from 3.11 g. (10.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octaneamide, M.P. 130–131° (from ethanol/water);

from 1.21 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-propionic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-propionamide;

from 1.84 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-dodecanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-dodecaneamide, M.P. 112–112.5° (from ethanol);

from 3.11 g. (10.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octaneamide, M.P. 140–141° (from ethanol);

from 1.84 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-dodecanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-dodecaneamide, M.P. 131.5–132.5° (from ethyl acetate);

from 1.64 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octaneamide, M.P. 135–136° (from ethanol);

from 1.64 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octaneamide, M.P. 107.5–109° (from ethanol/water).

Example 40

Dry hydrogen chloride gas is passed through the ice-cold solution of 1.40 g. (4.28 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-octanoic acid nitrile in 80 ml. of absolute chloroform and 4 ml. of absolute meth-

anol until saturation is obtained, whereby care is taken to prevent the temperature exceeding 5°. The reaction mixture is allowed to stand, whilst being stirred, for a further 4 hours at room temperature; it is then concentrated in vacuo. The oily residue is heated for a further 10 minutes to 90° in a water-jet vacuum. As frothing up occurs, methyl chloride is split off. The desired product is obtained direct in crystalline form. After recrystallization from methanol is obtained 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-octaneamide, M.P. 116–117° (from methanol).

Analogously are obtained

from 1.50 g. (4.58 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-octanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-octaneamide, M.P. 150–150.5° (from methanol);

from 1.72 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-octanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-octaneamide, M.P. 106–109° (from methanol).

Example 41

In a round-bottomed flask fitted with stirrer, gas-inlet tube, thermometer, and drying tube containing potassium hydroxide, a solution of 3.11 g. (10 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid nitrile in 50 ml. of absolute chloroform and 5 ml. of absolute ethanol is saturated at 0–5° with dry hydrogen chloride; the solution is then stirred for 20 hours at room temperature, and subsequently concentrated at 30° in vacuo. The residue is taken up in 40 ml. of dioxane, 4 ml. of water are added, and the thus obtained solution is stirred for 3 hours at 40°. The solution is again concentrated by evaporation, the residue taken up in benzene, the benzene solution dried over magnesium sulphate, and again concentrated by evaporation. After one hour's drying at 100° and at 0.1 torr is obtained crude 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid ethyl ester, which is purified by column chromatography (silica gel 0.05–0.2 mm., Merck, solvent: benzene). The benzene fractions containing the desired ester are combined and concentrated by evaporation. After drying under high vacuum is obtained pure 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid ethyl ester in the form of a pale yellow oil, n_D^{25} : 1.5227.

Analogously are obtained

from 2.41 g. (10.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-propionitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-propionic acid ethyl ester, n_D^{20} : 1.5408;

from 2.97 g. (10.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid ethyl ester, n_D^{20} : 1.5241;

from 3.67 g. (10.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-dodecanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-dodecanoic acid ethyl ester, n_D^{22} : 1.5133;

from 4.23 g. (10.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-hexadecanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-hexadecanoic acid, n_D^{20} : 1.5062;

from 3.11 g. (10.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octanoic acid ethyl ester, n_D^{20} : 1.5233;

from 3.27 g. (10.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid ethyl ester, n_D^{20} : 1.5465;

from 3.27 g. (10.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanoic acid ethyl ester, n_D^{20} : 1.5517.

Likewise analogously is obtained from 2.97 g. (10.0 mMol) of 2 - (6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid nitrile, using 5 ml. of absolute methanol instead of ethanol, 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-heptanoic acid methyl ester, n_D^{20} : 1.5320.

Example 42

To 3.11 g. (10.0 mMol) of 2 - (6,7,8,9 - tetrahydrodibenzofuran - 2 - yloxy)-octanoic acid nitrile in the mixture of 50 ml. of ethanol, 5 ml. of water, and 3 ml. of 30% aqueous hydrogen peroxide solution is added, at 20°, 1.0 ml. of 2-n. sodium hydroxide solution. After the evolution of oxygen has ceased, the reaction solution is heated for a further 30 minutes to 50°, and subsequently intensively concentrated in vacuo. The concentrate is distributed between chloroform and water, the chloroform phase washed with water, dried over potassium carbonate, and the solvent evaporated off. The residue is crystallized from ethanol/water, whereby 2 - (6,7,8,9 - tetrahydrodibenzofuran-2-yloxy)-octaneamide, M.P. 130–131°, is obtained.

Example 43

A solution of 1.50 g. (4.58 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-octanoic acid nitrile in 50 ml. of absolute chloroform and 5 ml. of absolute ethanol is saturated at 0–5° with dry hydrogen chloride; the solution is then stirred for 15 hours at room temperature, and subsequently concentrated at 30° in vacuo. The residue is taken up in 20 ml. of dioxane and 4 ml. of water, and the reaction mixture stirred for a further 5 hours at 40°. After concentration in vacuo, the reaction product is taken up in benzene, the benzene solution dried over magnesium sulphate, and again concentrated by evaporation. Purification of the crude product is effected by chromatography on silica gel [elution with benzene/hexane (2:1)], whereby is obtained 2 - (6,7,8,9 - tetrahydrodibenzothiophen - 2 - yloxy)octanoic acid ethyl ester; n_D^{20} : 1.5498.

Analogously are obtained

from 2.62 g. (8.0 mMol) of 2 - (6,7,8,9 - tetrahydrodibenzothiophen - 3 - yloxy)-octanoic acid nitrile: 2-(6,7,8,9 - tetrahydrodibenzothiophen-3-yloxy)-octanoic acid ethyl ester; n_D^{20} : 1.5481;

from 1.0 g. (3.04 mMol) of 2 - (6,7,8,9 - tetrahydrodibenzothiophen - 2 - ylthio)-heptanoic acid nitrile: 2-(6,7,8,9 - tetrahydrodibenzothiophen - 2 - ylthio)-heptanoic acid ethyl ester; n_D^{20} : 1.5787;

from 1.72 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen - 3 - ylthio)-octanoic acid nitrile: 2-(6,7,8,9-tetrahydrodibenzothiophen - 3 - ylthio)-octanoic acid ethyl ester; n_D^{20} : 1.5754.

Example 44

To a solution of 1.1 g. (11.0 mMol) of diisopropylamine in 8 ml. of absolute tetrahydrofuran is added, under nitrogen and with stirring, butyllithium in hexane (5.2 ml. of a 2.12 molar solution, corresponding to 11.0 mMol), the temperature being kept below 0°. To the thus obtained cold basic solution are added, in small portions, 1.23 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-acetic acid, and stirring at below 0° is continued. After a further 15 minutes are added dropwise at 5°, to the now yellow colored solution, 2.03 ml. (11.5 mMol) of hexamethylphosphoric acid triamide, and the whole then stirred again for 15 minutes, whereby the color of the solution turns brown. The solution is cooled to 0°, and 0.745 ml. (5.3 mMol) of n-hexylbromide are then added, whereby the temperature rises to 10°. Stirring proceeds for a further 2 hours at room temperature; the solution is afterwards acidified with 2-n. hydrochloric acid, 50 ml. of water are added, and the solution is extracted with ether. The thus obtained ethereal solution is extracted with ca. 40 ml. of 0.5-n. sodium hydroxide solution, the alkaline extract acidified with hydrochloric acid, and again extracted with ether.

After drying over magnesium sulphate, the ethereal solution is concentrated in vacuo. Thus obtained is a brown oil which contains in addition to the desired 2-(6,7,8,9 - tetrahydrodibenzofuran-2-yloxy)-octanoic acid, and apart from other impurities, the 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-acetic acid used as starting material. The oil is subsequently purified by column chromatography [neutral silica gel 0.05–0.2 mm., Merck, solvent: benzene/glacial acetic acid (9:1)]. The fractions containing the desired acid are combined, concentrated by evaporation, and the thus obtained solid residue recrystallized twice from hexane. In this manner is obtained pure 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-octanoic acid, M.P. 99–100°.

Analogously is obtained

from 1.23 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-acetic acid and 0.745 ml. (5.3 mMol) of hexylbromide: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-octanoic acid, M.P. 78–70° (from hexane).

The 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-acetic acid used as starting material is obtained as follows:

(a) To a solution of 1.15 g. (50.0 mMol) of sodium in 20 ml. of absolute ethanol are added, under nitrogen, 9.40 g. (50.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol. To the solution are then added dropwise, with stirring, 9.2 g. (55.0 mMol) of 2-bromoacetic acid ethyl ester, and refluxing is carried out for 4 hours. After cooling, the reaction mixture is concentrated in vacuo, and the residue is distributed between water and ether. The ether phase is washed with water, dried over magnesium sulphate, concentrated by evaporation, and the crude product remaining behind purified from a small amount of starting materials by column chromatography on neutral silica gel (0.05–0.2 mm., Merck, solvent: benzene). The obtained 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-acetic acid ethyl ester is crystallized from ethanol, M.P. 75–76°.

Analogously is obtained

from 3.76 g. (20.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol and 3.67 g. (22.0 mMol) of 2-bromoacetic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-acetic acid ethyl ester, M.P. 54–55° (from hexane).

(b) An amount of 8.22 g. (30.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-acetic acid ethyl ester is refluxed in a solution of 3.36 g. (60.0 mMol) of potassium hydroxide in 100 ml. of methanol and 10 ml. of water for 4 hours. After cooling, the reaction mixture is concentrated by evaporation, the residue distributed between dilute hydrochloric acid and ether, the ether phase separated, and the acid aqueous phase extracted with ether. The combined ether solutions are washed with water until neutral, dried over magnesium sulphate, and concentrated by evaporation. The crude 2-(6,7,8,9-tetrahydrodibenzofuran-2-yloxy)-acetic acid remaining behind is recrystallized from ethanol, M.P. 185–186°.

Analogously is obtained

from 4.0 g. (14.6 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-acetic acid ethyl ester: 2-(6,7,8,9-tetrahydrodibenzofuran-3-yloxy)-acetic acid, M.P. 163–165° (from ethanol/water).

Example 45

Analogously to Example 44 is obtained

from 1.31 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-acetic acid and 0.745 ml. (5.3 mMol) of hexylbromide: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-octanoic acid, M.P. 92–93° (from hexane).

Likewise analogously to Example 44 are obtained

from 1.31 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-acetic acid and 0.745 ml. (5.3 mMol) of hexylbromide: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-octanoic acid, M.P. 62–63° (from hexane);

from 1.31 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrobenzofuran-3-ylthio)-acetic acid and 1.042 g. (5.3 mMol) of decylbromide: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-dodecanoic acid, M.P. 73.5–74.5° (from hexane).

The 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-acetic acid used as starting material is obtained as follows:

(a) To a solution of 0.46 g. (20.0 mMol) of sodium in 40 ml. of absolute ethanol are added 4.08 g. (20.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-thiol. To the thus obtained sodium salt solution is added a solution (prepared in the same manner) of the sodium salt of 2.78 g. (20.0 mMol) of 2-bromoacetic acid in 80 ml. of absolute ethanol, and the mixture refluxed for 4 hours. After cooling, the reaction mixture is filtered under suction, and the filtrate concentrated in vacuo. The residue is dissolved, together with the suction-filter residue, in water, the aqueous solution decolorized with active charcoal, and acidified with concentrated hydrochloric acid. The precipitated crude product is filtered off with suction, and recrystallized from ethanol/water. The obtained 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-acetic acid melts at 122–123°.

Analogously is obtained

from 4.08 g. (20.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-thiol and 2.78 g. (20.0 mMol) of 2-bromoacetic acid: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-acetic acid, M.P. 103.5–104.5° (from ethanol/water).

Example 46

To a solution, cooled to -10° , of 1.11 g. (11.0 mMol) of diisopropylamine in 10 ml. of absolute tetrahydrofuran are added dropwise, with stirring and whilst nitrogen is being fed in, 5.2 ml. of a 2.12 molar solution of butyllithium in hexane (11.0 mMol). To the reaction mixture are then added in portions 1.39 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-acetic acid, whereby care is taken to see that the temperature does not exceed -5° . The reaction mixture is stirred for 30 minutes at 0° , 2.06 g. (11.5 mMol) of hexamethylphosphoric acid triamide are then added dropwise, and stirring proceeds for a further 30 minutes at -5° to 0° . At -5° are finally added 0.875 g. (5.3 mMol) of freshly distilled hexylbromide, and stirring is continued for 2 hours at room temperature. The reaction mixture is then distributed between dilute hydrochloric acid and ether. After drying of the ether extracts over sodium sulphate and concentration in vacuo, the crude product is purified by chromatography on silica gel [elution with benzene and benzene/glacial acetic acid (50:1)]. Thus obtained is 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-octanoic acid, M.P. 91–92° (from hexane).

Analogously is obtained

from 1.39 g. (5.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-acetic acid and 0.875 g. (5.3 mMol) of hexyl bromide: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-octanoic acid; n_D^{20} : 1.5718, after chromatographic purification on silica gel, elution with benzene and benzene/glacial acetic acid (49:1).

The starting materials are produced analogously to Example 45(a). Thus are obtained

from 1.76 g. (8.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophene-2-thiol and 1.112 g. (8.0 mMol) of bromoacetic acid: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-acetic acid, M.P. 132–134° (from ether/hexane);

from 1.76 g. (8.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophene-3-thiol and 1.112 g. (8.0 mMol) of bromoacetic acid: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-acetic acid.

Example 47

Analogously to Example 46 are obtained

from 2.62 g. (10.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-acetic acid and 1.70 g. (10.3 mMol) of hexyl bromide: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-octanoic acid, M.P. 90–91° (from hexane);

from 2.62 g. (10.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-acetic acid and 1.70 g. (10.3 mMol) of hexyl bromide: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-octanoic acid, M.P. 106–107° (from hexane).

The starting materials are produced analogously to Examples 44 (a) and (b).

(a) From 5.10 g. (25.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-2-ol and 4.18 g. (25.0 mMol) of bromoacetic acid ethyl ester is obtained: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-acetic acid ethyl ester, M.P. 112–113° (from ethanol), and

from 5.10 g. (25.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophen-3-ol and 4.18 g. (25.0 mMol) of bromoacetic acid ethyl ester is obtained: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-acetic acid ethyl ester.

(b) From 4.35 g. (15.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-acetic acid ethyl ester is obtained: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-ylthio)-acetic acid, M.P. 218–220° (from ethanol), and from 4.35 g. (15.0 mMol) of 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-acetic acid ethyl ester is obtained: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-ylthio)-acetic acid.

Example 48

7.52 g. (4.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-ol and 14.2 g. (8.0 mMol) of 1,1,1-trichloro-2-methyl-2-propanol (acetone chloroform) are dissolved in 130 ml. of distilled acetone; the solution is cooled to 0° , and to it are then added 4.27 g. of powdered sodium hydroxide (a third of in all 12.8 g.=320 mMol). The temperature is allowed to rise, whilst stirring is maintained, within 2 hours to 25° . The solution is again cooled to 0° and the second portion of 4.27 g. of sodium hydroxide is then added; and finally, using the same procedure, the last portion is added after 2 hours. Again the temperature is allowed to rise within 2 hours to 25° . The mixture is stirred for a further 5 hours at this temperature, and is then concentrated by evaporation in a rotary-evaporator. The residue is dissolved in water, the dark solution acidified with concentrated hydrochloric acid, and extracted with ether. The ether solution, in its turn, is extracted with 2-n. sodium bicarbonate solution, and the alkaline extract acidified. The precipitated crude 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-2-methylpropionic acid is triturated twice with petroleum ether, and filtered off. The thus purified acid is dissolved in 100 ml. of methanol, the solution decolorized with active charcoal, and then 90 ml. of water are added. The precipitated crystals are filtered off, and again recrystallized from methanol/water. M.P. of the pure acid=136.5–138°.

In an analogous manner are obtained, using the same amounts of 1,1,1-trichloro-2-methyl-2-propanol, sodium hydroxide, and acetone,

from 7.52 g. (4.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-ol: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-2-methylpropionic acid, M.P. 78–80° (from hexane);

from 8.16 g. (4.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-2-thiol: 2-(6,7,8,9-tetrahydrodibenzofuran-2-ylthio)-2-methylpropionic acid, M.P. 146–147° (from ether/hexane);

from 8.16 g. (4.0 mMol) of 6,7,8,9-tetrahydrodibenzofuran-3-thiol: 2-(6,7,8,9-tetrahydrodibenzofuran-3-ylthio)-2-methylpropionic acid;

from 8.16 g. (4.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophen - 2-ol: 2-(6,7,8,9-tetrahydrodibenzothiophen-2-yloxy)-2-methylpropionic acid, M.P. 121-122° (from methylene chloride/hexane);
 from 8.16 g. (4.0 mMol) of 6,7,8,9-tetrahydrodibenzothiophen - 3-ol: 2-(6,7,8,9-tetrahydrodibenzothiophen-3-yloxy)-2-methylpropionic acid;
 from 8.80 g. (4.0 mMol) of 6,7,8,9 - tetrahydrodibenzothiophene - 2 - thiol: 2 - (6,7,8,9 - tetrahydrodibenzothiophen-2-ylthio)-2-methylpropionic acid;
 from 8.80 g. (4.0 mMol) of 6,7,8,9 - tetrahydrodibenzothiophene - 3 - thiol: 2 - (6,7,8,9 - tetrahydrodibenzothiophen-3-ylthio)-2-methylpropionic acid.

Example 49

An amount of 1.1 g. (3.5 mMol) of 2-(6,7,8,9-tetrahydrodibenzofuran - 2 - yloxy) - heptanoic acid is dissolved in 20 ml. of absolute ethanol. To the obtained solution is added a solution of 69 mg. (3.0 mMol) of sodium in 5 ml. of absolute ethanol; the whole is concentrated by evaporation to dryness, and the solid white residue triturated with ca. 20 ml. of ether. Filtration under suction and subsequent washing with ether are carried out. Thus obtained is the pure sodium salt in the form of a white powder that melts between 290 and 308°, with decomposition.

Example 50

Analogously to Example 49 is obtained

from 3.465 g. (10.0 mMol) of 2 - (6,7,8,9 - tetrahydrodibenzothiophen - 3 - yloxy) - octanoic acid: the sodium salt of 2 - (6,7,8,9 - tetrahydrodibenzothiophen-3-yloxy)-octanoic acid, M.P. 320-322°.

Example 51

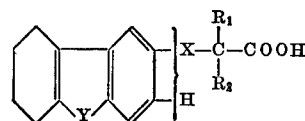
An amount of 110 mg. (2.75 mMol) of calcium is decomposed in 10 ml. of water under nitrogen. To the thus obtained calcium hydroxide suspension are added 2.05 g. (6.22 mMol) of 2 - (6,7,8,9 - tetrahydrodibenzofuran - 2 - yloxy)-octanoic acid in 50 ml. of methanol, and the mixture is refluxed for 15 minutes. After cooling, the thus obtained white suspension is concentrated to ca. 20 ml., the precipitating crude calcium salt filtered off under suction, and washed with a little ether. It is subsequently extracted three times using 120 ml. of boiling methanol each time. The methanol extracts are combined, filtered and concentrated to ca. 20 ml., whereby the calcium salt crystallizes out. The methanol phase is diluted with ca. 30 ml. of ether, the crystallizate is then filtered off with suction, and washed with ether. After drying in high vacuum is obtained the pure calcium salt of 2 - (6,7,8,9 - tetrahydrodibenzofuran - 2 - yloxy)-octanoic acid, which melts between 305 and 315°, with decomposition.

Example 52

To a suspension of calcium hydroxide, produced by decomposition of 137 mg. (3.42 mMol) of calcium in 15 ml. of water, is added, with stirring and whilst nitrogen is being fed in, a solution of 2.50 g. (7.2 mMol) of 2-(6,7,8,9 - tetrahydrodibenzothiophen - 2 - yloxy)-octanoic acid in 80 ml. of methanol. The reaction mixture is refluxed for 15 minutes, and concentrated in vacuo. The precipitated crude calcium salt is filtered off, washed with ether, and recrystallized twice from absolute methanol. Thus obtained is the pure calcium salt of 2-(6,7,8,9-tetrahydrodibenzothiophen - 2 - yloxy)-octanoic acid, which decomposes between 290 and 305° with a brown coloration.

What is claimed is:

1. A compound of the formula



(I)

wherein

R₁ represents an alkyl group having at most 14 carbon atoms, or a cycloalkyl group having 5-7 carbon atoms, R₂ represents hydrogen or the methyl group, and

X and Y represent, independently of each other, oxygen or sulphur, or an alkali metal salt or alkaline-earth metal salt thereof.

2. A compound according to claim 1 which is 2-(6,7,8,9 - tetrahydrodibenzofuran - 2 - yloxy)-octanoic acid or an alkali metal salt or alkaline-earth metal salt thereof.

3. A compound according to claim 1 which is 2-(6,7,8,9 - tetrahydrodibenzofuran - 2 - yloxy)-dodecanoic acid or an alkali metal salt or alkaline-earth metal salt thereof.

4. A compound according to claim 1 which is 2-(6,7,8,9 - tetrahydrodibenzofuran - 3 - yloxy) - octanoic acid or an alkali metal salt or alkaline-earth metal salt thereof.

5. A compound according to claim 1 which is 2-(6,7,8,9 - tetrahydrodibenzofuran - 3 - yloxy)-dodecanoic acid or an alkali metal salt or alkaline-earth metal salt thereof.

6. A compound according to claim 1 which is 2-(6,7,8,9 - tetrahydrodibenzofuran - 3 - ylthio) - octanoic acid or an alkali metal salt or alkaline-earth metal salt thereof.

7. A compound according to claim 1 which is 2-(6,7,8,9 - tetrahydrodibenzofuran - 3 - ylthio) - dodecanoic acid or an alkali metal salt or alkaline-earth metal salt thereof.

8. A compound according to claim 1 which is 2-(6,7,8,9 - tetrahydrodibenzofuran - 3 - ylthio) - octanoic acid or an alkali metal salt or alkaline-earth metal salt thereof.

9. A compound according to claim 1 which is 2-(6,7,8,9 - tetrahydrodibenzofuran - 3 - ylthio) - octanoic acid or an alkali metal salt or alkaline-earth metal salt thereof.

10. A compound according to claim 1 which is 2-(6,7,8,9 - tetrahydrodibenzofuran - 3 - ylthio) - octanoic acid or an alkali metal salt or alkaline-earth metal salt thereof.

11. A compound according to claim 1 which is 2-(6,7,8,9 - tetrahydrodibenzofuran - 3 - ylthio) - octanoic acid or an alkali metal salt or alkaline-earth metal salt thereof.

12. 2 - (6,7,8,9 - tetrahydrodibenzofuran - 2 - yloxy)-octaneamide.

13. 2 - (6,7,8,9 - tetrahydrodibenzofuran - 2 - yloxy)-heptanoic acid ethyl ester.

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HARRY I. MOATZ, Primary Examiner

U.S. Cl. X.R.

260-242, 244 R, 330.5, 586 R; 424-245, 275, 285

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(5/69)UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTIONPatent No. 3,784,602 Dated January 8, 1974Inventor(s) JORG FREI ET AL

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

Column 46, line 13, after "or sulphur, or" insert
-- an alkyl ester in which alkyl has at
most 3 carbon atoms, the amide, --;
line 39, after "tetrahydrodibenzofuran-"
delete "3" and insert -- 2 --;
line 43, delete "ylthio" and insert
-- yloxy --;
line 51, delete "tetrahydrodibenzofuran-3"
and insert -- tetrahydrodibenzothiophen-2 --.

Signed and sealed this 2nd day of July 1974.

(SEAL)
Attest:

EDWARD M. FLETCHER, JR.
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents