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HEXAHYDRO-FLUOREN-2-YLOXY ALKANOIC ACIDS AND ESTERS THEREOF

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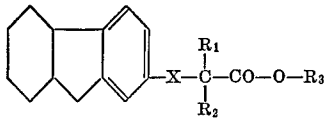
ABSTRACT OF THE DISCLOSURE

2-(4b,5,6,7,8,8a-hexahydrofluoren - 2 - yloxy)- and 2-(4b,5,6,7,8,8a-hexafluoren - 2 - ylthio)-alkanoic acids and esters thereof, as well as alkali-metal and alkaline-earth-metal salts of such acids, which compounds exhibit hypolipemic and anti-inflammatory activity. An illustrative embodiment is 2-(4b,5,6,7,8,8a-hexahydrofluoren - 2 - yloxy)-heptanoic acid.

DETAILED DESCRIPTION

The present invention relates to certain aryloxy- and arylthio-acetic acid derivatives including the lower alkyl esters thereof and alkali-metal and alkaline-earth-metal salts of such acids, pharmaceutical compositions containing these compounds and their use.

More particularly, the present invention relates to compounds of Formula I,



(I)

wherein

R_1 is alkyl having from 1 to 10 carbon atoms or benzyl,
R_2 is hydrogen or methyl,
R_3 is hydrogen or alkyl having from 1 to 3 carbon atoms, and
X is oxygen or sulfur,

and the alkali-metal and alkaline-earth-metal salts of such compounds, wherein R_3 is hydrogen.

Is has now been found that the above compounds possess valuable pharmacological properties. In particular, they exhibit hypolipemic activity in a wide sense, which can be shown, for example, by the lowering of the serum and liver cholesterol and triglyceride levels in the case of repeated oral administration.

The hypolipemic activity of the compounds of the invention may be illustratively demonstrated in rats according to the following method:

To a group of ten male rats each weighing between 120 and 130 g., and fed with a standardized diet and water ad libidum, is administrated, orally through an oesophageal sound a 2.5% suspension of 2-(4b,5,6,7,8,8a-hexahydrofluoren - 2 - yloxy)-heptanoic acid in 1% gum arabic. The active compound is administered this way in daily dosages of 2×10 mg./kg. on four consecutive days. The animals are abstained from food for the last sixteen hours of the experiment and then sacrificed. Extraction of serum and liver lipids is carried out according to J. Folch et al. [cf. J. Biol. Chem. 226,497 (1957)]. Triglycerides and total cholesterol are determined with an autoanalyzer according to the method of G. Kessler and

H. Lederer [Technicon Symposium, vol. 1, page 863 (1965)], and W. D. Block et al., ibid., page 970, respectively. The lipid content of this group is compared with the lipid content of a control group. Changes in the serum cholesterol level may be determined directly according to R. Richerich and K. Lauber [Klin. Wochenschrift 40, 1252 (1962)], for example by firstly taking an orbital blood sample from male rats as aforesaid, under carbondioxide/oxygen anaesthesia and determining the serum cholesterol, subjecting the rats to a feeding/dosage administration regimen as detailed above, and finally taking a second blood sample sixteen hours after the last administration of active substance and determining the serum cholesterol once more.

In the above manner it is possible to demonstrate that e.g. the specified compound 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid [as well as other compounds according to the present invention such as 2-(4b,5,6,7,8,8a-hexahydro - 2 - yloxy)-5-methyl-hexanoic acid; 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-octanoic acid; and 2-(4b,5,6,7,8,8a-hexahydrofluoren - 2 - ylthio)-heptanoic acid] lower the cholesterol and triglyceride levels of the serum and liver to a significant extent.

In addition to the foregoing, certain of the substances according to the present invention, in particular 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid, exhibit anti-inflammatory activity, which may again be demonstrated according to standard test procedures, for example, by measuring the influence of the test substances on oedema of rat paws, induced by injecting a 10% suspension of bolus alba [G. Wilhelmi: Japanese J. Pharmacol. 15, 187–198 (1965)].

Test animals of groups of 10 to 20 white male rats weighing between 110 and 130 g. are used for each dosage. The compounds to be tested are administered orally in form of a 5% tragacanth suspension. One hour later, 0.1 cc. of a 10% suspension of bolus alba is injected subcutaneously into one hind paw of each of the test animals. The animals are sacrificed five hours later and the hind paws amputated. The swelling is determined by measuring the weight differences between the left, normal paw, and the right swollen paw. The average weight of the swelling is compared with the average weight of the swelling of a control group which has not received the test compounds but has been treated the same way as previously described with bolus alba. The reduction of the swelling is a measure for the anti-inflammatory activity, and is expressed as a percentage over the control.

In accordance with the above procedures it can be shown that the stated compound 2-(4b,5,6,7,8a-hexahydrofluoren-2-yloxy)-heptanoic acid exhibits anti-inflammatory activity of an appreciable order at dosages of e.g. 50 mg./kg.

At the same time the acids, esters and salts embraced by the present invention are characterized by a favourably low toxicity on e.g. oral administration demonstrated in mice, rats, guinea pigs and rabbits.

These favourable properties render the compounds of the invention suitable for (a) the treatment of hyperlipemic conditions, and (b) the relief of inflammatory conditions in mammals.

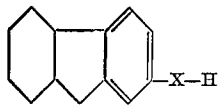
In the compounds of Formula I, R_1 as alkyl having from 1 to 10 carbon atoms is, e.g., methyl, ethyl, propyl, butyl, isobutyl, pentyl, isopentyl, 2,2-dimethylpropyl, hexyl, isohexyl, 3,3-dimethylbutyl, heptyl, octyl, nonyl or decyl.

Examples of R_3 as alkyl having from 1 to 3 carbon atoms, are methyl, ethyl, propyl and isopropyl.

Specific examples of compounds according to the present invention are:

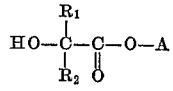
(1) 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid;
(2) 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-5-methyl-hexanoic acid;
(3) 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-octanic acid, and
(4) 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-ylthio)-heptanoic acid.

To produce the new compounds of Formula I and the alkali- and alkaline-earth-metal salts of the free carboxylic acids falling under this formula, an alkali-metal salt of compound of Formula II,



(II)

wherein X has the meaning given for Formula I, is reacted with a reactive ester of a compound of Formula III,



(III)

wherein

A is alkali metal, alkaline earth metal or lower alkyl, and R_1 and R_2 have the meaning given for Formula I, and a resulting carboxylic acid of Formula I is optionally converted into an alkali- or alkaline earth-metal salt.

Examples of reactive esters of compounds of Formula III which can be employed in the process according to the invention are, for example halides, in particular chlorides or bromides, or sulfonic acid esters, in particular methane-sulfonic acid esters, or o- or p-toluene-sulfonic acid esters.

Examples of A in Formula III as alkali or alkaline-earth-metal are sodium, potassium or calcium, and as lower alkyl methyl, ethyl, propyl or isopropyl.

The reaction is preferably performed in a solvent or diluent. Examples of such are e.g. optionally hydrous, lower alkanols such as ethanol, or solvents having no hydroxy groups such as N,N-dimethyl-formamide, N,N-dimethyl-acetamide or N,N,N',N',N'',N''-hexamethyl-phosphoric acid triamide. Reaction temperatures are between 50 and 150° C., preferably at the boiling point of the solvent used. If necessary, the reaction temperature can be kept above the boiling point by performing the reaction in a closed vessel. Salts of the first as well as of the second reaction component are preferably formed in situ, e.g. by the addition of an alkali-metal alcoholate, hydroxide or hydride, depending on whether an anhydrous or a hydrous alkanol or a solvent not having any hydroxy groups, is used as the reaction medium. Instead of an alkali-metal hydride, a corresponding amide can also be employed.

One starting material of Formula II, namely 4b,5,6,7,8,8a-hexahydrofluoren-2-ol, is produced, e.g., as follows: 2-(m-methoxy-benzylidene)-cyclohexanone [cf. R. Baltzli et al., J. Am. Chem. Soc. 77, 624 (1955)] is used as starting material, which is reduced in the presence of Raney nickel to 2-(m-methoxy-benzyl)-cyclohexanone; the reduction product, in the presence of concentrated sulfuric acid, splits-off intramolecularly one mol of water and with ring closure forms 2-methoxy-5,6,7,8-tetrahydrofluorene, which is catalytically hydrogenated in the presence of palladium charcoal to 2-methoxy-4b,5,6,7,8,8a-hexahydrofluorene; the ether obtained is split with hydroiodic acid. To produce the second starting material of Formula II, 4b,5,6,7,8,8a-hexahydrofluoren-2-thiol, the compound 1,2,3,4,4a,9a-hexahydrofluorene [cf. W. Treibs and E. Heyner, Chem. Ber. 90, 2285 (1957)] is used as starting material. Concentrated sulfuric acid and acetic anhydride convert this compound to crude 4b,5,6,7,8,8a-hexahydrofluoren-2-sulfonic acid, which is converted with phosphorus oxychloride into 4b,5,6,7,8,8a-hexahydrofluoren-2-sulfonyl chloride. The sulfonyl chloride is reduced with the aid of lithium aluminium hydride to the thiol.

Examples of chlorides, bromides, methane sulfonic acid esters, o- or p-toluene sulfonic acid esters of compounds of Formula III, which can be used in the process according to the invention, are compounds whose radicals X, R_1, R_2 and A coincide with the groups which are listed after Formulae I and III. Such starting materials, e.g. 2-bromo-propionic acid ethyl ester [cf. A. Schreiner, Ann. 197, 13 (1879)], are described in the literature. Other compounds of this type can be produced analogously.

According to a second process according to the invention, compounds of Formula I in which R_3 is hydrogen, or alkali-metal or alkaline-earth-metal salts of free carboxylic acids falling under Formula I, are obtained by hydrolysing a functional derivative of a carboxylic acid of Formula I, in which R_1, R_2 and X have the meaning there given, and, if desired, converting the resultant carboxylic acid of Formula I to an alkali-metal or alkaline-earth-metal salt.

Suitable as functional derivatives of such carboxylic acids are lower alkyl esters—which also fall under Formula I—in addition, other esters such as e.g. cyclohexyl, phenyl, or benzyl esters, as well as nitriles, amides and lower imidoalkyl esters.

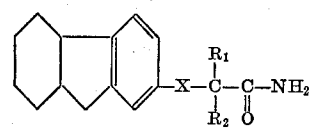
The hydrolysis is performed, for example, by heating in alkanoic or aqueous alkanolic alkali hydroxide solutions to temperatures between about 50° C. and the boiling temperature of the reaction medium employed. From the alkali-metal-salt solutions of acids of Formula I, which are first obtained, either the corresponding pure alkali metal salts can be obtained by concentration or evaporation and recrystallization, or first the carboxylic acid can be set free using an acid and then, if desired, converting these carboxylic acids into alkali metal or alkaline-earth-metal salts.

Functional derivatives of carboxylic acids which fall under Formula I, can also be hydrolysed in an acid medium, e.g. by boiling in 60 to 70% sulfuric acid or in a mixture of concentrated hydrochloric acid and glacial acetic acid, to the free carboxylic acid.

The lower alkyl esters of carboxylic acids of Formula I used as starting materials can be produced, e.g. by the first process. Analogously, other esters, e.g. phenyl esters, can be produced.

A second group of starting materials for the process according to the invention are nitriles of the following Formula VII. Examples of such nitriles are compounds which radicals X, R_1 and R_2 coincide with the groups which are named following Formula I. The production of these compounds will be discussed following the seventh process.

A third group of starting materials which may be used, are amides of Formula IIIa,



(IIIa)

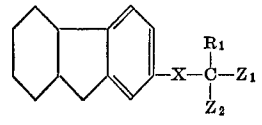
wherein X, R_1 and R_2 have the meaning given for Formula I.

Examples of amides of Formula IIIa which may be used in the process according to the invention, are compounds which groups are X, R_1 and R_2, coincide with the radicals listed following Formula I. Such amides can be obtained from the nitriles of Formula VII by partial hydrolysis, e.g. in 80% sulfuric acid or by means of hydrogen peroxide in the presence of sodium hydroxide.

The production of the imidoalkyl esters of the following Formula VIII, under which a fourth group of starting materials fall, will be explained following the seventh process. Examples of such starting materials are compounds which radicals X, R_1, R_2 and R'_3 coincide with the groups which are listed following Formula I and Formula VIII.

Instead of using either lower alkyl esters falling under Formula I, nitriles of Formula VII, or amides of Formula IIIa, mixtures of such compounds with the free carboxylic acids which fall under Formula I, may be employed for the hydrolysis according to the invention. A mixture of amides of Formula IIIa and of carboxylic acids falling under Formula I is obtained, e.g. when a substituted 4b,5,6,7,8,8a,-hexahydrofluoren - 2 - yloxy-cyano-acetic acid alkyl ester falling under Formula IV is refluxed for several hours in hydrous ethanol with substantially more than the equimolar amount of potassium hydroxide and then the mixture which is isolated after acidification, containing the desired carboxylic acid and its amide together with the corresponding, substituted 4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy-malonamic acid, is heated, for example, for a short time in xylene to decarboxylate the malonamic acid.

According to a third process of the invention, carboxylic acids falling under Formula I and whose radical R_2 is hydrogen as well as the salts of such carboxylic acids, are produced by heating a compound of Formula IV,

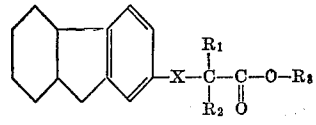


(IV)

wherein

Z_1 and Z_2, independently of each other, are lower alkoxycarbonyl or cyano, and

R_1 and X have the meaning given for Formula I,



(I)

Z_1 and Z_2 is completely hydrolysed and the other is reunder hydrolysing conditions until one of the groups placed by hydrogen, and if desired, converting a resultant carboxylic acid of Formula I into an alkali-metal or alkaline-earth-metal salt.

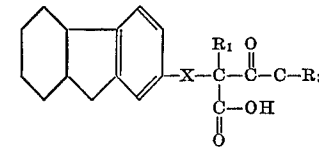
According to one embodiment of the process, a compound of Formula IV is heated in an aqueous mineral acid, e.g. 70 to 80% sulfuric acid or concentrated hydrochloric acid and, if desired, the obtained carboxylic acid is converted into an alkali or alkaline earth metal salt. If necessary, the reaction is carried out in the presence of an inert, water miscible, organic solvent which enhances the solubility of the starting material in the reaction medium. Such like solvents are, for example, low alkanols, tetrahydrofurane or glacial acetic acid.

According to a second embodiment of the process, a compound of Formula IV is heated with alkanolic alkali hydroxide, for example in a solution of potassium hydroxide in methanol, optionally in the presence of water, and if desired, the obtained alkali-metal salts of the carboxylic acids obtained are converted into the free acids. When the process is carried out in alkaline reaction medium, sometimes mixtures are obtained consisting of the desired final product and incompletely hydrolysed and incompletely decarboxylated intermediates. These mixtures can be converted into uniform final products by heating in an aqueous mineral acid, optionally in the presence of an organic solvent, which is miscible with water according to the first embodiment of the process.

The process is performed by heating the substituted malonic acid dialkylesters of Formula IV under reflux in the aforementioned reaction mediums for several hours. The malonic acid dinitriles and cyanoacetic acid esters of Formula IV are reacted analogously. These compounds, however, as a rule, need more severe reaction conditions, i.e. higher temperautres and longer reaction times. Higher temperatures can be obtained by carrying out the process in a closed reaction vessel at elevated pressure.

The substituted (4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)- and (4b,5,6,7,8,8a-hexahydro-fluoren - 2 - ylthio)-malonic acid diethyl esters, -cyanoacetic acid alkyl esters and -malonitriles falling under Formula IV, are new compounds. They are obtained, for example, analogously to the first process starting from 4b,5,6,7,8,8a-hexahydrofluoren-2-ol or -2-thiol, the production of which has been elucidated following the first process. These compounds are converted, e.g. with sodium ethylate in ethanol into the sodium derivatives and reacted with bromomalonic acid dialkyl esters, bromocyano-acetic acid alkyl esters or bromomalonitriles substituted by R_1. Of the bromo compounds mentioned, some are known, e.g. the bromobutylmalonic acid diethyl esters [cf. A. W. Dox and L. Yoder, J. Am. Chem. Soc. 44, 1578–1581 (1922)]. Other compounds of this type can be produced analogously.

A fourth process according to the invention for the production of compounds of Formula I in which R_2 is hydrogen and the alkali-metal and alkaline-earth-metal salts of carboxylic acids falling under Formula I, consists in heating a compound of Formula V,



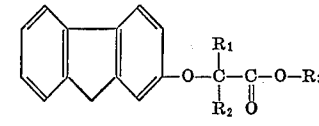
(V)

wherein R_1, R_3 and X have the meaning given for Formula I, or an acid alkali-metal or alkaline-earth-metal salt of a dicarboxylic acid falling under Formula V, until an equimolar amount of carbon dioxide is split-off and, if desired, converting a resultant carboxylic acid of Formula I into an alkali-metal or alkaline-earth-metal salt.

The thermal decomposition is performed at temperatures between about 50° and 200° C. until the development of carbon dioxide has been completed. Optionally, the decarboxylation is accelerated by the addition of catalysts such as powdered copper, or of organic bases such as quinoline.

The dicarboxylic acids falling under Formula V (R_3=hydrogen) are obtained, for example, by hydrolysis of their lower alkyl esters falling under Formula IV in aqueous/ethanolic potassium hydroxide solution. In place of pure dicarboxylic acids or dicarboxylic acid monoalkyl esters of Formula V, crude hydrolysis products of dicarboxylic acid dialkyl esters of Formula IV, which besides a compound of Formula V may already contain a certain portion of the end porduct, can also be used for the decarboxylation according to the invention.

According to a fifth process of the invention, compounds of Formula I, in which X is oxygen, are obtained by reducing a compound of Formula VI,



(VI)

wherein

R_1' is alkyl having at most 10 carbon atoms.

and R_2 and R_3 have the meaning given for Formula Ia, I and, if desired, converting a resultant carboxylic acid of Formula I into an alkali-metal or alkaline-earth-metal salt.

The reduction is preferably performed by hydrogenation in the presence of a catalyst in a solvent. Suitable catalysts are metals of the eighth group of the periodic

system, e.g. Raney nickel, Raney cobalt, noble metal catalysts, e.g. ruthenium, rhodium, platinum and, in particular, palladium. It is advantageous to employ the catalysts on carriers, e.g. on charcoal, aluminum oxide or barium sulfate. Suitable solvents are, e.g. lower alkanols such as methanol, ethanol or isopropanol, ether-type liquids such as tetrahydrofuran or, in particular, dioxane, carboxylic acid ethyl esters such as acetic acid ethyl ester, water, and for the noble metal catalysts also carboxylic acids such as glacial acetic acid. When Raney catalysts are used, at least 1 molar equivalent of an alkali hydroxide, e.g. sodium hydroxide, is added to the reaction solution in the case where R_3 is hydrogen. The hydrogenation can be performed at a temperature of about 20° to 150° C., and under pressure of 1 to 200 atmospheres, and is interrupted after 3 molar equivalents of hydrogen have been taken up.

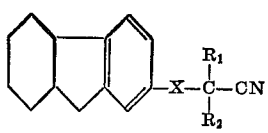
According to a sixth process of the invention, carboxylic acid esters of Formula I in which R_3 represents a lower alkyl group, are produced by converting a carboxylic acid falling under Formula I, into a lower alkyl ester.

For example, the carboxylic acid is reacted according to the invention, in the presence of an agent splitting-off water with a lower alkanol, e.g. methanol, ethanol, propanol or isopropanol. Suitable as agent which splits-off water are, e.g., hydrogen chloride, sulfuric acid, o- or p-toluene sulfonic acid or dicyclohexylcarbodiimide. In addition, a carboxylic acid can be reacted according to the invention with a diazoalkane, in particular with diazomethane.

According to a modification of the esterification, the carboxylic acid falling under Formula I, can first be converted into a reactive functional derivative and this can then be reacted with a lower alkanol.

For example, from the carboxylic acid with thionyl chloride or oxalyl chloride, preferably in the presence of an acid-binding agent such as pyridine, the corresponding carbonyl chloride can be produced, and the carbonyl chloride obtained can be converted with a lower alkanol into the corresponding alkyl ester. According to another modification of the esterification, the carboxylic acid can be first converted into a metal salt, in particular an alkali metal salt such as sodium or potassium salt, or into a silver or lead salt, and then the salt obtained is reacted with a reactive ester of a lower alkanol. Suitable reactive esters of lower alkanols are, e.g. alkyl halides such as methyl, ethyl, propyl or isopropyl chloride or the corresponding bromides, furthermore methyl or ethyl esters of sulfonic acids, e.g. of methane sulfonic acid or of o- or p-toluene sulfonic acid, and esters of sulfuric acid, e.g. dimethyl or diethyl sulfate. The reaction is optionally performed in an organic solvent, e.g. in a hydrocarbon such as benzene or toluene, or in an ether-type liquid such as ether, tetrahydrofuran or dioxane, and completed by heating.

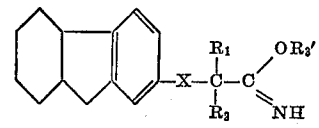
According to a seventh process of the invention, carboxylic acids of Formula I in which R_3 represents a lower alkyl group, are produced by reacting a nitrile of Formula VII



(VIII)

wherein X, R_1 and R_2 have the meanings given for Formula I, in the presence of water and a mineral acid with a low alkanol.

According to one embodiment of the process, a lower alkanol can be added to a nitrile of Formula IV, to obtain a salt of the corresponding imidoalkylester of Formula VIII,



(VIII)

wherein

R_3' is low alkyl, and R_1 and R_2 have the meanings given under Formula I, and hydrolysing that imidoalkylester salt to obtain the desired ester of Formula I. The conversion of the nitriles of Formula VII into imidoalkylester salts is advantageously performed in a solvent such as excess alkanol, ether or chloroform, at temperatures between 0° and 10° C. The subsequent hydrolysis of the imidoalkylester salt can be performed in water or in a mixture of water and a lower alkanol corresponding to the imidoalkylester at temperatures between 20° and 50° C.

According to another embodiment of the process, a nitrile of Formula VII is refluxed in the presence of the equimolar amount of sulfuric acid and water with an excess of a low alkanol. The final product is separated by diluting the reaction mixture with water and taking up the ester with an organic solvent such as ether or chloroform.

According to a third embodiment of the process, a nitrile of Formula VII is treated with water to obtain the corresponding amide, which is subjected to alcoholysis to obtain the desired ester. The conversion of the nitrile into the amide is carried out, for example, in 80 to 95% sulfuric acid at room temperature or slightly elevated temperature.

To the obtained solution of the amide in sulfuric acid, excess alkanol is added, and the whole is heated under reflux. The final products are precipitated by dilution of the reaction mixture with water.

As lower alkanol in the process according to the invention, there is employed, e.g., methanol, ethanol, propanol or isopropanol.

Examples of starting materials of Formula VII are those nitriles whose radicals X, R_1 and R_2 coincide with the groups listed following Formula I. These nitriles can be obtained, e.g., analogously to the first process, when 4b,5,6,7,8,8a-hexahydrofluoren-2-ol or -2-thiol is used as starting material, the production of which was elucidated following the first process, this compound is converted by means of sodium ethylate in methanol into the sodium derivative, and this sodium derivative is reacted with 2-halogeno-alkane nitriles, or α-halogeno-hydrocinnamonitriles.

The compounds of Formula I contain three asymmetric carbon atoms. Accordingly, eight enantiomeric forms and four racemates are possible. In the compounds obtained by catalytic hydrogenation, the hydrogen atoms at carbon atoms 4b and 8 are in cis-position. In this case only four enantiomeric forms and two racemates are possible. This occurrence of stereoisomers can lead to difficulties in the isolation of the final products, inasmuch as the racemates formed show different tendency to crystallisation. For this reason, the formation of non-crystallising racemates results in a decrease in the yield of final products. In other cases, a mixture of two crystalline racemates can be obtained, which results in a melting point lying between the melting points of the pure components. The non-crystallisable racemates of the carboxylic acids embraced by Formula I can be transformed to crystallisable racemates by esterifying the acids, epimerising the esters by heating in a solvent in the presence of strong bases and subsequently reconverting the esters to the carboxylic acids by hydrolysis. The amount of crystallisable racemate thus obtained depends on the position

of the equilibrium of epimerisation. If necessary, the treatment can be repeated.

Examples of suitable alkali-metal and alkaline-earth-metal salts of carboxylic acids falling under Formula I are their sodium, potassium, lithium, magnesium and calcium salts. These salts are produced, for example, by combining acid and base in a suitable solvent, such as methanol, ethanol, acetone/water. Salts which have been formed which are relatively difficultly soluble, can be isolated by filtration, those which are readily soluble by evaporation of the solvent. Furthermore, salts which are relatively difficultly soluble in the solvent used, may also be produced by double reaction of another salt of the acid with the base or a suitable salt thereof.

The compounds of Formula I and the alkali-metal and alkaline-earth-metal salts of the free carboxylic acids falling under this formula, may be administered, e.g., orally or rectally. The daily dosages range from 0.5–10 mg./kg. for warm-blooded animals. Suitable dosage unit forms, such as dragées, tablets, suppositories and capsules contain preferably 10–250 mg., e.g. 50 or 100 mg. of a compound of Formula I or of an alkali-metal or alkaline-earth-metal salt of a free carboxylic acid falling under Formula I, as active ingredient.

Dosage units for oral administration preferably contain between 10 and 90% of a compound of Formula I. They are produced by combining the active ingredient, 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, for example, with concentrated sugar solutions which can also contain, e.g., gum arabic, talcum and/or titanium dioxide, or with a lacquer dissolved in easily volatile organic solvents or mixtures of solvents. Dyestuffs can be added to these coatings, e.g. to indicate various dosages of active substance.

Other suitable dosage units for oral administration are hard gelatine capsules and also soft closed capsules made of gelatine and a softener such as glycerine. The hard gelatine capsules preferably contain the active substance 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 metabisulfite ($Na_2S_2O_5$) or ascorbic acid. In soft capsules, the active substance is preferably dissolved or suspended in suitable liquids, such as liquid polyethylene glycols.

Suitable dosage units for rectal administration are, for example, suppositories, consisting of a combination of an active substance with a suppository foundation substance. Suitable suppository foundation substances are, e.g., natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. Furthermore, gelatine rectal capsules are also suitable, which consist of a combination of the active ingredient and a foundation substance. Suitable as foundation substance are, e.g., liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

The following prescriptions illustrate more in detail the production of tablets, dragées, suppositories and capsules:

(a) 100 g. of 2-(4b,5,6,7,8,8a-hexahydro-fluoren-2-yl-oxy)-heptanoic acid or 2-(4b,5,6,7,8,8a-hexahydro-fluoren-2-ylthio)-heptanoic acid are mixed with 550 g. of lactose and 292 g. of potato starch. The mixture is moistened with an alcoholic solution of 8 g. of gelatine and granulated through a sieve. After the granulate has been dried, 60 g. of potato starch, 60 g. of talcum and 10 g. of magnesium stearate and 20 g. of highly dispersed silicon dioxide are mixed in and the mixture is pressed into 10,000 tablets, each weighing 200 mg. and each containing 100 mg. of active substance. Optionally, the tablets can be provided with grooves for more precise adjustment of the dosage amount.

(b) 100 g. of 2-(4b,5,6,7,8,8a-hexahydro-fluoren-2-yl-oxy)-heptanoic acid are 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 about 70 ml. of isopropyl alcohol and is then granulated through a sieve III (Ph. Helv. V). The granulate is dried for about 14 hours and is afterwards put through a sieve II–IIIa. It is then mixed with 16 g. of maize starch, 16 g. of talcum and 2 g. of magnesium stearate and pressed into 1000 dragée cores. These are coated with a concentrated syrup made from 2 g. of lacca, 7.5 g. of gum arabic, 0.15 g. of dyestuff, 2 g. of highly dispersed silicon dioxide, 25 g. of talcum and 53.35 g. of sugar, and then dried. The dragées obtained each weigh 260 mg. and each contain 100 ml. of active substance.

(c) A suppository mixture is prepared from 10.0 g. of 2-(4b,5,6,7,8,8a-hexahydro-fluoren - 2 - yloxy)-heptanoic acid or 2-(4b,5,6,7,8,8a-hexahydro-fluoren-2-ylthio)-heptanoic acid and 163.5 g. of *Adeps solidus* and from the mixture there are poured 100 suppositories each containing 100 mg. of active substance.

(d) To produce 1000 capsules each containing 75 mg. of active substance, 75 g. of 2-(4b,5,6,7,8,8a-hexahydro-fluoren-2-yloxy)-heptanoic acid or 2-(4b,5,6,7,8,8a-hexahydro-fluoren-2-ylthio)-heptanoic acid are mixed with 198.0 g. of lactose, the mixture is evenly moistened with an aqueous solution of 20 g. of gelatine and granulated through a suitable sieve (e.g. sieve III acording to Ph. Helv. V). The granulate is mixed with 10.0 g. of dried maize starch and 15.0 g. of talcum and evenly filled into 1000 hard gelatine capsules of size 1.

The following examples illustrate more in detail the production of the compounds of general Formula I and salts thereof; they do not, however, in any way limit the scope of the invention. The temperatures are given in degrees centigrade.

Example 1

(a) While excluding atmospheric moisture, 0.5 g. (0.0217 mol) of sodium is dissolved in 50 ml. of absolute ethanol, the solution is treated with stirring with 3.95 g. (0.0217 mol) of 4b,5,6,7,8,8a-hexahydro-fluoren-2-ol, and 5.0 g. (0.021 mol) of 2-bromo-heptanoic acid ethyl ester is added dropwise at 20° thereto. The reaction mixture is refluxed for 6 hours and then evaporated in vacuum. The residue is distributed between ether and water. The ethereal phase is washed with water, dried over sodium sulfate and concentrated by evaporation. The residue is chromatographed on a column of 210 g. of silica gel [(Merck®, granular size 0.05–0.2 mm.) by the "pass-through" method with benzene/ethyl acetate (19:1)]. The combined fractions of the crude product are concentrated by evaporation and the residual oil is freed from excess 2-bromo-heptanoic acid ethyl ester under vacuum at 100° and 0.1 mm. Hg. 5.8 g. of 2-(4b,5,6,7,8,8a-hexahydro-fluoren-2-yloxy)-heptanoic ethyl ester, n_D^{20}: 1.5121, is obtained, yield 80.6% of theory.

The starting product, 4b,5,6,7,8,8a-hexahydro-fluoren-2-ol, is produced as follows:

(b) A solution of 33.5 g. (0.155 mol) of 2-(m-methoxy-benzylidene)-cyclohexanone [cf. R. Baltzli et al., J. Am. Chem. Soc. 77, 624 (1955)] is hydrogenated with hydrogen in the presence of 3 g. of Raney nickel in 350 ml. of absolute ethanol at room temperature and normal pressure. After 1 mol of hydrogen has been taken up, the catalyst is removed from the reaction solution by filtration and the solvent is concentrated by evaporation in vacuum. The residue, 2-(m-methoxybenzyl)-cyclohexanone, is an oil (n_D^{20}: 1.5374) which can be used directly in the next step.

(c) A solution of 9.7 g. (0.0444 mol) of the compound obtained according to (b) is cooled in an ice bath. Then

117 ml. (2.1 mol) of concentrated sulfuric acid are added dropwise with stirring during 20 minutes at 0–5°, stirring is continued for another hour and the orange-colored reaction mixture is poured onto ice. The mixture is then extracted with ether, the ethereal solution is washed with 2 N sodium carbonate solution and water, dried over sodium sulfate and concentrated by evaporation. The residue which crystallizes is recrystallized several times from ethanol. 6.5 g. of pure 2-methoxy-5,6,7,8-tetrahydrofluorene, M.P. 59°, which is unstable at room temperature is obtained; (yield 73%).

(d) 13.5 g. (0.067 mol) of the compound obtained according to (c) are dissolved in 200 ml. of absolute ethanol, and a slurry of 1.5 g. of (5%) palladium on carbon in ethanol is added to the solution. The solution is hydrogenated at room temperature and atmospheric pressure until 1 mol of hydrogen is taken up; the catalyst is then removed by filtration and the solvent is concentrated by evaporation in vacuum. 12.8 g. of a colourless oil which solidifies as crystals upon standing in the cold, is obtained. Recrystallization from ethanol yields 11.7 g. of pure 2-methoxy-4b,5,6,7,8,8a-hexahydro-fluorene, M.P. 29°. (Yield 85.8% of theory).

(e) A solution of 10.9 g. (0.054 mol) of the compound obtained according to (d) is refluxed in 50 ml. of glacial acetic acid and 50 ml. of 57% aqueous hydroiodic acid (d:1.70) for one hour. The reaction mixture is then poured onto ice and extracted with ether. The organic phase is washed with 2 N sodium carbonate solution and water, dried over sodium sulfate and concentrated by evaporation. The residue is recrystallized from benzine to yield 7.5 g. (73.9% of theory) of 4b,5,6,7,8,8a-hexahydrofluoren-2-ol, M.P. 92–94°.

(a') The following compounds are obtained analogously to part (a) above.

(i) from 5.64 g. (0.03 mol) of 4b,5,6,7,8,8a-hexahydrofluoren-2-ol and 8.10 g. (0.0315 mol) of α-bromo-hydrocinnamic acid ethyl ester, 2.85 g., 26.1% of theory, of α- (4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-hydrocinnamic acid ethylester, n_D^{20}: 1.5540, and

(ii) form 1.05 g. (7.95 m.mol)4b,5,6,7,8,8a-hexahydrofluoren-2-ol and 2.13 g. (8.47 m.mol)2-bromo-heptanoic acid propyl ester, 2.29 g. (80.1% theoretical) of 2-(4b,5,6,7,8,8a-hexahydrofluoren - 2 -yloxy)-heptanoic acid-n-propyl ester, n_D^{20}=1.5093.

Example 2

3.76 g. (0.02 mol) of 4b,5,6,7,8,8a-hexahydro-fluoren-2-ol are added to a solution of 0.46 g. (0.02 mol) of sodium in 25 ml. of absolute ethanol. With stirring and exclusion of atmospheric moisture, an ethanolic solution of the sodium salt of 2-bromoheptanoic acid, produced from 0.46 g. (0.02 mol) of sodium in 75 ml. of absolute ethanol and 4.2 g. (0.02 mol) of 2-bromoheptanoic acid, is added dropwise to the first mixture. The reaction mixture is refluxed for 6 hours, evaporated in vacuum, and the residue is taken up in water. The crude carboxylic acid is precipitated with concentrated hydrochloric acid and extracted with ether. The ethereal solution is washed with water, dried over sodium sulfate and concentrated by evaporation. The residue is purified chromatographically according to the "pass-through" method on a column of neutral silica gel (Merck® granular size 0.05–0.2 nm.). Benzene:glacial acetic acid (85:15) is used as eluant. The fractions containing the crude product are concentrated by evaporation and recrystallized from pentane. The resultant 2 - (4b,5,6,7,8,8a-hexahydro-fluoren - 2 - yloxy)-heptanoic acid melts at 81–82°.

Example 3

(a) Under nitrogen, excluding atmospheric moisture and carbon dioxide, there is added with stirring 2.04 g. (0.01 mol) of 4b,5,6,7,8,8a-hexahydro-fluorene-2-thiol to a solution of 0.25 g. (0.011 mol) of sodium in 40 ml. of absolute ethanol. A solution of the sodium salt of 4b,5,6,7,8,8a-hexahydro-fluorene-2-thiol is obtained. While stirring is continued, 2,6 g. (0.011 mol) of 2-bromo-heptanoic acid ethyl ester is added dropwise to this solution. The reaction mixture is refluxed for 2 hours, cooled, the precipitated sodium bromide is removed by filtration under suction and washed with ethanol. The ethanolic solution is then concentrated by evaporation in vacuum. The oily residue is purified by elution chromatography on a column of neutral silica gel (Merk®, granular size 0.05–0.2 mm.) with benzene as eluant. The combined fractions of the crude product are evaporated in vacuum. After drying in high vacuum. 3.18 g. (88.3% of theory) of pure 2 - (4b,5,6,7,8,8a - hexahydro-fluoren - 2 - ylthio)-heptanoic acid ethyl ester are obtained as a light yellow-coloured oil, n_D^{20}:1.5360.

The starting material, 4b,5,6,7,8,8a-hexahydro-fluorene-2-thiol, is obtained as follows:

(b) While stirring, cooling with ice and excluding atmospheric moisture, 25.50 g. (0.25 mol) of 98% sulfuric acid and 52.0 g. (0.5 mol) of acetic acid anhydride are mixed, and 43.0 g. (0.25 mol) of 1,2,3,4,4a,9a-hexahydrofluorene are added at room temperature. The reaction mixture is stirred for one hour at room temperature and then 2 hours at 50°, poured onto ice, made alkaline with concentrated sodium hydroxide solution and extracted with ether. The ether extract is concentrated by evaporation and 17.7 g. of unreacted 1,2,3,4,4a,9a - hexahydrofluorene is recovered as residue. The aqueous phase is acidified with concentrated hydrochloric acid and concentrated by evaporation in vacuum. The residue, which contains besides inorganic salts mainly a mixture of 4b,5,6,7,8,8a-hexahydro-fluorene-2-sulfonic acid and 4b,5,6,7,8,8a-hexahydro-fluorene-3-sulfonic acid, is extracted with absolute ethanol and the suspended salts of the ethanol solution are separated. The ethanolic extract is concentrated by evaporation in vacuum. The residue, which besides the sulfonic acid mixture contains inorganic salts, is used as crude product.

(c) 38.0 g. of the residue obtained according to (b) are added in portions, while stirring and excluding atmospheric moisture, to 170 ml. of phosphorus oxychloride which has been heated to 80°. Stirring of the mixture is continued for 3 hours at 90° obtaining a green reaction solution. This solution is cooled and poured onto water; the mixture is extracted with ether. The ether extract is dried over magnesium sulfate and concentrated by evaporation in vacuum. The residue, a greenish oil is purified by means of elution chromatography on a column of neutral silica gel (Merck®, granular size 0.05–0.2 mm.). Benzene is used as eluant. The combined fractions of the crude product are concentrated by evaporation in vacuum. The residue, which consists of about equal parts of 4b,5,6,7,8,8a-hexahydro-fluorene-2-sulfonyl chloride and 4b,5,6,7,8,8a-hexahydro-fluorene-3-sulfonyl chloride, is recrystallized twice from glacial acetic acid. 6.7 g. of 4b,5,6,7,8,8a-hexahydro-fluorene-2-sulfonyl chloride, M.P. 93–94°, is obtained; yield 17% calculated on 25.3 g. of the 1,2,3,4,4a,9a - hexahydro-fluorene reacted according to (b).

(d) 2.7 g. (0.07 mol) of lithium aluminum hydride in 100 ml. of absolute ether are refluxed with stirring and exclusion of moisture, and during 20 minutes a solution of 5.4 g. (0.02 mol) of 4b,5,6,7,8,8a-hexahydro-fluorene-2-sulfonyl chloride in 100 ml. of ether is added dropwise thereto. The mixture is subsequently refluxed for 2 hours, cooled, carefully treated with 7 ml. of ethyl acetate and 84 ml. of 2 N sulfuric acid, and extracted with ether. The ether extract is washed with water, dried over magnesium sulfate and concentrated by evaporation. 3.8 g. (93.1% of theory) of pure 4b,5,6,7,8,8a-hexahydro-fluorene-2-thiol are obtained as a yellow oil, n_D^{20}:1.5996.

Example 4

The following end products are obtained analogously to Example 3(a):

(a) From 2.04 g. (0.01 mol) of 4b,5,6,7,8,8a-hexahydro-fluorene-2-thiol and 2.0 g. (0.011 mol) of 2-bromo-propionic acid ethyl ester, 2.55 g., 83.8% of theory, of 2-(4b,5,6,7,8,7a - hexahydro-fluoren - 2-ylthio)-propionic acid ethyl ester, n_D^{22}:1.5522;

(b) From 2.04 g. (0.01 mol) of 4b,5,6,7,8,8a-hexahydro-fluorene-2-thiol and 2.15 g. (0.011 mol) of 2-bromo-2-methyl-propionic acid ethyl ester, 2.75 g., 86.5% of theory, of 2-(4b,5,6,7,8,8a-hexahydro-fluoren-2-ylthio)-2-methyl-propionic acid ethyl ester, n_D^{20}:1.5480; and

(c) From 1.5 g. of 4b,5,6,7,8,8a-hexahydro-fluorene-2-thiol and 2.4 g. of 2-bromo-dodecanoic acid ethyl ester, 2.8 g., 88.6% of theory, of 2-(4b,5,6,7,8,8a-hexahydro-fluoren-2-ylthio)-dodecanoic acid ethyl ester, n_D^{20}:1.5200.

Example 5

(a) A solution of 1.25 g. (0.022 mol) of potassium hydroxide in 5 ml. of water is added to a solution of 5.5 g. (0.0159 mol) of 2-(4b,5,6,7,8,8a - hexahydro-fluoren-2-yloxy)-heptanoic acid ethyl ester in 80 ml. of methanol. The mixture is refluxed for 30 minutes and concentrated by evaporation in vacuum. The residue is distributed between water and ether. The aqueous phase is acidified with 2 N hydrochloric acid and the crude carboxylic acid which precipitates is extracted with ether. The ether extract is washed with water, dried over sodium sulfate and concentrated by evaporation. The crude product is recrystallized from pentane; the 2 - (4b,5,6,7,8,8a - hexahydro-fluoren-2-yloxy)-heptanoic acid obtained then melts at 81–82°.

(b) Analogously are obtained:

From 2.25 g. (0.00617 mol) of α-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-hydrocinnamic acid ethyl - ester, 1.57 g., 75.7% of theory, of α-(4b,5,6,7,8,8a-hexahydro-fluoren-2-yloxy)-hydrocinnamic acid, M.P. 113–114° (from pentane).

From 1.50 g. (0.0052 mol) of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-propionic acid ethyl ester, 1.23 g., 90.8% of theory, of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)propionic acid, M.P. 142–145° (from hexane).

From 1.12 g. (0.00338 mol) 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid methyl ester, 0.28 g., 26.2% of theory, of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid, M.P. 81–82° (from pentane).

From 3.58 g. (0.01 mol) of 2-(4b,5,6,7,8,8a-hexahydro-fluoren-2-yloxy)heptanoic acid-n-propyl ester, 0.91 g., 28.8% of theory, of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid, M.P. 81–82° (from pentane).

Example 6

2.7 g. (0.0075 mol) of 2-(4b,5,6,7,8,8a-hexahydro-fluoren-2-ylthio)-heptanoic acid ethyl ester are refluxed for 3 hours in a solution of 2.2 g. (0.039 mol) of potassium hydroxide in 45 ml. of methanol and 5 ml. of water. The reaction mixture is then concentrated by evaporation, the residue is suspended in a little water and the suspension is acidified with concentrated hydrochloric acid. The oil which precipitates is extracted with chloroform. The chloroform extract is washed with water, dried over magnesium sulfate and evaporated. The residue is purified on a column of neutral silica gel (Merck®, granular size 0.05–0.2 mm.) by the "pass-through" method. Benzene:glacial acetic acid (9:1) is used as eluant. The fractions containing the crude product are concentrated by evaporation. The residual oil is taken up in ether, the ethereal solution is washed with water to remove the acetic acid and then concentrated by evaportaion. After drying in high vacuum, 2.05 g. (83% of theory) of 2-(4b,5,6,7,8,8a-hexahydro-fluoren-2-ylthio)-heptanoic acid are obtained as a yellow oil, n_D^{20}: 1.5538.

Example 7

The following end products are obtained analogously to Example 6:

(a) From 2.4 g. (0.008 mol) of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-ylthio)-propionic acid ethyl ester, 2.1 g. 96.4% of theory, of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-ylthio)-propionic acid, n_D^{20}: 1.5765;

(b) From 2.65 g. (0.008 mol) of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-ylthio)-2-methyl-propionic acid ethyl ester, 2.35 g., 96.8% of theory, of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-ylthio)-2-methyl - propionic acid, n_D^{20}: 1.5660; and

(c) From 2.7 g. of 2-(4b,5,6,7,8,8a-hexahydro-fluoren-2-ylthio)-dodecanoic acid ethyl ester, 2.35 g., 93.2% of theory, of 2 - (4b,5,6,7,8,8a-hexahydrofluoren-2-ylthio)-dodecanoic acid, n_D^{20}: 1.5366.

Example 8

2.5 g. (0.00725 mol) of 2-(4b,5,6,7,8,8a-hydrohexafluoren-2-yloxy)-heptanaoic acid ethyl ester are dissolved in 25 ml. of glacial acetic acid and after addition of 5 ml. of 5 N sulphuric acid the whole is refluxed for 2.5 hours. After cooling to room temperature, the reaction mixture is evaporated in vacuo and the residue is distributed between water and ether. The ethereal extract is washed with water, dried over sodium sulphate and the ether is evaporated. The crude acid obtained is purified by column chromatography using silica gel (Merck; grain size 0.05–0.2 mm.) as solid phase and benzene:ethyl acetate=9:1 and benzene; glacial acetic acid=50:1 as eluent. Thus 0.67 g., 29.2% of theory, of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid, M.P. 81–82° are obtained.

Example 9

To a solution of 1.78 g. (0.006 mol) of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid nitrile in 60 ml. of ethanol a solution of 1.80 g. of potassium hydroxide in 12 ml. of water is added and the whole is refluxed for 24 hours. Then the reaction mixture is evaporated close upon dryness and the residue is taken up with water. The aqueous solution is extracted with ether and subsequently acidified with 2 N hydrochloric acid and the precipitated product is taken up with ether. The ethereal solution containing the desired acid is washed with water until neutral, dried over sodium sulphate and evaporated in vacuo. The remaining oil can be crystallised from pentane. 0.29 g., 15.3% of theory, of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid, M.P. 81–82°, are obtained.

The satrting material, the 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid nitrile can be obtained in the following manner:

To 140 ml. of dry dimethyl formamide 1.68 g. (0.035 mol) of a 50% sodium hydride dispersion in mineral oil and subsequently 6.59 g. (0.035 mol) of 4b,5,6,7,8,8a-hexahydrofluoren-2-ol are added and the obtained mixture is heated to 35°. Then, while stirring and keeping the mixture under an atmosphere of nitrogen 7.6 g. (0.04 mol) of 2-bromo-heptanoic acid nitrile are added dropwise. After heating to 60° for 3 hours, the temperature is raised to 70° for 1 hour and subsequently the solvent is evaporated in vacuo. The oily residue is distributed between water and ether. The ethereal phase is washed at first with 1 N sodium hydroxide and then with water, dried over sodium sulphate and the ether is evaporated. The crude nitrile thus obtained is purified by column chromatography using silica gel (Merck; grain size 0.05–0.2 mm.) and benzene. 6.22 g., 59.8% of theory, of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid nitrile n_D^{21}: 1.5239 are obtained.

By elution with benzene:ethyl acetate=9:1 2.2 g. of 4b,5,6,7,8,8a-hexahydrofluoren-2-ol are recovered.

Example 10

1.485 g. (0.005 mol) of 2-(4b,5,6,7,8,8a-hexahydroflouren-2-yloxy)-heptanoic acid nitrile are dissolved in 50 ml. of chloroform and 5 ml. of absolute methanol. The solution is saturated at a temperature of 0–5° with dry

hydrogen chloride gas, left standing overnight and evaporated to dryness in vacuo at a temperature of 30–35°. The residue is taken up with 10 ml. of dioxane and 2 ml. of water and the solution is stirred at a temperature of 40° for 5 hours. Then 2.0 g. of potassium hydroxide and 10 ml. of methanol are added and the whole is refluxed for 2 hours. After evaporation of the solvent the residue is distributed between 2 N hydrochloric acid and ether, the ethereal phase is washed with water until neutral, dried over sodium sulphate and the ether is evaporated. After purification of the crude reaction product by column chromatography using silica gel (Merck; grain size 0.05–0.2 mm.) and benzene:ethyl acetate=9:1 and benzene glacial acetic acid=50:1, 0.22 g. 13.9% of theory of 2-(4b,5,6,7,8,8a-hexahydrofluoren - 2 - yloxy)-heptanoic acid, M.P. 81–82° (from pentane) are obtained.

Example 11

1.26 g. (0.004 mol) of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid amide are dissolved in 30 ml. of ethanol. After addition of a solution of 4.0 g. of potassium hydroxide in 30 ml. of water, the whole is refluxed for 24 hours. Then the ethanol is evaporated in vacuo. The remaining solution is acidified with 2 N hydrochloric acid and extracted with ether. The ether extract is washed with water, dried over sodium sulphate and the ether is distilled off in vacuo. The oily residue is purified by column chromatography using silica gel (Merck; grain size 0.005–0.2 mm.). At first it is eluted with a mixture consisting of 9 parts of benzene and one part of ethyl acetate and then with a mixture consisting of 2 parts of benzene and one part of ethyl acetate, to the latter mixture being admixed at the same time 1% of glacial acetic acid. The product obtained by evaporation of the solvent from the fractions containing the desired acid is recrystallized from pentane. One obtains 0.27 g., 21.3% of theory, of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid, M.P. 81–82°.

The starting material, the 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid amide can be obtained in the following manner:

A solution of 1.10 g. (0.0037 mol) of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid nitrile in 40 ml. of absolute chloroform and 2 ml. of absolute methanol is cooled with ice and a stream of dry hydrogen chloride gas is passed through the solution until saturation is achieved, while the temperature is kept below +5°. The reaction mixture is stirred overnight at room temperature and then concentrated in vacuo. When the major part of the solvent is distilled off the oily residue is heated in vacuo to a temperature of 90° for 10 minutes. The crude product is purified by column chromatography using silica gel (Merck; grain size 0.05–0.2 mm.) and benzene:ethyl acetate=9:1 and the obtained 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid amide (0.92 g.) is recrystallized once from pentane. Thus, 0.75 g., 64.3% of theory, of pure amide, M.P. 96–101°, are obtained.

Example 12

To a stirred solution of 1.62 g. (0.00389 mol) of 4b,5,6,7,8,8a-hexahydroflouren-2-yloxy-n-pentyl-malonic acid diethyl ester in 22 ml. of glacial acetic acid 4.4 ml. of 5 N sulfuric acid are added and the whole is refluxed for 10 hours. Then the reaction mixture is concentrated in vacuo and the residue is distributed between ether and water. The ethereal phase is washed with water, dried over sodium sulphate and the ether is distilled off in vacuo. The oily residue is purified by column chromatography using silica gel (Merck; grain size 0.05–0.2 mm.) and benzene:ethyl acetate=9:1 and benzene:glacial acetic acid=50:1. The chromatographically purified product is recrystallized once from pentane. One obtains 0.32 g., 26% of theory, of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid, M.P. 81–82°.

Analogously are obtained from 2.09 g. (0.0043 mol) 4b,5,6,7,8,8a - hexahydrofluoren-2-yloxy-n-decyl-malonic acid diethyl ester 0.54 g., 32% of theory, 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-dodecanoic acid, M.P. 98–101° (from pentane).

The 4b,5,6,7,8,8a - hexahydrofluoren-2-yloxy-n-decyl-malonic acid diethyl ester used as starting material can be obtained in the following way:

To a solution of 0.245 g. (0.01064 mol) of sodium in 20 ml. of absolute ethanol 2.0 g. (0.01064 mol) of 4b,5,6,7,8,8a-hexahydrofluoren-2-ol are added. While passing nitrogen through the reaction vessel 4.03 g. (0.01064 mol) of bromo-n-decyl-malonic acid diethyl ester are added dropwise to this solution and the whole reaction mixture is refluxed for 4 hours. Then the solvent is distilled off in vacuo and after distributing the residue between water and ether, drying the ethereal phase with sodium sulphate and evaporating the ether in vacuo 5.2 g. of a brown oil are obtained which is purified by column chromatography using silica gel (Merck; grain size 0.05–0.2 mm.) and benzene. Yield: 2.44 g., 47.2% of theory, of pure 4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy-n-decyl-malonic acid diethyl ester, n_D^{20}: 1.4978.

Analogously are obtained from 1.50 g. (0.00798 mol) of 4b,5,6,7,8,8a-hexahydrofluoren-2-ol and 2.465 g. (0.00798 mol) of bromo-n-pentyl malonic acid diethyl ester 1.91 g., 57.5% of theory, of 4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy-n-pentyl-malonic acid diethyl ester, n_D^{20}: 1.5034.

Example 13

While passing nitrogen through the reaction vessel an aqueous solution of 2.7 g. of 86% potassium hydroxide in 18 ml. of water is added to a solution of 2.60 g. (0.006 mol) of 4b,5,6,7,8,8a-hexahydrofluoren-2-ylthio-n-pentyl-malonic acid diethyl ester in 90 ml. of ethanol and the whole is refluxed for 10 hours. Then the solvent is distilled off in vacuo and the residue is taken up in water. The aqueous solution is acidified with 2 N hydrochloric acid whereupon the crude 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-ylthio)-heptanoic acid precipitates. It is taken up with ether, the ethereal solution is washed with water, dried over sodium sulphate, the ether is distilled off in vacuo and the crude product thus obtained is purified by column chromatography using silica gel (Merck; grain size 0.05–0.2 mm.) and at first benzene and then benzene:glacial acetic acid=50:1. After evaporation of the solvent from the fraction containing the desired product 0.85 g., 42.5% of theory, of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-ylthio)-heptanoic acid are obtained as a pale oil; n_D^{20}: 1.5536.

The 4b,5,6,7,8,8a-hexahydro-2-ylthio-n-pentyl-malonic acid diethyl ester used as starting material can be prepared in the following manner:

While passing nitrogen through the reaction vessel a solution of 3.0 g. (0.0147 mol) of 4b,5,6,7,8,8a-hexahydrofluoren-2-thiol in 10 ml. of absolute ethanol is added to a solution of 0.338 g. (0.0147 mol) of sodium in 10 ml. of absolute ethanol at 0° and the whole mixture is stirred for 30 minutes at 0°. Then the ethanol is distilled off in vacuo and the residue is distributed between ether and water.

The ethereal phase is washed with water, dried over sodium sulphate and the ether is distilled off. The residue is purified by column chromatography using silica gel (Merck; grain sinze 0.05–0.2 mm.) as the stationary phase and benzene and benzene:glacial acetic acid=50:1 as eluents. One obtains 3.56 g., 52.8% of theory of pure 4b,5,6,7,8,8a - hexahydrofluoren-2-ylthio-n-pentyl-malonic acid diethyl ester, n_D^{20}: 1.5255.

Example 14

1.46 g. of crude 4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy-n-decyl-malonic acid are heated under nitrogen at 140° for 1 hour. The product obtained is purified by column chromatography using silica gel (Merck; grain

size 0.05–0.2 mm.) as the stationary phase and benzene and subsequently benzene:glacial acetic acid=9:1 as eluents. After evaporation of the solvent from the fractions containing the desired product and recrystallization from pentane 0.51 g., 38.7% of theory, of pure 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-dodecanoic acid, M.P. 99–101°, are obtained.

Analogously are obtained from 1.50 g. (0.00435 mol) of crude 4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy-n-pentyl malonic acid 0.25 g., 18.2% of theory, of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-ylory)-heptanoic and, M.P. 81–82° (from pentane).

The crude substituted malonic acids used as starting materials can be prepared in the following manner:

1.66 g. (0.0034 mol) 4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy-n-decyl-malonic acid diethylester are added to a solution of 0.50 g. (0.0125 mol) of sodium hydroxide in 35 ml. of methanol and 2 ml. of water and the whole is refluxed for 20 hours. Then the solvent is evaporated and the residue is taken up in water. The aqueous solution is extracted with ether and then acidified with 2 N hydrochloric acid, whereupon the desired acid precipitates in the form of an oil, which is taken up in ether. The crude 4b,5,6,7,8,8a - hexahydrofluoren - 2-yloxy-n-decyl-malonic acid obtained after drying the ethereal solution over sodium sulphate and evaporating off the ether is an oil which is used without further purification.

Analogously is obtained from 1.81 g. (0.00435 mole) 4b,5,6,7,8,8a - hexahydrofluoren-2-yloxy-n-pentyl-malonic acid diethylester the crude 4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy-n-pentyl-malonic acid as an oil.

Example 15

1.90 g. of crude 4b,5,6,7,8,8a - hexahydrofluoren-2-ylthio-n-pentyl-malonic acid are heated for 30 minutes at 140° and then purified by chromatography on silica gel (Merck; 0.05–0.2 mm.) using benzene and benzene:glacial acetic acid 50:1 as solvents for elution. 1.15 g. of pure 2 - (4b,5,6,7,8,8a - hexahydrofluoren - 2 - ylthio)-heptanoic acid are obtained in the form of a pale yellow oil, n_D^{20}:1.5534 (yield 53.4% of theoretical).

The starting material, 4b,5,6,7,8,8a-hexahydrofluoren-2-ylthio-n-pentyl-malonic acid is obtained as follows:

An aqueous solution of potassium hydroxide (2.8 g. KOH 86% in 20 ml. of water) is added, while stirring, to a solution of 2.80 g. (6.47 mmol) of 4b,5,6,7,8,8a-hexahydrofluoren-2-ylthio-malonic acid diethylester in an atmosphere of nitrogen and the resulting mixture is refluxed for 7 hours. The mixture is then left to stand overnight, the alcohol is evaporated off in a rotary evaporator and the residue is taken up in water. After extraction with ether the aqueous phase is acidified with concentrated hydrochloric acid and the precipitated malonic acid is taken up with ether.

The ethereal phase is then washed neutral with water, dried over sodium sulphate, and evaporated in vacuo whereby crude 4b,5,6,7,8,8a-hexahydrofluoren-2-ylthio-n-pentyl malonic acid is obtained as an oil.

Example 16

2.90 g. (6.7 mmol) of crude 4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy-methyl-malonic acid monoethyl ester are decarboxylated for 2 hours in an atmosphere of nitrogen. After purifying by means of column chromatograph on silica gel (Merck; 0.5–0.2 mm.) using benzene and benzene:ethyl acetate 9:1 as solvents for elution, 1.60 g. of 2 - (4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-propionic acid diethyl ester are obtained, n_D^{20}:1.5232 (yield 61.8% of theoretical).

The starting material 4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy-methyl-malonic acid monoethyl ester, is obtained as follows:

An ethanolic solution of potassium hydroxide (0.576 g. [8.94 mmol] of 87% KOH in 25 ml. of absolute ethanol) is added dropwise to a solution of 3.25 g. (9.03 mmol) of 4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy-methyl-malonic acid diethyl ester at a temperature of 20°. The reaction mixture is then stirred for 20 hours at room temperature, cooled to 0° and acidified with 0.84 ml. of concentrated hydrochloric acid. The solvent is then removed on a rotary evaporator (water bath temperature 25°) and the residue is taken up in water. The aqueous solution is then extracted with ether and the ether phase is washed with water, dried over sodium sulphate and evaporated in vacuo at room temperature. The oily residue is then placed in a column containing silica gel (Merck; 0.05–0.2 mm.) and, after removal of the unreacted starting material with benzene, the product of the saponification is eluated with benzene:glacial acetic acid 9:1. The product is 4b,5,6,7,8,8a - hexahydrofluoren - 2 - yloxy - methyl-malonic acid monoethyl ester.

Example 17

(a) A solution of 14.5 g. (0.046 mol) of 2-(fluoren-2-yloxy)-heptanoic acid in 100 ml. of dioxane is hydrogenated for a period of 15 hours at 100° and under 100 atmospheres of pressure in the presence of 3 g. of palladium charcoal (5% palladium). The catalyst is then removed by filtration; the solution is washed with dioxane and concentrated by evaporation in vacuum. The residue is purified by elution chromatography on a column of neutral silica gel (Merck ®, granular size 0.05–0.2 mm.). Benzene:glacial acetic acid (85:15) is used as eluant. The combined fractions containing the crude product are concentrated by evaporation. The residue is taken up in ether; the ethereal solution is washed with water, dried over sodium sulfate and concentrated by evaporation. The residue which is recrystallized from pentane yields 4.7 g. (31.8% of theory) of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid, M.P. 81–82°.

The starting material, 2-(fluoren-2-yloxy)-heptanoic acid is produced as follows:

(b) 6.0 g. (0.033 mole) of fluoren-2-ol are added under nitrogen, with stirring and exclusion of moisture, to a solution of 0.945 g. (0.041 mol) of sodium in 40 ml. of absolute ethanol. To the resultant solution of sodium fluorene-2-olate) there are added dropwise 8.2 g. (0.0346 mole) of 2-bromo-heptanoic acid ethyl ester, and the mixture is refluxed for 3 hours. The reaction mixture is concentrated by evaporation in vacuum and the residue is distributed between water and ether. The ether phase is shaken out with 0.5 N sodium hydroxide solution, washed neutral with water, dried over magnesium sulfate and concentrated by evaporation. A dark yellow oil is obtained which crystallizes. The crude product is chromatographed on a column of 200 g. of netural silica gel (Merk ®, grandular size 0.05–0.2 mm.) by the "pass-through" method. Benzene is used as eluant. The fractions containing the crude product are concentrated by evaporation. The residue is recrystallized from benzine (B.P. 65–100°) to yield 10.1 g. (90.6% of theory) of 2-(fluoren-2-yloxy)-heptanoic acid ethyl ester, M.P. 58–61°.

(c) 10.0 g. of 2-(fluoren-2-yloxy)-heptanoic acid ethyl ester are added to a solution of 4.0 g. of potassium hydroxide in 150 ml. of methanol and the mixture is refluxed for 30 minutes. Then the reaction mixture is concentrated by evaporation and the residue is distributed between ether and water. The aqueous phase is acidified with concentrated hydrochloric acid and extracted with ether. The ether extract is washed with water, dried over magnesium sulfate and concentrated by evaporation. The residue is recrystallized from methanol/water and yields 8.0 g. (78.5% of theory) of 2-(fluoren-2-yloxy)-heptanoic acid, M.P. 133–136°.

Example 18

(a) The following end products are obtained analogously to Example 17(a):

From 2.5 g. (0.009 mol) of 2-(fluoren-2-yloxy)-pro-

pionic acid, 1.35 g., 52.8% of theory, of crystalline 2-(4b, 5,6,7,8,8a-hexahydro-fluoren - 2 - yloxy)-propionic acid, M.P. 120–126° (from pentane);

From 2.8 g. (0.01 mol) of 2-fluoren-2-yloxy)-butyric acid, 1.2 g., 44.0% of theory, of crystalline 2-(4b,5,6,7, 8,8a-hexahydro-fluoren-2-yloxy)-butyric acid, M.P. 119–120° (from pentane);

From 2.5 g. (0.009 mol) of 2-(fluoren-2-yloxy)-2-methyl-propionic acid, 2.02 g., 79.0% of theory, of 2-(4b, 5,6,7,8,8a-hexahydro-fluoren-2-yloxy) - 2 - methyl-propionic acid, $n_D^{20.5}$: 1.5349 [crystallization sample M.P. 64–67° (from pentane)];

From 2.5 g. (0.009 mol) of 2-(fluoren-2-yloxy)-valeric acid, 2.1 g., 82.4% of theory, of 2-(4b,5,6,7,8,8a-hexahydro-fluoren-2-yloxy)-valeric acid, n_D^{20}: 1.5356;

From 2.5 g. (0.008 mol) of 2-(fluoren-2-yloxy)-hexanoic acid, 1.84 g., 73.5% of theory, of 2-(4b,5,6,7,8,8a-hexahydro-fluoren-2-yloxy)-hexanoic acid, n_D^{21}: 1.5311 [crystallization sample M.P. 88–91° (from pentane)];

From 2.5 g. (0.008 mol) of 2-(fluoren-2-yloxy)-5-methyl-hexanoic acid, 1.4 g., 56.0% of theory, of 2-(4b,5,6,7, 8,8a-hexahydro-fluoren - 2 - yloxy) - 5 - methyl-hexanoic acid, n_D^{20}: 1.5209;

From 2.5 g. (0.008 mol) of 2-(fluoren-2-yloxy)-octanoic acid, 1.8 g., 70.6% of theory, of 2-(4b,5,6,7,8,8a-hexahydro-fluoren-2-yloxy)-octanoic acid, n_D^{20}: 1.5275 [crystallization sample M.P. 90–92° (from pentane)];

From 2.5 g. (0.008 mol) of 2-(fluoren-2-yloxy)-5,5-dimethyl-hexanoic acid, 1.64 g., 65.6% of theory, of 2-(4b,5,6,7,8,8a-hexahydro - fluoren - 2 - yloxy) - 5,5 - dimethyl-hexanoic acid, n_D^{21}: 1.5167 [crystallization sample M.P. 95–97° (from pentane)];

From 4.0 g. (0.01 mol) of 2-(fluoren-2-yloxy)-dodecanoic acid, 1.0 g., 24.6% of theory, of crystalline 2-(4b, 5,6,7,8,8a-hexahydro-fluoren - 2 - yloxy)-dodecanoic acid, M.P. 99–101° (from pentane);

(b) The following intermediate products are produced analogously to Example 17(b):

From 5.5 g. (0.03 mol) of fluoren-2-ol and 5.43 (0.032 mol) of 2-bromo-propionic acid ethyl ester, 6.7 g., 78.6% of theory, of 2-(fluoren-2-yloxy)-propionic acid ethyl ester, n_D^{19}: 1.5869;

From 4.0 g. (0.022 mol) of fluoren-2-ol and 4.40 g. (0.023 mol) of 2-bromo-butyric acid ethyl ester, 2-(fluoren-2-yloxy)-butyric acid ethyl ester (crude product);

From 11.0 g. (0.06 mol) of fluoren-2-ol and 12.5 g. (0.064 mol) of 2-bromo-2-methyl-propionic acid ethyl ester, 9.7, 55% of theory, of 2-(fluoren-2-yloxy)-2-methyl-propionic acid ethyl ester, M.P. 63–64° (from methanol);

From 5.0 g. (0.0275 mol) of fluoren-2-ol and 6.26 g. (0.03 mol) of 2-bromo-valeric acid ethyl ester, 6.0 g., 70.4% of theory, of 2-(fluoren-2-yloxy)-valeric acid ethyl ester, M.P. 55–57° (from methanol/water);

From 5.5 g. (0.03 mol) fluoren-2-ol and 7.15 g. (0.032 mol) of 2-bromo-hexanoic acid ethyl ester, 6.4 g., 66% of theory, of 2-(fluoren-2-yloxy)-hexanoic acid ethyl ester, M.P. 64–65° (from methanol);

From 5.5 g. (0.03 mol) of fluoren-2-ol and 7.6 g. (0.032 mol) of 2-bromo-5-methyl-hexanoic acid ethyl ester, 5.6 g., 55% of theory, of 2-(fluoren-2-yloxy)-5-methyl-hexanoic acid ethyl ester, M.P. 58–60° (from methanol);

From 5.5 g. (0.03 mol) of fluoren-2-ol and 8.03 g. (0.032 mol) of 2-bromo-octanoic acid ethyl ester, 8.5 g., 80% of theory, of 2-(fluoren-2-yloxy)-octanoic acid ethyl ester, M.P. 53–54° (from methanol);

From 5.5 g. (0.03 mol) of fluoren-2-ol and 8.03 g. (0.032 mol) of 2-bromo-5,5-dimethyl-hexanoic acid ethyl ester, 9.6 g., 91% of theory, of 2-(fluoren-2-yloxy)-5,5-dimethyl-hexanoic acid ethyl ester, M.P. 62–63° (solidified);

From 4.4 g. (0.024 mol) of fluoren-2-ol and 7.06 g. (0.023 mol) of 2-bromo-dodecanoic acid ethyl ester, 2-(fluoren-2-yloxy)-dodecanoic acid ethyl ester (crude product);

(c) Moreover, the following starting materials are produced analogously to Example 17(c)

From 6.3 g. (0.0225 mol) of 2-(fluoren-2-yloxy)-propionic acid ethyl ester, 5.1 g., 90% of theory, of 2-(fluoren-2-yloxy)-propionic acid, M.P. 175–178° (from methanol);

From crude 2-(fluoren-2-yloxy)-butyric acid ethyl ester [produced from 4.0 g. of fluoren-2-ol and 4.40 g. (0.023 mol) of 2-bromo-butyric acid ethyl ester], 5.2 g., 88.2% of theory calculated on fluoren-2-ol, of 2-(fluoren-2-yloxy)-butyric acid, M.P. 154–156° (from ethyl acetate);

From 9.3 g. (0.0315 mol) of 2-(fluoren-2-yloxy)-2-methylpropionic acid ethyl ester, 7.8 g., 93% of theory, of 2-(fluoren-2-yloxy)-2-methylpropionic acid, M.P. 150–151° (from methanol);

From 5.5 g. (0.0177 mol) of 2-(fluoren-2-yloxy)-valeric acid ethyl ester, 4.15 g., 82.9% of theory, of 2-(fluoren-2-yloxy)-valeric acid, M.P. 158–159° (from benzene/benzine);

From 5.9 g. (0.0184 mol) of 2-(fluoren-2-yloxy)-hexanoic acid ethyl ester, 5.2 g., 96% of theory, of 2-(fluoren-2-yloxy)-hexanoic acid, M.P. 153–154° (from methanol/water);

From 5.2 g. (0.0154 mol) of 2-(fluoren-2-yloxy)-5-methylhexanoic acid ethyl ester, 4.5 g., 94% of theory, of 2-(fluoren-2-xyloxy)-5-methylhexanoic acid, M.P. 144–145° (from methanol/water);

From 8.3 g. (0.0236 mol) of 2-(fluoren-2-yloxy)-octanoic acid ethyl ester, 7.5 g., 98% of theory, of 2-(fluoren-2-xyloxy)-octanoic acid, M.P. 134+135° (from methanol/water);

From crude 2-(fluoren-2-yloxy)-dodecanoic acid ethyl ester (produced from 4.4 g. of fluoren-2-ol and 7.06 g. of 2-bromododecanoic acid ethyl ester), 6.8 g., 74% of theory calculated on fluoren-2-ol, of 2-(fluoren-2-yloxy)-dodecanoic acid, M.P. 120–122° (from methanol/water).

Example 19

19.37 g. (0.558 mol) of 2-fluoren-2-yloxy)-heptanoic acid ethyl ester are dissolved in 200 ml. of ethyl acetate and, after addition of 2 g. of palladium charcoal (5% palladium), hydrogenated within 5.5 hours at a temperature of 80°. The catalyst is then removed by filtration, washed through with ethyl acetate and the combined filtrates are evaporated in vacuo. The residue is then subjected to vacuum distillation. 10.39 g. of the desired 2-(4b,5,6,7, 8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid ethyl ester are obtained, B.P. 164–166°/0.04 torr, n_D^{20}: 1.5121 (yield 52.7% of theoretical).

Example 20

A solution of 150 g. (0.483 mol) of 2-(fluoren-2-yloxy)heptanoic acid is hydrogenated within 5.5 hours at a temperature of 80° and a pressure of 12 atmospheres and in the presence of 15 g. of palladium charcoal (5% palladium). The catalyst is then removed by filtration, washed through with ethyl acetate and the combined filtrates are evaporated in vacuo. The solvent-free residue is dissolved in 700 ml. of pentane with gentle heating until a clear solution is obtained. The solution is then placed in a closed flask and cooled to −30° in a mixture of Dry Ice and acetone and within 10–15 minutes the desired product crystallizes. The precipitate is filtered off under suction and washed through with 250 ml. of pentane cooled to −30°. After drying at 50° and 60 torr 77.1 g. of crystals are obtained which are again recrystallized from 1.2 litres of pentane. To promote crystallization the solution is kept for 3–4 hours at −10° to −15°, and the obtained precipitate is filtered under suction and washed through with 200 ml. of pentane cooled to −30°. After drying, 65.1 g. of 2-(4b,5,6,7,8,8a-hexahydrofluo-

ren-2-yloxy)-heptanoic acid are obtained, M.P. 81–82° (yield 43% of theoretical).

The second diastereomeric isomer which is noncrystallizable and remains in the mother liquor can be converted into the crystallizable first diastereometric isomer, M.P. 81–82°, in the following manner:

(a) The combined mother liquors form the crystallization of the first isomer are evaporated in vacuo and then the residue (86.5 g./0.274 mol) is dissolved in 600 ml. benzene, 50 ml. (0.86 mol) of absolute ethanol and 1 g. of p-toluene sulphonic acid as catalyst are added and the resulting clear solution is esterified for 15 hours under reflux in a water-free azeotrope. The solution is then evaporated in vacuo and the residue is taken up in 400 ml. of ether, washed once with saturated sodium bicarbonate solution and then with water until the washings are neutral. The ethereal solution is dried over magnesium sulphate, filtered and evaporated in vacuo. The residue (93.4 g.) is then distilled at 0.04 torr. The fractions having a boiling point of between 164° and 167° are used for the next step of the reaction, n_D^{23}: 1.5110 (yield 77.8 g., 82.6% of theoretical).

(b) 77.65 g. (0.226 mol) of the ester obtained in step (a) are added to a solution of 0.518 g. (0.0226 mol) of metallic sodium in 500 ml. of ethanol and refluxed for 40 hours with the exclusion of moisture. A solution of 28.3 g. (0.429 mol) of potassium hydroxide (85% puriss.) in 150 ml. of water is then added and the resulting solution is refluxed for a further 1.5 hours. The reaction mixture is then evaporated in vacuo and the oily residue is dissolved in ca. 1 litre of water and 250 ml. of 2 N hydrochloric acid are added.

The oil which now separates out is taken up in ca. 400 ml. of ether and the ethereal solution is separated off and washed neutral with water. After drying over magnesium sulphate the ethereal solution is filtered, decolourised with animal charcoal, again filtered and then evaporated in vacuo.

The residue is completely freed of solvent at 90° and 11 torr and 72 g. of the oily crude product are obtained. This oil is then dissolved in 350 ml. of pentane and cooled with seeding in a closed flask to −30° with a mixture of Dry Ice and acetone. After 10–15 minutes, when crystallization is completed, the solution is filtered under suction and the residue washed through with 150 ml. of pentane cooled to −50° and then dried at 50° and 60 torr. The 29 g. of crystals obtained are again recrystallized from 500 ml. of pentane. After drying 25 g. of the tanoic acid, M.P. 81–82°, are obtained (yield 16.5% of theoretical value calculated on the basis of the original quantity of 2-[fluoren-2-yloxy]-heptanoic acid employed).

A further 14.6 g. of product are obtained by repetition of steps (a) and (b) on the mother liquor (yield 9.6% of theoretical value calculated on theb asis of the original quantity of 2-[fluoren-2-yloxy]-heptanoic acid employed).

Example 21

0.66 ml. (6.98 m. mol) of dimethyl sulphate and 0.91 g. (10.84 m. mol) of sodium bicarbonate are added to a solution of 1.58 g. (5 m. mol) of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid in 10 ml. of absolute dimethylformamide. The suspension is then heated within 10 minutes to a temperature of 90°, with stirring and kept at this temperature until the development of carbon dioxide ceases (ca. 15 minutes). After cooling the reaction mixture is poured into water and repeatedly extracted ether. The ethereal extract is washed thoroughly with water, dried over sodium sulphate and evaporated in vacuo. The oily residue is chromatographed on silica gel (Merck; 0.05–0.2 mm.) using benzene as solvent for elution. 120 g. of pure 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid methyl ester are obtained n_D20: 1.5168 (yield 72.7% of theoretical).

Example 22

0.3 ml. of concentrated sulphuric acid are added to a solution of 1.58 g. (5 m.mol) of 2-(4b,5,6,7,8,8a-hexahydro fluoren-2-yloxy)-heptanoic acid in 30 ml. of absolute ethanol and the mixture is stirred for 1.5 hours under reflux. After cooling the reaction mixture is poured into 100 ml. of water and the aqueous solution is extracted with ether. The ether extract is washed with 2 N sodium hydroxide solution and water, dried over sodium sulphate and evaporated in vacuo. The resulting oil is put into a silica gel column (Merck; 0.05–0.2 mm.) and eluted with benzene. 1.60 g. of pure 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid ethyl ester are obtained in the form of a colourless oil; n_D^{20}: 1.5110 (yield 92.9% of theoretical).

Example 23

A solution of 1.60 g. (5.84 m.mol) of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-butyric acid in 10 ml. of absolute benzene is added, whilst stirring, to a solution of 0.86 ml. (11.76 m.mol) of thionylchloride and 0.2 ml. of dimethylformamide in 10 ml. of absolute benzene. The resulting mixture is refluxed for 6 hours and then evaporated in vacuo. The excess thionyl chloride is removed from the residue by repeated addition of benzene and evaporation in vacuo. The residue is dissolved in 15 ml. of absolute benzene and 2.4 ml. of absolute methanol are added dropwise at room temperature whilst stirring. The resulting reaction mixture is refluxed for 1.5 hours. After evaporation of the reaction mixture in vacuo the residue is partitioned between ether and water. The ethereal phase is extracted with sodium bicarbonate solution, washed neutral with water, dried over sodium sulphate, filtered and evaporated in a rotary evaporator. The purification of the oily residue is achieved by chromatography on silica gel (Merck; 0.05–0.2 mm.) using benzene as solvent for elution.

1.40 g. of pure 2 - (4b,5,6,7,8,8a - hexahydrofluoren-2-yloxy)-butyric acid methylester are obtained n_D^{20}: 1.5258 (yield 83.3% of theoretical).

Example 24

0.3 ml. of concentrated sulphuric acid are added to a solution of 1.50 g. (4.51 m.mol) of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-ylthio)-heptanoic acid in 30 ml. of absolute ethanol and the mixture is stirred for 1.5 hours under reflux. After cooling the reaction mixture is poured into 100 ml. of wate and the aqueous solution is extrated with ether. The ether extract is washed with 2 N sodium hydroxide solution and water, dried over sodium sulphate and evaporated in vacuo. The purification of the oily residue is achieved by chromatography on silica gel (Merck; 0.05–0.2 mm.) using benzene:petrol=2:1 as solvent for elution. 0.95 g. of pure 2-(4b,5,6,7,8,8a-hexahydrofluoren-2- ylthio)-heptanoic acid ethylester are obtained, n_D^{20}: 1.5370 (yield 58.4% of theoretical).

Analogously 1.41 g. of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-ylthio)-dodecanoic acid ethyl ester are obtained, n_D^{20}: 1.5200, starting from 2.01 g. (5 m.mol) of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-ylthio)dodecanoic acid.

Example 25

1.485 g. (5 m.mol) of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid nitrile are dissolved in 50 ml. of chloroform and 5 ml. of absolute ethanol and a stream of dry hydrogen chloride gas is passed through the resulting solution at a temperature of 0–5°. The resulting hydrogen chloride saturated solution is left to stand overnight at room temperature and the blue-green solution is evaporated in vacuo at a temperature of 30–35°. The residue is taken up in 10 ml. of dioxan and 2 ml. of water and stirred for 5 hours at a temperature of 40°. After evaporation of the dioxan in vacuo and azeotropic removal of the water by repeated distillation with benzene the crude product is taken up in benzene and the solution is filtered to remove the precipitated

ammonium chloride. The filtrate is evaporated in a rotary evaporator and the crude ester obtained as residue is purified by chromatography on silica gel (Merck; 0.05–0.2 mm.) using benzene as solvent for elution. 1.34 g. of 2-(4b,5,6,7,8,8a-hexahydrofluoren - 2 - yloxy)-heptanoic acid ethyl ester is obtained in the form of a colourless oil, n_D^{20}: 1.5112 (yield 77.9% of theoretical).

The starting material, 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid nitrile, is obtained as follows:

In the space of 20 minutes 20 ml. of an ethanolic potassium hydroxide solution (0.415 g. KOH 86%; 6.36 m.mol) are added dropwise to a stirred solution of 2.24 g. (6.06 m.mol) of 4b,5,6,7,8,8a - hexahydrofluoren-2-yloxy-n-pentyl-cyanoacetic-acid ethylester in 40 ml. of absolute ethanol at room temperature and the solution is allowed to stand for 15 hours at a temperature of 20°. This solution is then evaporated in vacuo, the residue is dissolved in ca. 100 ml. of water and to the aqueous solution are added 6.4 ml. of 1 N hydrochloric acid. The solution is then extracted with ether and the organic phase is washed with water, dried over sodium sulphate, filtered and evaporated in vacuo. 2.06 g. of 4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy-n-pentyl-cyanoacetic acid are obtained which are heated, without further purification, for 2.5 hours at 140°. The decarboxylated product is purified by chromatography on silica gel (Merck; 0.05–0.2 mm.) using benzene as solvent for elution. 1.08 g. acid nitrile are obtained as a colourless oil, n_D^{20}: 1.5230 (yield 59.9% of theoretical).

Example 26

A solution of 59 mg. (3.0 m. mol) of sodium in 6 ml. of ethanol is added to a solution of 1 g. of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid in 10 ml. of absolute ethanol and then evaporated to dryness. The solid residue is ground together with ether, the slurry is then filtered under suction and the residue thoroughly washed through with ether. 1.0 g. of the pure sodium salt are obtained. The salt is weakly hygroscopic and decomposes between 290 and 300° with gradual brown colouration (yield 99.5% of thoretical).

Example 27

0.2 g. of metallic calcium (5 m. mol) are dissolved in 20 ml. of water with the exclusion of carbon dioxide. 3.79 g. (12 m. mol) of 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid dissolved in 150 ml. of methanol are then added to the suspension of calcium hydroxide and the resulting clear solution is refluxed for 10 minutes. The reaction mixture is then evaporated in vacuo and the oily residue is taken up in petrol. The small amount of insoluble solid product being removed by filtration. The petrol solution is evaporated in vacuo to give an amorphous foam which is dissolved in hot methanol and allowed to stand for 20 hours at a temperature of 0°. The calcium salt which crystallizes is filtered off under suction and washed through with a little cold methanol. 2.1 g. of the pure calcium salt are obtained which decompose between 290 and 300° with gradual brown colouration (yield 62.7% of theoretical).

Example 28

3.8 g. (18.6 m.mol) of 4b,5,6,7,8,8a-hexahydrofluoren-2-thiol are added to a solution of 0.43 g. (18.6 m.mol) of sodium in 25 ml. of absolute ethanol.

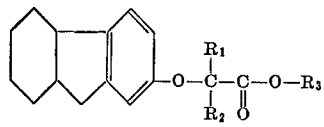
To this mixture is then added, dropwise, an ethanolic solution of the sodium salt of 2-bromo-heptanoic acid prepared from 0.43 g. (18.6 m.mol) of sodium in 70 ml. of absolute ethanol and 3.89 g. (18.6 m.mol) of 2-bromo-heptanoic acid, the addition being carried out with stirring and the exclusion of moisture.

The reaction mixture is then stirred for 5 hours at room temperature and refluxed for a further 20 minutes. After removal of the solvents in vacuo the residue is taken up in water and acidified with concentrated hydrochloric acid. The resulting crude carboxylic acid is extracted with ether and the ethereal phase is washed with water. The ethereal phase is then dried over sodium sulphate, filtered and the filtrate is evaporated to remove the ether. The obtained crude product is purified by chromatography on Kieselgel (Merck 0.05–0.2 mm.) using benzene/ethyl acetate 9:1 as solvent for elution.

4.37 g. of pure 2-[4b,5,6,7,8,8a-hexahydrofluoren-2-ylthio]-heptanoic acid are obtained in the form of a pale yellow coloured oil (Yield 70.6% of theoretical).

What is claimed is:

1. A compound of the Formula I



(I)

wherein

R_1 is alkyl having from 1 to 10 carbon atoms or benzyl,

R_2 is hydrogen or methyl, and

R_3 is hydrogen or alkyl having from 1 to 3 carbon atoms, or a pharmaceutically acceptable alkali-metal or alkaline-earth-metal salt of said compound, wherein R_3 is hydrogen.

2. A compound according to claim **1**, which is 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-heptanoic acid.

3. A compound according to claim **1**, which is 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-5-methyl - hexanoic acid.

4. A compound according to claim **1**, which is 2-(4b,5,6,7,8,8a-hexahydrofluoren-2-yloxy)-octanoic acid.

References Cited

House et al.: Chem. Abst. 54, 21011c.

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260—399, 410.9, 465 D, 465 F, 465.7, 470, 473 F, 487, 505 C, 516, 520, 543 R, 559 B, 590, 609 D, 612 R, 619 F; 424—308, 317,318.