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4-HYDROXY-5-PHENYL-3-THIOPHENE ACETIC ACIDS AND THEIR DERIVATIVES

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No Drawing. Continuation-in-part of abandoned application Ser. No. 277,126, Aug. 1, 1972. This application Feb. 22, 1973, Ser. No. 334,671

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U.S. Cl. 260—332.2 A 29 Claims

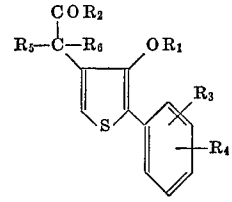
ABSTRACT OF THE DISCLOSURE

The invention concerns substituted or non-substituted 4-hydroxy-5-phenyl-3-thiophene acetic acids which are useful as antiphlogistics and anti-arthritis agents.

This application is a continuation-in-part of Ser. No. 277,126, filed August 1, 1972, now abandoned.

The present invention relates to heterocyclic compounds and more specifically to substituted 2-phenylthiophene compounds.

The present invention provides compounds of formula I,



I

wherein R_1 is hydrogen or alkyl of 1 to 4 carbon atoms,

R_2 is hydroxy, alkoxy of 1 to 4 carbon atoms, cycloalkyloxy of 3 to 6 carbon atoms, cycloalkylalkoxy of 3 to 6 ring carbon atoms and 1 to 4 alkoxy carbon atoms, amino, monoalkylamino of 1 to 4 carbon atoms or dialkylamino, each alkyl substituent having 1 to 4 carbon atoms,

or R_1 and R_2 together denote a single bond,

R_3 is hydrogen, chlorine or alkyl of 1 to 4 carbon atoms,

or when R_1 is hydrogen, or when R_1 and R_2 together denote a single bond, then R_3 may be hydroxy,

or when R_1 is alkyl of 1 to 4 carbon atoms, then R_3 may be alkoxy of 1 to 4 carbon atoms,

R_4 is hydrogen, chlorine, bromine or alkyl of 1 to 4 carbon atoms,

or when R_1 is hydrogen, or when R_1 and R_2 together denote a single bond, then R_4 may be hydroxy,

or when R_1 is alkyl of 1 to 4 carbon atoms, then R_4 may be alkoxy of 1 to 4 carbon atoms,

or when R_3 is hydrogen, then R_4 may be fluorine or trifluoromethyl,

R_5 is hydrogen or alkyl of 1 to 4 carbon atoms, and

R_6 is hydrogen or methyl.

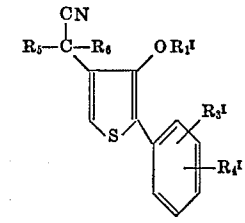
It is to be understood that when any of the above groups is or includes a non-cyclic alkyl group of more than 2 carbon atoms, this may be straight or branched chain.

The present invention also provides a process for producing a compound of formula I, which comprises

(a) Solvolysing —CN to —COR_2^I,

wherein R_2^I is hydroxy, amino, primary or secondary alkoxy of 1 to 4 carbon atoms or cycloalkylalkoxy of 3 to 6 ring carbon atoms and 1 to 4 alkoxy carbon atoms, or cycloalkyloxy of 3 to 6 carbon atoms,

in a compound of formula II,



II

wherein R_1^I is hydrogen or alkyl of 1 to 4 carbon atoms,

R_3^I is hydrogen, chlorine, or alkyl of 1 to 4 carbon atoms,

or when R_1^I is hydrogen, then R_3^I may be hydroxy,

or when R_1^I is alkyl of 1 to 4 carbon atoms, then R_3^I may be alkoxy of 1 to 4 carbon atoms,

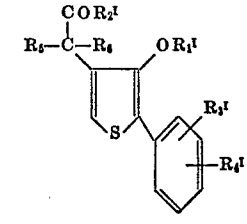
R_4^I is hydrogen, chlorine, bromine, or alkyl of 1 to 4 carbon atoms,

or when R_1^I is hydrogen, then R_4^I may be hydroxy,

or when R_1^I is alkyl of 1 to 4 carbon atoms, then R_4^I may be alkoxy of 1 to 4 carbon atoms, or when R_3^I is hydrogen, then R_4^I may be fluorine or trifluoromethyl, and

R_5 and R_6 are as defined above,

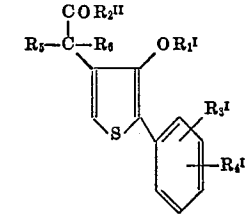
to produce a compound of formula I*a*,



Ia

wherein R_5, R_6, R_1^I, R_2^I, R_3^I and R_4^I are as defined above, or

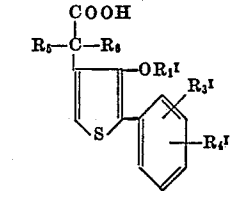
(b) Hydrolyzing a compound of formula I*c*,



Ic

wherein R_1^I, R_3^I, R_4^I, R_5 and R_6 are defined above, and R_2^{II} is alkoxy of 1 to 4 carbon atoms, cycloalkyloxy of 3 to 6 carbon atoms or cycloalkylalkoxy of 3 to 6 ring carbon atoms and 1 to 4 alkoxy carbon atoms,

to produce a compound of formula I*b*,

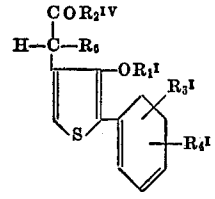


Ib

wherein R_2^I, R_3^I, R_4^I, R_5 and R_6 are as defined above, or

(c) Esterifying an acid of formula I*b*, or a reactive acid derivative thereof, to produce a compound of formula I*c*, or

(d) Reacting a compound of formula Ie, Ia, Ic, or



Ie

wherein R_1^I, R_3^I, R_4^I and R_6 are as defined above, and R_2^{IV} is hydroxy, alkoxy of 1 to 4 carbon atoms, cycloalkoxy of 3 to 6 carbon atoms, cycloalkylalkoxy of 3 to 6 ring carbon atoms and 1 to 4 alkoxy carbon atoms, amino, monoalkylamino of 1 to 4 carbon atoms or dialkylamino, each alkyl substituent having 1 to 4 carbon atoms,

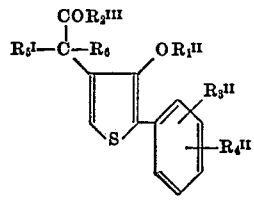
with a compound of formula III,

$$R_5^I X \qquad \text{III}$$

wherein R_5^I is alkyl of 1 to 4 carbon atoms, and X is iodine, chlorine, bromine, $R_5^I SO_2$

wherein R_5^I is as defined above, or an organic sulphonate group,

to produce a compound of formula Id,



Id

wherein R_1^{II} is alkyl of 1 to 4 carbon atoms, R_2^{III} is alkoxy of 1 to 4 carbon atoms, cycloalkylalkoxy of 3 to 6 carbon atoms, cycloalkylalkoxy of 3 to 6 ring carbon atoms and 1 to 4 alkoxy carbon atoms, or dialkylamino, each alkyl substituent having 1 to 4 carbon atoms,

R_3^{II} is hydrogen, chlorine, alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms,

R_4^{II} is hydrogen, chlorine, bromine, alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms,

or when R_3^{II} is hydrogen, then R_4^{II} may be fluorine or trifluoromethyl, and

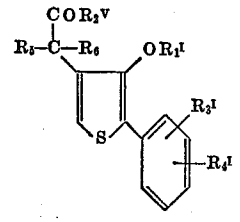
R_6 and R_5^I are as defined above, or

(e) Reacting an acid of Formula Ib, or a reactive acid derivative thereof, with a compound of formula IV,

$$HR_2^V \qquad \text{IV}$$

wherein R_2^V is amino, monoalkylamino of 1 to 4 carbon atoms or dialkylamino, each alkyl substituent having 1 to 4 carbon atoms,

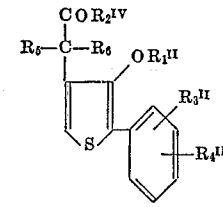
to produce a compound of formula If,



If

wherein R_1^I, R_3^I, R_4^I, R_5, R_6 and R_2^V are as defined above, or

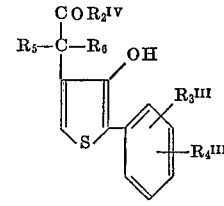
(f) Splitting the ether groups to form hydroxy groups in a compound of formula Ih,



Ih

wherein R_1^{II}, R_2^{IV}, R_3^{II}, R_4^{II}, R_5 and R_6 are as defined above,

to produce a compound of formula Ig,



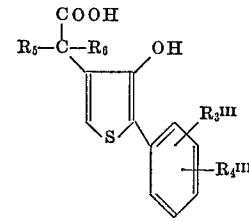
Ig

wherein R_2^{IV}, R_5 and R_6 are as defined above,

R_3^{III} is hydrogen, chlorine, alkyl of 1 to 4 carbon atoms or hydroxy, and

R_4^{III} is hydrogen, chlorine, bromine, alkyl of 1 to 4 carbon atoms or hydroxy, or when R_3^{III} is hydrogen, then R_4^{III} may be fluorine or trifluoromethyl, or

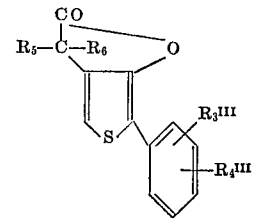
(g) Cyclizing a compound of formula Ij,



Ij

wherein R_3^{III}, R_4^{III}, R_5 and R_6 are as defined above,

to produce a compound of formula Ii,



Ii

wherein R_3^{III}, R_4^{III}, R_5 and R_6 are as defined above.

The compounds of formula I, wherein R_2 is hydroxy and/or R_1 is hydrogen, may exist either in free acidic form or in salt form. Salt forms may be formed from free acidic forms in manner known *per se* and *vice versa*.

The compounds of formula I wherein R_5 is different to R_6 exist in optical isomeric forms. It is to be understood that formula I embraces the optically pure forms as well as the racemic forms of such compounds.

Process (a) may be effected according to the standard methods for solvolysing cyanides. As will be readily appreciated, the nature of the resulting compound, i.e. acid, amide or ester, will depend on the reaction conditions and solvolysing agent employed.

As will also be appreciated, the choice of the appropriate hydrolysis conditions is determined by the reactivity of the nitrile substituent of the compound of formula II, which is dependent on the degree and nature of the substituents on the carbon atom α to the nitrile substituent.

Thus, for example, an amide of formula Ia may be produced by alkaline or acid hydrolysis of the cyanide

of formula II. Alkaline hydrolysis may be effected in the presence of a dilute aqueous alkali metal hydroxide solution, e.g. 0.5 to 5 N caustic soda solution at a temperature of between room temperature and 100° C. Alternatively, alkaline hydrolysis may be effected with hydrogen peroxide in the presence of a dilute aqueous alkaline solution. Acid hydrolysis may be effected by employing the required amount of aqueous mineral acid at about room temperature.

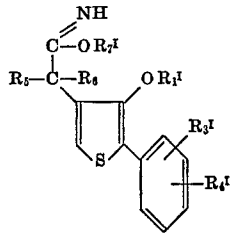
A carboxylic acid of formula I*a* may be produced, for example, by hydrolysis in the presence of a strong basic catalyst, e.g. 2 N to 50% alkaline solution, or in the presence of a strong acid catalyst, e.g. a strong mineral acid, such as concentrated hydrochloric acid or 20 to 75% sulphuric acid. The hydrolysis may be effected at a temperature between 60 and 160° C., optionally in a bomb tube.

A carboxylic acid ester of formula I*a* may be produced by solvolysis with an aqueous alcohol (containing 1 to 3 mols of water per mol of the compound of formula II) of formula V*b*,

$$R_7^{I}OH \qquad Vb$$

wherein R_7^{I} is primary or secondary alkyl of 1 to 4 carbon atoms or cycloalkylalkyl of 3 to 6 ring carbon atoms and 1 to 4 side chain alkyl carbon atoms, or cycloalkyl of 3 to 6 carbon atoms,

in the presence of an acid, e.g. hydrogen chloride gas or sulphuric acid. Preferably, however, the reaction is effected by first converting a compound of formula II, with an alcohol of formula V*b* in the presence of an acid catalyst, into an imino ether of formula VI,



VI

wherein R_1^{I}, R_3^{I}, R_4^{I}, R_5, R_6 and R_7^{I} are as defined above,

and then hydrolysing the resulting compound with the required amount of water. Thus the reaction may, for example, be effected by passing hydrogen chloride gas through a solution of a compound of formula II in an alcohol of formula V*b*, at a reduced temperature, preferably at a temperature between −10 and +10° C., subsequently allowing reaction at a temperature between 0° and 100° C. for 10 to 25 hours, and then hydrolysing the resulting compound of formula VI, optionally after evaporating excess solvent which may have been used, with 1 to 3 mols of water calculated on one mol of the compound of formula VI, for approximately 1 to 5 hours at a temperature of approximately 50 to 100° C., preferably at the boiling temperature of the reaction mixture.

As will be readily appreciated, the solvolysis reactions hereinbefore described may, if desired, be effected in the presence of a water-miscible inert organic solvent.

Process (b) may be carried out in accordance with the usual methods for ester hydrolysis. For example, the compounds of formula I*c* may be allowed to react with water, optionally in an inert water-miscible organic solvent, e.g. an alkanol such as methanol or ethanol, acetone, tetrahydrofuran or dioxane, in the presence of a basic catalyst, e.g. an alkali metal or alkali earth metal hydroxide, or in the presence of an acid catalyst, e.g. a mineral acid such as hydrochloric or sulphuric acid, or an organic sulphonic acid, at a temperature between room temperature and approximately 100° C. for 1 to 50 hours. Hydrolysis is preferably effected in an alkaline medium, e.g. with at least one equivalent amount of an aqueous alkali metal hydroxide, at room temperature or at slightly elevated temperature, whereby an alkali metal salt of a compound of formula I*b* is obtained. Alkaline hydrolysis is particularly preferred when R_1^{I} in the compounds of formula I*b* is hydrogen, since lactone formation, which may otherwise occur as side reaction in an acid medium, is avoided or reduced.

Process (c) may be carried out in accordance with the usual processes for ester formation. For example, a solution of an acid of formula I*b* in an excess of an alcohol of formula V,

$$R_7OH \qquad V$$

wherein R_7 is alkyl of 1 to 4 carbon atoms, cycloalkyl of 3 to 6 carbon atoms, cycloalkylalkyl of 3 to 6 ring carbon atoms and 1 to 4 side chain alkyl carbon atoms,

may be allowed to react in the presence of an acid condensation agent, e.g. sulphuric acid, hydrogen chloride gas, an organic sulphonic acid or an acid ion exchange substance, optionally with the addition of an inert organic solvent, e.g. an ether or an aromatic hydrocarbon such as benzene or toluene, at a temperature between room temperature and approximately 100° C. Removal of the water formed during esterification by azeotropic distillation may generally be found to be advantageous.

Production of a tertiary ester may be effected by using the ester form of the alcohol of formula V, preferably an ester thereof with a carboxylic acid, especially the formate. Reactive derivatives of the acid of formula I*b* may also be employed. Suitable reactive derivatives of an acid of formula I*b* are, for example, the acid halides thereof, the mixed anhydrides of an acid of formula I*b* with a suitable organic carboxylic acid, or a suitable alkyl ester of an acid of formula I*b*. Thus, for example, the acid of formula I*b* may first be converted into its acid chloride by reaction with a suitable inorganic acid chloride, e.g. phosphorus trichloride, phosphorus pentachloride or thionyl chloride, and the resulting acid chloride may subsequently be esterified with an alcohol of formula V, optionally in the presence of an acid-binding agent, e.g. an organic base such as pyridine or a tertiary amine. It is also possible to react the alcohol in the form of a Grignard derivative of formula V*a*,

$$R_7OMgY \qquad Va$$

wherein R_7 is as defined above, and Y is chlorine or bromine,

with an acid chloride or an acid of formula I*b*. The latter reaction is particularly applicable to the production of esters of tertiary alcohols. The exchange of ester radicals of an alkyl ester of an acid of formula I*b* with a tertiary alcohol is likewise particularly suited to the production of esters of tertiary alcohols. This reaction is preferably effected in the presence of a catalytic amount of metallic sodium, at a temperature between approximately 80 and 150° C., by melting. The production of a methyl ester may, for example, also be effected by reacting the acid of formula I*b* with diazomethane in conventional manner.

The alkylation of process (d) may, for example, be effected by converting a compound of formula I*e*, in the presence of an inert solvent, e.g. liquid ammonia, an organic aprotic, preferably polar, solvent, e.g. dimethyl formamide, dimethyl sulphoxide or hexamethyl phosphoric acid triamide, a suitable ether such as 1,2-dimethoxyethane or tetrahydrofuran, or an aromatic hydrocarbon such as benzene or toluene, into its anion, with a strong basic condensation agent, e.g. an alkali metal, an alkali metal amide such as sodamide, an alkali metal hydride such as sodium hydride, or an alkali metal alcoholate, and reacting the resulting compound with a compound of formula III at a temperature of approximately −50 to approximately +60° C. When R_1^{I} is hydrogen or any of R_2^{IV}, R_3^{I} or R_4^{I} are hydroxy in the compounds of formula I*e*, these are converted into alkoxy groups, and when R_2^{IV} is amino or monoalkylamino, this is alkylated to a

dialkylamino group. When R_6 in the compounds of formula Ie denotes hydrogen, and it is desired to obtain a monoalkylation on the carbon atom to which it is attached, the reaction is preferably effected in liquid ammonia, in the presence of an equivalent amount of sodamide, at a reduced temperature, and the alkylating agent is added slowly. When R_1^I in formula Ie denotes hydrogen, the reaction is preferably effected in a polar organic solvent, e.g. dimethyl formamide or dimethyl sulphoxide, using sodium hydride as condensation agent, in order to obtain complete etherification.

Process (e) may be carried out in accordance with the usual methods of acid amide production. Thus, for example, an acid of formula Ib may be allowed to react at a temperature between approximately 100 and 250° C., with a compound of formula IV, preferably with excess of the latter. The reaction may, for example, be effected by melting, or effected in an inert solvent, e.g. an aromatic hydrocarbon such as benzene or toluene, conveniently with the removal of the resulting water by azeotropic distillation. In place of the free acids of formula Ib it is also possible to react reactive derivatives thereof, e.g. acid halides, suitably alkyl esters or mixed anhydrides of an acid of formula Ib with a suitable carboxylic acid, with a compound of formula IV. The reaction with acid halides or mixed anhydrides of an acid of formula Ib may, for example, be effected by using an excess of a compound of formula IV, or in the presence of an acid-binding agent, e.g. an alkali metal hydroxide or an organic base, e.g. pyridine or a tertiary amine, in the presence of water, and optionally in an inert water-miscible organic solvent, preferably at room temperature or at a slightly elevated temperature. An alkyl ester of an acid of formula Ib may be reacted with a compound of formula IV, for example at a temperature between approx. 100 and 250° C., optionally in an autoclave, optionally with the addition of an inert organic solvent, e.g. an alkanol.

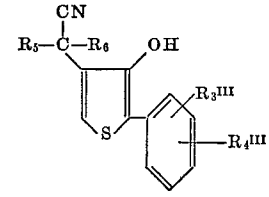
Process (f) may be carried out in accordance with the usual methods for ether splitting. Thus, for example, a compound of formula Ih may be allowed to react with a Lewis acid, e.g. boron tribromide or aluminium chloride, in an inert organic solvent, e.g. a halogenated hydrocarbon such as methylene chloride or carbon tetrachloride, or an aromatic hydrocarbon such as toluene or benzene, at −80 to +70° C. It is also possible to treat the compound of formula Ih for a short time with a strong mineral acid, e.g. hydrobromic or hydriodic acid, optionally at an elevated temperature, e.g. at approx. 20 to 100° C., optionally with the addition of glacial acetic acid. Any ester or amide groups in the compounds of formula Ih are thus simultaneously hydrolyzed to the carboxyl group. The ether splitting of the compounds of formula Ih with an alkali metal alkyl mercaptide, or an alkali metal or alkali metal hydride/alkyl mercaptane combination, e.g. sodium hydride/ethyl mercaptane, in an inert polar organic solvent, e.g. dimethyl formamide, at a temperature between approx. 50 and 150° C., preferably 80 to 120° C., has been found to be specially convenient. In this reaction any ester and amide groups in the compounds of formula Ih are also split when using an excess of reagent. However, such groups are generally not affected when using an equimolar amount of reagent. In accordance with a further process variant, lithium iodide may be allowed to react with a compound of formula Ih in the presence of 2,4,6-trimethyl pyridine at a temperature between 100 and 150° C.

The cyclization of the invention in accordance with process (g) may, for example, be effected by heating a compound of formula Ij to a temperature of approx. 80 to 180° C. The reaction is preferably effected in the presence of an acid condensation agent, optionally with the addition of an inert organic solvent, e.g. an aromatic hydrocarbon such as benzene or toluene. Acetic anhydride is preferred as acid condensation agent, optionally with benzene as solvent. Examples of other suitable condensation agents are strong mineral acids, e.g. polyphosphoric acid or sulphuric acid.

The compounds of formula I may be isolated from the reaction mixture and purified in known manner; the free acidic compounds of formula I, wherein R_2 is hydroxy and/or R_1 is hydrogen, may be converted into salt form in conventional manner. Such salt forms include alkali metal salts, e.g. sodium and potassium salts. If desired, the racemates of the compounds of formula I, wherein R_5 is different to R_6, may be separated into their optical isomers in known manner, e.g. the racemic acids of formula I may be converted into a mixture of their diastereoisomeric salts with optically active bases, the salts separated by physical methods, and the optical isomers of the acids of formula I isolated therefrom.

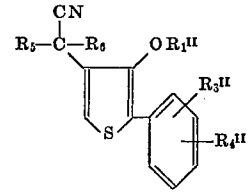
The starting materials may, for example, be obtained as follows:

(a') A compound of formula IIa,



IIa

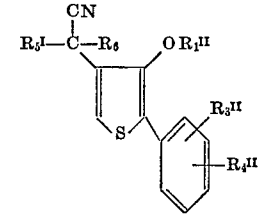
wherein R_3^{III}, R_4^{III}, R_5 and R_6 are as defined above, may, for example, be obtained by splitting the ether groups into hydroxy groups in a compound of formula IIb,



IIb

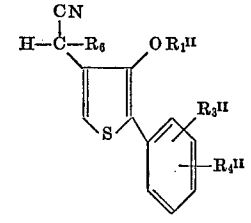
wherein R_1^{II}, R_3^{II}, R_4^{II}, R_5 and R_6 are as defined above. The ether splitting may, for example, be effected in manner analogous to that described in relation to process (f).

(b') A compound of formula IIc,



IIc

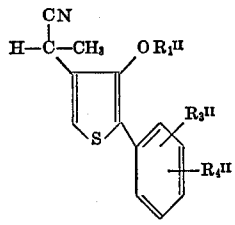
wherein R_1^{II}, R_3^{II}, R_4^{II}, R_5^I and R_6 are as defined above, may, for example, be obtained by alkylating a compound of formula IId,



IId

wherein R_1^{II}, R_3^{II}, R_4^{II} and R_6 are as defined above, with a compound of formula III. The reaction may, for example, be effected under the reaction conditions described in relation to process (d).

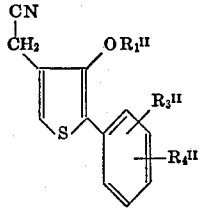
(c') A compound of formula II*e*,



II*e*

wherein R_1^{II}, R_3^{II} and R_4^{II} are as defined above,

may, for example, be obtained by reacting a compound of formula II*f*,

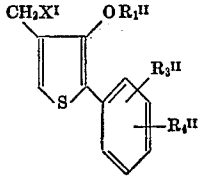


II*f*

wherein R_1^{II}, R_3^{II} and R_4^{II} are as defined above,

in liquid ammonia, with methyl iodide in the presence of sodamide in manner known *per se*.

(d') A compound of formula II*f* may, for example, be obtained by reacting a compound of formula VII,

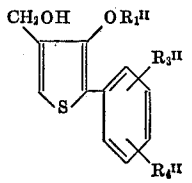


VII

wherein R_1^{II}, R_3^{II} and R_4^{II} are as defined above, and X^I is chlorine or bromine,

with a metal cyanide. An alkali metal cyanide such as as sodium or potassium cyanide, or copper(I) cyanide, is preferably used. The reaction may, for example, be effected in an inert organic solvent, or in a mixture of water and an organic solvent, e.g. acetone or a suitable alcohol, optionally with the addition of a metal iodide such as sodium iodide. The reaction temperature may be between 50 and 100° C., preferably the boiling temperature of the reaction mixture. The reaction may have a duration between approx. 2 and 24 hours.

(e') A compound of formula VII may, for example, be obtained by treating a compound of formula VIII,

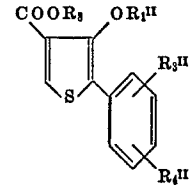


VIII

wherein R_1^{II}, R_3^{II} and R_4^{II} are as defined above,

with a suitable chlorinating or brominating agent, e.g. a thionyl or phosphorus halide. The reaction may, for example, be effected in an inert solvent, e.g. a chlorinated hydrocarbon such as chloroform, or an aromatic hydrocarbon such as benzene or toluene, optionally with the addition of an acid-binding agent such as pyridine or triethylamine, at a reduced temperature, preferably at a temperature between approx. −25 and 0° C.

(f') A compound of formula VIII may, for example, be obtained by reducing a compound of formula IX,

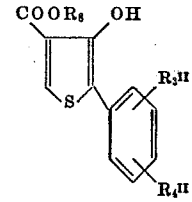


IX

wherein R_1^{II}, R_3^{II} and R_4^{II} are as defined above, and R_8 is alkyl of 1 to 4 carbon atoms.

The reduction may, for example, be effected with a complex metal hydride, e.g. lithium aluminum hydride or sodium dihydro-bis)2 - methoxyethoxy)aluminate, in an inert organic solvent, e.g. an ether such as diethyl ether, tetrahydrofuran, dioxane or 1,2-dimethoxyethane, or in an aromatic hydrocarbon such as benzene, and is preferably effected at room temperature.

(g') A compound of formula IX may, for example, be obtained in conventional manner, e.g. for the production of phenol ethers by etherifying a phenolic compound of formula X,



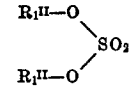
X

wherein R_3^{II}, R_4^{II} and R_8 are as defined above,

preferably in the form of a salt thereof, with a compound of formula XI*a*,

$$R_1^{II}—X^I \qquad \text{XI}a$$

or XI*b*,

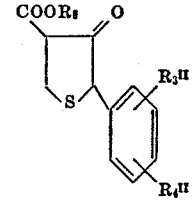


XI*b*

wherein R_1^{II} and X^I are as defined above,

in the presence of a basic condensation agent. Examples of basic condensation agents which may be used are alkali metal hydroxides, alkali metal alcoholates, sodamide or sodium hydride, in a suitable solvent. Examples of solvents which may be used are alcohol, dimethyl formamide or an excess of the alkylating agent. The reaction with an alkyl halide in the presence of sodium hydride in dimethyl formamide and the reaction with dimethyl sulphate with the addition of a 50% sodium hydroxide solution have been found to be specially convenient.

(h') A compound of formula X may, for example, be produced by oxidizing a compound of formula XII,

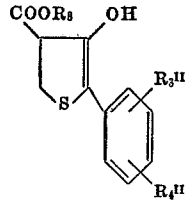


XII

wherein R_3^{II}, R_4^{II} and R_8 are as defined above.

Oxidation of the compounds of formula XII is conveniently effected in an inert polar solvent, e.g. an aliphatic alcohol such as ethanol. In such a solvent a compound

of formula XII is probably partially present in the enol form of formula XII*a*,

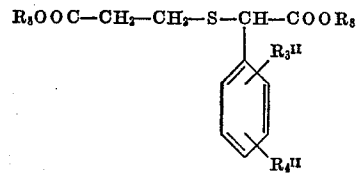


XII*a*

wherein R_3^{II}, R_4^{II} and R_8 are as defined above.

Examples of oxidizing agents which may be used are atmospheric oxygen, hydrogen peroxide, chlorine, bromosuccinimide, manganese dioxide, potassium permanganate or lead dioxide.

(i') A compound of formula XII may, for example, be obtained by cyclization of a compound of formula XIII,

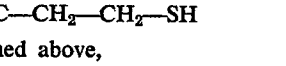


XIII

wherein R_3^{II}, R_4^{II} and R_8 are as defined above,

in conventional manner.

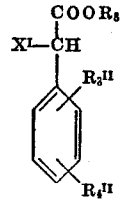
(j') A compound of formula XIII may, for example, be produced by reacting a β-mercaptopropionic acid alkyl ester of formula XIV,



XIV

wherein R_8 is as defined above,

with a compound of formula XV,

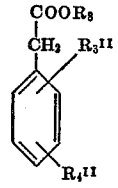


XV

wherein R_3^{II}, R_4^{II}, R_8 and X^I are as defined above,

in the presence of a basic condensation agent e.g. an alkali metal alcoholate, in an inert organic solvent.

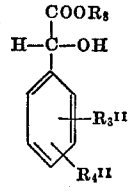
(k') A compound of formula XV may, for example, be obtained by reacting a compound of formula XVI,



XVI

wherein R_3^{II}, R_4^{II} and R_8 are as defined above,

with bromosuccinimide in an inert organic solvent, in the presence of an organic peroxide, or by chlorinating a compound of formula XVII,



XVII

wherein R_3^{II}, R_4^{II} and R_8 are as defined above,

with a chlorinating agent, e.g. thionyl chloride or phosphorus pentachloride, in conventional manner.

Insofar as the production of the starting materials is not described, these are known or may be produced in accordance with known processes, or in a manner analogous to the processes described herein or to known processes.

The compounds of formula I have hitherto not been described in the literature. They are useful because they exhibit pharmacodynamic properties in animals, e.g. mammals. In particular, they are useful as antiphlogistics for the inhibition of exudation in inflammations or edemas, as indicated by standard tests, e.g. the Carrageen paw edema test in the rat, wherein inhibition of edma formation is observed at a dose of 5 to 30 mg./kg. animal body weight, or in the subchronic granuloma cyst test in the rat, wherein inhibition of cyst formation is observed at a dose of approximately 20 to 80 mg./kg. animal body weight. For the abovementioned use, doses to be used will naturally vary depending on the compound used, the mode of administration and the condition to be treated. However, in general satisfactory results are obtained when administered orally or parenterally at a daily dosage of from 1 to 80 mg./kg. animal body weight, conveniently given in divided doses 2 or 3 times a day or in sustained release form. For the larger mammals the total daily dosage amounts to from 50 to 300 mg. and dosage forms siutable for oral administration contain approximately 15 to 150 mg. of the compounds, aside from solid or liquid pharmaceutical carriers or diluents.

The compounds 4 - methoxy - 5 - phenyl - 3 - thiophene acetic acid and 2 - (4 - methoxy - 5 - phenyl - 3 - thienyl) propionic acid and pharmaceutically acceptable salts thereof, especially (+) - 2 - (4 - methoxy - 5 - phenyl - 3 - thienyl) propionic acid, have been found to be particularly effective. Specific daily doses suitable for oral administration are as follows, viz:

(i) 4-methoxy-5-phenyl-3-thiophene acetic acide: about 1 to 22 mg./kg. animal body weight.
(ii) 2-(4-methoxy-5-phenyl-3-thienyl) propionic acid: about 1 to 40 mg./kg. animal body weight and
(iii) (+)-2-(4-methoxy-5-phenyl-3-thienyl) propionic acid: about 1 to 40 mg./kg. animal body weight.

The compounds of formula I are also useful as arthritis-inhibiting agents as indicated by standard tests. Thus, for example, in the Freund adjuvant arthritis latent period test in rats, they inhibit swelling at a dose of approximately 30 to 100 mg./kg. animal body weight. For such use the dosage to be used will naturally vary depending on the compound used, the mode of administration and the condition to be treated. However, in general, satisfactory results are obtained when administered orally or parenterally at a daily dosage of from about 1 to 100 mg./kg. animal body weight, conveniently given in divided doses 2 or 3 times a day, or in sustained release form. For the larger mammals, the total daily dosage is in the range of from about 100 to 500 mg. and dosage forms suitable for oral administration, contain from about 30 to 250 mg. of the new compounds, aside from solid or liquid pharmaceutical carriers or diluents.

The compounds 2-(4-methoxy-5-phenyl-3-thienyl) propionic acid and pharmaceutically acceptable salts thereof, especially (+)-2-(4-methoxy-5-phenyl-3-thienyl) propionic acid, have been found to be particularly effective. Specific daily doses suitable for oral administration are as follows, viz:

(i) 2-(4-methoxy-5-phenyl-3-thienyl) propionic acid: 1 to 100 mg./kg. animal body weight and
(ii) (+) - 2 - (4 - methoxy - 5 - phenyl - 3 - thienyl) propionic acid: 1 to 100 mg./kg. animal body weight.

The new compounds or where appropriate their water-soluble, pharmaceutically acceptable salts, e.g., the sodium or potassium salts, may be used as medicaments on their own or in the form of a pharmaceutical composition comprising a compound of formula I, where appropriate

in free acidic or pharmaceutically acceptable salt form, in association with a pharmaceutical carrier or diluent. Suitable forms of composition for oral administration are tablets and capsules which may be produced in conventional manner and contain, aside from pharmaceutical carriers or diluents, conventional adjuvants.

One preferred group of compounds are the compounds of formula I wherein

R_1 is alkyl of 1 to 4 carbon atoms, particularly methyl,
R_2 is hydroxy,
R_3 and R_4 are each independently hydrogen alkyl of 1 to 4, preferably 1 to 3, carbon atoms or alkoxy of 1 to 4, preferably 1 to 3, carbon atoms, particularly hydrogen, methyl or methoxy, and/or one of R_5 and R_6 is hydrogen.

When R_2 is mono- or dialkylamino, the or each alkyl substituent preferably has 1 to 2 carbon atoms, e.g. methyl.

When R_5 is alkyl, this preferably has 1 to 3 carbon atoms, particularly 1 or 2 carbon atoms, e.g. methyl.

When R_5 is different to R_6 in the compounds of formula I, e.g. 2-(4-methoxy-5-phenyl-3-thienyl) propionic acid, then the compounds possess an asymmetric centre, i.e. the carbon atom to which R_5 and R_6 are bonded, and as hereinbefore described, the compounds may exist in optically pure forms, i.e. in the form of the optical isomers, as well as in racemic form. Of the optically pure forms, in general, the preferred form is that form having a configuration at the abovementioned asymmetric centre identical to (+)-2-(4-methoxy-5-phenyl-3-thienyl) propionic acid. This form of the compounds will hereinafter be referred to as the "D' form" of the compounds and is to be distinguished from the "L' form," i.e. that form having identical configuration to (—)-2-(4-methoxy-5-phenyl-3-thienyl) propionic acid. Determination of the relative configuration of optical isomers of compounds of formula I, wherein R_5 is different to R_6, with respect to (+)-2-(4-methoxy-5-phenyl-3-thienyl) propionic acid may be effected in conventional manner.

Examples of the present invention will now be described. In the following examples all temperatures are indicated in degrees centigrade.

Example 1: 4-Methoxy-5-phenyl-3-thiophene acetic acid

(A) 2 g. of 4-methoxy-5-phenyl-3-thiophene acetonitrile are boiled at reflux for 18 hours in 40 cc. of 2 N caustic soda solution with the addition of a small amount of ethanol. The reaction solution is then rendered acid to Congo red with 2 N sulphuric acid, is extracted with ether, and the ethereal phase is washed with a saturated sodium chloride solution. Drying is effected over magnesium sulphate, the ether is evaporated and the resulting title compound is recrystallized from ether/pentane. M.P. 88–94°.

(B) A solution of 100 g. of 4-methoxy-5-phenyl-3-thiophene acetonitrile in 500 cc. of ethanol is saturated with hydrochloric acid gas while cooling with ice. The reaction solution is then boiled at reflux for 8 hours, is cooled and is diluted with 50 cc. of water while cooling. The reaction mixture is kept at 80° for 1 hour, is evaporated to dryness, and the flask residue is heated to 50° for 3 hours in a solution of 20 g. of potassium hydroxide in 250 cc. of water and 100 cc. of ethanol. The reaction solution is evaporated to dryness, and the residue is divided between benzene and water. The aqueous layer is rendered acid to Congo red with 2 N sulphuric acid and is extracted with benzene. Drying is effected over magnesium sulphate, the solvent is evaporated, and the resulting 4-methoxy-5-phenyl-3-thiophene acetic acid is recrystallized from ether/petroleum ether. M.P. 88–94°.

The starting material may be obtained as follows:

(a) 10 g. of 4-hydroxy-5-phenyl-3-thiophene carboxylic acid ethyl ester are heated to 60° for 15 minutes with 0.97 g. of sodium hydride dispersed in 40 cc. of dimethyl formamide. 5.5 g. of methyl iodide dissolved in 20 cc. of dimethyl formamide are then added dropwise to the reaction mixture which has again been cooled to room temperature, and stirring is effected at room temperature for 2½ hours. The reaction mixture is subsequently poured on ice, is extracted with methylene chloride, and the methylene chloride layer is extracted with a 2 N caustic soda solution cooled with ice. The crude 4-methoxy-5-phenyl-3-thiophene carboxylic acid ethyl ester, obtained after evaporating the methylene chloride phase which has been washed with sodium chloride solution and dried over magnesium sulphate, is distilled in a Hickmann flask (B.P. 144°/0.09 mm. Hg) and crystallizes upon cooling. M.P. 55–57°.

(b) A solution of 542 g. of 4-methoxy-5-phenyl-3-thiophene carboxylic acid ethyl ester in 1.5 litres of tetrahydrofuran is added dropwise in an atmosphere of nitrogen to a suspension of 100 g. of lithium aluminium hydride in 1.5 litres of tetrahydrofuran within 2 hours, and the reaction mixture is stirred at room temperature for a further 16 hours. The slightly exothermic reaction can be kept at a reaction temperature of 20–35° by occasional cooling with ice water. The excess lithium aluminium hydride is subsequently decomposed by the addition of a saturated aqueous sodium sulphate solution while cooling well. Dilution is effected with 2 litres of benzene, the resulting precipitate is filtered off, washing is effected with benzene, and the combined filtrates are concentrated by evaporation. The resulting crude 4-methoxy-5-phenyl-3-thenyl alcohol is distilled in a Hickmann flask. B.P. 139–141°/0.1 mm. Hg. Yellow oil.

(c) 316 g. of thionyl chloride are added dropwise at —20° to a solution of 533 g. of 4-methoxy-5-phenyl-3-thenyl alcohol in 1.5 litres of chloroform. The reaction mixture is stirred at —20° for a further 2 hours, the solvent is evaporated and the residue is divided between chloroform and water. The chloroform phase, which has been washed with dilute sodium hydrogen carbonate solution and dried over magnesium sulphate, is concentrated by evaporation, and the resulting crude 4-methoxy-5-phenyl-3-thenyl chloride is distilled in a Hickmann flask. B.P. 138°/0.1 mm. Hg. 4-methoxy-5-phenyl-3-thenyl chloride is obtained as a viscous oil which crystallizes upon standing for a long time.

(d) A solution of 150 g. of 4-methoxy-5-phenyl-3-thenyl chloride in 200 cc. of acetone is added dropwise while stirring to 37 g. of sodium cyanide and 15 g. of sodium iodide in 60 cc. of water and 500 cc. of acetone, and the reaction mixture is subsequently heated at reflux while stirring for 20 hours. The acetone is then removed by evaporation and the residue is divided between benzene and water. After evaporating the benzene phase, crude 4-methoxy-5-phenyl-3-thiophene acetonitrile is obtained as yellow residue and is distilled in a Hickmann flask. B.P. 146°/0.1 mm. Hg.

The following compounds may be produced in a manner analogous to that described in Example 1A or 1B.

Ex. No.	Substance	Produced analog. to Ex. No.	Physical constants, observations
2	5-(4-fluorophenyl)-4-methoxy-3-thiophene acetic acid	1A	M.P. 114–116° (ether/petroleum ether).
	Starting material:		
	(a) 5-(4-fluorophenyl)-4-methoxy-3-thiophene carboxylic acid ethyl ester	1a	$B.P._{0.15}$ 160°, M.P. 94–95° (ethanol).
	(b) 5-(4-fluorophenyl)-4-methoxy-3-thenyl alcohol	1b	Unpurified.
	(c) 5-(4-fluorophenyl)-4-methoxy-3-thenyl chloride	1c	Unpurified oil.
	(d) 5-(4-fluorophenyl)-4-methoxy-3-thiophene acetonitrile	1d	Unpurified.

TABLE—Continued

Ex. No.	Substance	Produced analog. to Ex. No.	Physical constants, observations
3	5-(4-chlorophenyl)-4-methoxy-3-thiophene acetic acid	1A	M.P. 85–87° (ether/petroleum ether).
	Starting material:		
	(a) 5-(4-chlorphenyl)-4-methoxy-3-thiophene carboxylic acid ethyl ester	1a	M.P. 98–101° (ethanol).
	(b) 5-(4-chlorphenyl)-4-methoxy-3-thenyl alcohol	1b	Unpurified.
	(c) 5-(4-chlorophenyl)-4-methoxy-3-thenyl chloride	1c	Do.
	(d) 5-(4-chlorphenyl)-4-methoxy-3-thiophene acetonitrile	1d	Do.
4	4-methoxy-5-(4-methoxyphenyl)-3-thiophene acetic acid	1A	M.P. 101–104° (ether, sinters from 80°).
	Starting material:		
	(a) 4-methoxy-5-(4-methoxyphenyl)-3-thiophene carboxylic acid ethyl ester.	1a	B.P.$_{0.1}$ 160°, oil which solidifies in crystalline form.
	(b) 4-methoxy-5-(4 methoxyphenyl)-3-thenyl alcohol	1b	Unpurified.
	(c) 4-methoxy-5-(4-methoxyphenyl)-3-thenyl chloride	1c	Do.
	(d) 4-methoxy-5-(4-methoxyphenyl)-3-thiophene acetonitrile	1d	M.P. 75–77° (from petroleum ether).

Example 5: 5-(3-Chlorophenyl)-4-methoxy-3-thiophene acetic acid

5 - (3 - chlorophenyl) - 4 - methoxy-3-thiophene acetonitrile is reacted in accordance with the process described in Example 1A. M.P. of the title compound: 101–103° (from acetone/petroleum ether).

The starting material may be obtained as follows:

(a) 160.0 g. of β-mercaptopropionic acid ethyl ester are added dropwise at 60° within 90 minutes to a mixture of 58 g. of a 50% sodium hydride dispersion and 500 cc. of toluene in an atmosphere of nitrogen, the mixture is stirred at 90° for a further 30 minutes, is allowed to cool to 25°, and a solution of 330 g. of α-bromo-3-chlorophenyl acetic acid ethyl ester in 500 cc. of toluene is added dropwise. The reaction mixture is stirred at room temperature for 18 hours and is subsequently extracted with water while cooling with ice. Upon concentrating the toluene phase, α-[2-(carbethoxy)ethylthio]-3-chlorophenyl acetic acid ethyl ester is obtained as yellow viscous oil and is used for the next reaction without purification.

(b) A solution of 358 g. of crude α-[2-(carbethoxy) ethylthio]-3-chlorophenyl acetic acid ethyl ester in 500 cc. of toluene is added dropwise within 60 minutes to a sodium ethylate suspension produced from 55 g. of sodium in 1 litre of toluene, the reaction mixture is stirred at room temperature for 1 hour and is heated at reflux for a further 2 hours. After cooling, the reaction mixture is poured on a mixture of ice and 1 litre of 2 N sulphuric acid. The organic phase, which has been washed with an aqueous sodium hydrogen carbonate solution and water, is concentrated, whereby crude 5-(3-chlorophenyl)tetrahydro-4-oxo-3-thiophene carboxylic acid ethyl ester is obtained and used for the next reaction without purification.

(c) 400 cc. of a 40% hydrogen peroxide solution are added dropwise at 60° to a solution of 315 g. of 5-(3-chlorophenyl)tetrahydro - 4-oxo-3-thiophene carboxylic acid ethyl ester in 500 cc. of ethanol, the reaction mixture is kept at 60° for a further hour, is cooled in an ice bath, is diluted by the addition of 2 litres of water and is extracted with benzene. The 5-(3-chlorophenyl)-4-hydroxy-3-thiophene carboxylic acid ethyl ester, obtained after concentrating the benzene phase, is recrystallized from methanol. M.P. 84–87°.

(d) 5 - (3 - chlorophenyl) - 4-methoxy-3-thiophene carboxylic acid ethyl ester, produced in a manner analogous to that described in Example 1 (a). After recrystallization from ethanol/petroleum ether the product has a M.P. of 74–76°.

(e) 5 - (3 - chlorophenyl) - 4 - methoxy - 3 - thenyl alcohol, produced in a manner analogous to that described in Example 1(b), colourless viscous oil. B.P. 154–155°/0.1 mm. Hg.

(f) 5 - (3 - chlorophenyl) - 4-methoxy-3-thenyl chloride, produced in a manner analogous to that described in Example 1(c). The crude product is obtained as yellow viscous oil and is used as such for the next reaction.

(g) 5 - (3 - chlorophenyl) - 4 - methoxy-3-thiophene acetonitrile, produced in a manner analogous to that described in Example 1(d). B.P. 164–166°/0.08 mm. Hg, yellow viscous oil.

Example 6: 4-Methoxy-5-*o*-tolyl-3-thiophene acetic acid

4-methoxy-5-*o*-tolyl-3-thiophene acetonitrile is reacted in accordance with the process described in Example 1B. The crude compound is purified by chromatography on silica gel, eluant: toluene. M.P. of the title compound: 60–62° (from pentane).

The starting material may be obtained as follows:

(a) 100 g. of β-mercaptopropionic acid ethyl ester are added dropwise at 5–10° to a solution of 18 g. of sodium in 400 cc. of ethanol, in an atmosphere of nitrogen, 157 g. of α-chloro-*o*-tolyl acetic acid ethyl ester are then added dropwise, whereby the temperature should not exceed 40°; the reaction mixture is stirred at room temperature for 2 hours and is boiled at reflux for 1 hour, is concentrated and divided between water and ether. The crude 2-[2-(carbethoxy)ethylthio]-*o*-tolyl acetic acid ethyl ester, obtained as orange-coloured oil after concentrating the organic phase which has been washed with sodium chloride solution, is used for the next reaction without purification.

(b) Tetrahydro-4-oxo-5-*o*-tolyl-3-thiophene carboxylic acid ethyl ester, produced in a manner analogous to that described in Example 5(b). The crude compound is obtained as orange-coloured oil and is used for the next reaction without purification.

(c) 4-hydroxy-5-*o*-tolyl-3-thiophene carboxylic acid ethyl ester, produced in a manner analogous to that described in Example 5(c). Working up is effected by dividing the reaction mixture between an ice-cold 5% sodium chloride solution and chloroform, concentrating the organic phase which has been washed with sodium chloride solution and an iron II sulphate solution, and subjecting the resulting oil to chromatography on silica gel, whereby the compound is eluted with toluene. M.P. 43–45° (from pentane).

(d) 4-methoxy-5-*o*-tolyl-3-thiophene carboxylic acid ethyl ester, produced in a manner analogous to that described inn Example 1(a). The crude product is purified by chromatography on silica gel (eluant: toluene), and the resulting oil is used for the next reaction without further purification.

(e) A solution of 87 g. of the ester described above in 400 cc. of toluene is added dropwise at 60° in an atmosphere of nitrogen to a mixture of 185 cc. of a 70% benzene solution of sodium dihydro-bis(2-methoxyethoxy) aluminate and 400 cc. of toluene, the mixture is stirred at 60° for 2½ hours, 120 cc. of a 30% caustic soda solution are subsequently added dropwise while cooling with ice, dilution with 400 cc. of water and extraction with toluene are effected. Upon concentrating the toluene phase which has been washed with a 2 N caustic soda solution and sodium chloride solution, crude 4-methoxy-5-*o*-tolyl-3-thenyl alcohol is obtained as an oil which is used as such for the next reaction.

(f) 4-methoxy-5-*o*-tolyl-3-thenyl chloride, produced in a manner analogous to that described in Example 1(c). The crude compound obtained as an oil is used for the next reaction without purification.

(g) 4-methoxy-5-*o*-tolyl-3-thiophene acetonitrile, produced in a manner analogous to that described in Example 1(d). Reaction time 7 hours. The crude product is chromatographed on silica gel and the compound, ob-

tained as yellow oil after elution with toluene, is used as such for the next reaction.

The following compounds may be produced in a manner analogous to that described in Example 1A or 1B.

Ex. No.	Substance	Produced analog. to Ex. No.	Physical constants, observations
7	4-methoxy-5-*m*-tolyl-3-thiophene acetic acid	1B	M.P. 89–90° (ether/pentane).
	Starting material:		
	(a) 2-[2-(carbethoxy)ethylthio]-*m*-tolyl acetic acid ethyl ester	6a	Unpurified oil.
	(b) tetrahydro-4-oxo-5-*m*-tolyl-3-thiophene carboxylic acid ethyl ester	5b	Do.
	(c) 4-hydroxy-5-*m*-tolyl-3-thiophene carboxylic acid ethyl ester	6c	Do.
	(d) 4-methoxy-5-*m*-tolyl-3-thiophene carboxylic acid ethyl ester	6d	Do.
	(e) 4-methoxy-5-*m*-tolyl-3-thenyl alcohol	6e	Do.
	(f) 4-methoxy-5-*m*-tolyl-3-thenyl chloride	1c	Do.
	(g) 4-methoxy-5-*m*-tolyl-3-thiophene acetonitrile	6g	Unpurified.
8	4-methoxy-5-*p*-tolyl-3-thiophene acetic acid	1B	M.P. 88–90° (ether/pentane).
	Starting material:		
	(a) 2-[2-(carbethoxy)ethylthio]-*p*-tolyl acetic acid ethyl ester	6a	Unpurified oil.
	(b) tetrahydro-4-oxo-5-*p*-tolyl-3-thiophene carboxylic acid ethyl ester	5b	M.P. 75–76° (pentane), purification by chromatography on silica gel.
	(c) 4-hydroxy-5-*p*-tolyl-3-thiophene carboxylic acid ethyl ester	6c	M.P. 74–75° (pentane).
	(d) 4-methoxy-5-*p*-tolyl-3-thiophene carboxylic acid ethyl ester	6d	Unpurified oil.
	(e) 4-methoxy-5-*p*-tolyl-3-thenyl alcohol	6e	Do.
	(f) 4-methoxy-5-*p*-tolyl-3-thenyl chloride	1c	Do.
	(g) 4-methoxy-5-*p*-tolyl-3-thiophene acetonitrile	6g	Do.
9	5-(2-chlorophenyl)-4-methoxy-3-thiophene acetic acid	1B	M.P. 97–100° (pentane).
	Starting material:		
	(a) 2-[2-(carbethoxy)ethylthio]-2-chlorophenyl acetic acid ethyl ester	6a	Unpurified oil.
	(b) 5-(2-chlorophenyl)tetrahydro-4-oxo-3-thiophene carboxylic acid ethyl ester.	5b	Do.
	(c) 5-(2-chlorophenyl)-4-hydroxy-3-thiophene carboxylic acid ethyl ester	6c	M.P. 47–49°.
	(d) 5-(2-chlorophenyl)-4-methoxy-3-thiophene carboxylic acid ethyl ester	1a	Unpurified oil.
	(e) 5-(2-chlorophenyl)-4-methoxy-3-thenyl alcohol	6e	Do.
	(f) 5-(2-chlorophenyl)-4-methoxy-3-thenyl chloride	1c	Do.
	(g) 5-(2-chlorophenyl)-4-methoxy-3-thiophene acetonitrile	6g	Do.

Example 10: 5-(2,4-Dichlorophenyl)-4-methoxy-3-thiophene acetic acid

5-(2,4-Dichlorophenyl)-4-methoxy-3-thiophene acetonitrile is reacted in accordance with the process described in Example 1A. M.P. of the title compound: 107–109° (from diethyl ether/pentane).

The starting material may be obtained as follows:

(a) A solution of 310 g. of 2,4-dichlorobenzyl chloride in 600 cc. of ethanol is added dropwise to a solution heated to 100° in an oil bath of 120.5 g. of sodium cyanide in 96 cc. of water, and the mixture is heated at reflux for 1½ hours. The ethanol is then removed by distillation at reduced pressure, the residue is dissolved between diethyl ether and water, and the crude oily 2,4-dichlorophenyl acetonitrile, obtained after concentrating the ether extract, is distilled in a high vacuum. B.P. 140–143°/0.03 mm. Hg.

(b) A solution of 80.0 g. of 2,4-dichlorophenyl acetonitrile in 510 cc. of ethanol is saturated with hydrogen chloride gas at room temperature, is heated at reflux for 20 hours, 15 cc. of water are added, and heating at reflux is effected for a further 3 hours. The reaction mixture is subsequently completely concentrated at reduced pressure, the residue is taken up in benzene, is extracted with water, and the dried benzene phase is concentrated. The resulting crude 2,4-dichlorophenyl acetic acid ethyl ester is distilled in a high vacuum. B.P. 90°/0.05 mm. Hg.

(c) 95.0 g. of 2,4 - dichlorophenyl acetic acid ethyl ester, 80.3 g. of N-bromosuccinimide and 0.6 g. of dibenzoyl peroxide are heated at reflux for 16 hours in 350 cc. of carbon tetrachloride. After cooling to −20°, the succinimide is filtered off, and the filtrate is completely concentrated at reduced pressure. The resulting oily crude α-bromo-2,4-dichlorophenyl acetic acid ethyl ester is distilled in a high vacuum. B.P. 113–115°/0.06 mm. Hg.

(d) α-[2-(carbethoxy)ethylthio] - 2,4 - dichlorophenyl acetic acid ethyl ester, produced in a manner analogous to that described in Example 5(a). Solvent: benzene. Reaction time 30 minutes at room temperature, and 1 hour at 50°. Working up is effected by pouring the reaction mixture on ice/water, neutralizing the same with 0.5 N hydrochloric acid, separating the benzene phase, washing this with a saturated sodium chloride solution, drying and concentrating. The resulting oily crude compound (R_f value 0.3, adsorbent: silica gel, eluant: benzene, n_D^{24} = 1.5330) is used for the next reaction without purification.

(e) 5-(2,4-dichlorophenyl)tetrahydro - 4 - oxo-3-thiophene carboxylic acid ethyl ester, produced in a manner analogous to that described in Example 5(b). Reaction time 16 hours at room temperature. Working up is effected by pouring the reaction mixture on a mixture of ice water/hydrochloric acid having a pH of 3, extracting the aqueous phase with diethyl ether, concentrating the combined organic phases which have been washed with saturated sodium chloride solution, and recrystallizing the resulting compound from ethanol. M.P. 69–71°.

(f) 5-(2,4-dichlorophenyl) - 4 - hydroxy-3-thiophene carboxylic acid ethyl ester, produced in a manner analogous to that described in Example 5(c). Reaction time 18 hours in an oil bath at 60°. After cooling the reaction mixture to −10°, the compound precipitates in crystalline form, is filtered off and is washed twice with cold ethanol. M.P. 105–107°.

(g) 5-(2,4-dichlorophenyl) - 4 - methoxy-3-thiophene carboxylic acid ethyl ester, produced in a manner analogous to that described in Example 1(a). Reaction time 20 hours at room temperature. Working up is effected by pouring the mixture on ice water, adjusting the pH to 4 with 1 N hydrochloric acid, extracting with diethyl ether and concentrating the organic phase which has been washed with a saturated sodium chloride solution and purified over animal charcoal. The resulting compound is recrystallized from diethyl ether/pentane 1:2. M.P. 78–80°.

(h) 5-(2,4-dichlorophenyl) - 4 - methoxy - 3 - thenyl alcohol, produced in a manner analogous to that described in Example 6(e). The crude compound (R_f value 0.65, adsorbent: silica gel, eluant: chloroform/ethanol 9:1) is used for the next reaction without purification.

(i) 5-(2,4-dichlorophenyl) - 4 - methoxy - 3 - thenyl chloride, produced in a manner analogous to that described in Example 1(c). B.P. 150–160°/0.06 mm. Hg.

(j) 5-(2,4-dichlorophenyl) - 4 - methoxy-3-thiophene acetonitrile, produced in a manner analogous to that described in Example 1(d). Reaction time four hours at 60°. The crude oily compound (R_f value 0.35, adsorbent: silica gel, eluant: chloroform) is used for the next reaction without purification.

The following compounds may be produced in a manner analogous to that described in Example 1A or 1B.

Ex. No.	Substance	Produced analog. to Ex. No.	Physical constants, observations
11	5-(3-fluorophenyl)-4-methoxy-3-thiophene acetic acid	1A	M.P. 90–92° (diethyl ether/pentane).
	Starting material:		
	(a) α-Bromo-3-fluorophenyl acetic acid ethyl ester	10c	$B.P._{13}$ 138–140°.
	(b) α-[2-(carbethoxy)ethylthio]-3-fluorophenyl acetic acid ethyl ester.	10d	Unpurified oil (Rf value 0.3, adsorbent: silica gel, eluant: chloroform).
	(c) 5-(3-fluorophenyl)tetrahydro-4-oxo-3-thiophene carboxylic acid ethyl ester.	10e	Unpurified oil (Rf value 0.5, adsorbent: silica gel, eluant: chloroform).
	(d) 5-(3-fluorophenyl)-4-hydroxy-3-thiophene carboxylic acid ethyl ester.	10f	M.P. 60° (pentane) (Rf value 0.6, adsorbent: silica gel, eluant: chloroform).
	(e) 5-(3-fluorophenyl)-4-methoxy-3-thiophene carboxylic acid ethyl ester.	10g	M.P. 62–64° (diethyl ether/pentane).
	(f) 5-(3-fluorophenyl)-4-methoxy-3-thenyl alcohol	6e	Unpurified oil (Rf value 0.65, adsorbent: silica gel, eluant: chloroform/ethanol 9:1).
	(g) 5-(3-fluorophenyl)-4-methoxy-3-thenyl chloride	1c	Unpurified oil (Rf value 0.6, adsorbent: silica gel, eluant: chloroform).
	(h) 5-(3-fluorophenyl)-4-methoxy-3-thiophene acetonitrile	1d	Unpurified oil (Rf value 0.45, adsorbent: silica gel, eluant: chloroform).
12	5-(3,4-dichlorophenyl)-4-methoxy-3-thiophene acetic acid	1A	M.P. 125–127° (diethyl ether/pentane).
	Starting material:		
	(a) 3,4-dichlorophenyl acetic acid ethyl ester	10b	$B.P._{0.1}$ 115°, n_D^{32} 1.5310.
	(b) α-Bromo-3,4-dichlorophenyl acetic acid ethyl ester	10c	$B.P._{0.1}$ 146°, n_D^{33} 1.5650.
	(c) α-[2-(carbethoxy)ethylthio]-3,4-dichlorophenyl acetic acid ethyl ester.	6a	Unpurified, $B.P._{0.04}$ 155°.
	(d) 5-(3,4-dichlorophenyl)tetrahydro-4-oxo-3-thiophene carboxylic acid ethyl ester.	5b	(Rf value 0.3, adsorbent: silica gel, eluant: benzene/ethanol/concentrated ammonia 75:15:10).
	(e) 5-(3,4-dichlorophenyl)-4-hydroxy-3-thiophene carboxylic acid ethyl ester.	5c	M.P. 103–105° (chloroform/pentane).
	(f) 5-(3,4-dichlorophenyl)-4-methoxy-3-thiophene carboxylic acid ethyl ester.	10g	M.P. 87–89° (diethyl ether/pentane).
	(g) 5-(3,4-dichlorophenyl)-4-methoxy-3-thenyl alcohol	6e	$B.P._{0.1}$ 170–180°, M.P. 91–92° (ether/pentane).
	(h) 5-(3,4-dichlorophenyl)-4-methoxy-3-thenyl chloride	1c	M.P. 67–68° (chloroform/pentane).
	(i) 5-(3,4-dichlorophenyl)-4-methoxy-3-thiophene acetonitrile.	1d	Unpurified (Rf value 0.4, adsorbent: silica gel, eluant: chloroform).
13	5-(3,4-dimethoxyphenyl)-4-methoxy-3-thiophene acetic acid	1A	M.P. 123–126° (benzene/petroleum ether).
	Starting material:		
	(a) α-[2-(carbethoxy)ethylthio]-3,4-dimethoxyphenyl acetic acid ethyl ester.	6a	Unpurified.
	(b) 5-(3,4-dimethoxyphenyl)tetrahydro-4-oxo-3-thiophene carboxylic acid ethyl ester.	5b	M.P. 79–80° (ethanol).
	(c) 5-(3,4-dimethoxyphenyl)-4-hydroxy-3-thiophene carboxylic acid ethyl ester.	5c	M.P. 80–82° (ethanol).
	(d) 5-(3,4-dimethoxyphenyl)-4-methoxy-3-thiophene carboxylic acid ethyl ester.	1a	$B.P._{0.05}$ 183°, M.P. 74–77° (petroleum ether).
	(e) 5-(3,4-dimethoxyphenyl)-4-methoxy-3-thenyl alcohol	1b	M.P. 79–82° (petroleum ether).
	(f) 5-(3,4-dimethoxyphenyl)-4-methoxy-3-thenyl chloride	1c	M.P. 94–97° (ether/petroleum ether).
	(g) 5-(3,4-dimethoxyphenyl)-4-methoxy-3-thiophene actonitrile.	1d	Unpurified oil.
14	4-isopropoxy-5-phenyl-3-thiophene acetic acid	1A	M.P. 63° (ether/petroleum ether).
	Starting material:		
	(a) 4-isopropoxy-5-phenyl-3-thiophene carboxylic acid ethyl ester.	1a	Unpurified oil, $B.P._{0.05}$ 140°.
	(b) 4-isopropoxy-5-phenyl-3-thenyl alcohol	1b	Unpurified oil.
	(c) 4-isopropoxy-5-phenyl-3-thenyl chloride	1c	Do.
	(d) 4-isopropoxy-5-phenyl-3-thiophene acetonitrile	1d	Do.
15	4-ethoxy-5-phenyl-3-thiophene acetic acid	1A	M.P. 53–57° (pentane).
	Starting material:		
	(a) 4-ethoxy-5-phenyl-3-thiophene carboxylic acid ethyl ester.	1a	Unpurified.
	(b) 4-ethoxy-5-phenyl-3-thenyl alcohol	1b	Do.
	(c) 4-ethoxy-5-phenyl-3-thenyl chloride	1c	Do.
	(d) 4-ethoxy-5-phenyl-4-thiophene acetonitrile	1d	Do.

Example 16: 2-(4-Methoxy-5-phenyl-3-thienyl) propionic acid

2 - (4-methoxy-5-phenyl-3-thienyl)propionitrile is reacted in accordance with the process described in Example 1A, using a 50% caustic soda solution. Reaction time 16 hours. M.P. of the title compound (racemate): 101–102° (from ether/petroleum ether).

M.P. of the sodium salt of the title compound: 236–238° (decomp., from ethanol/acetone).

The optical antipodes may be obtained from the racemic compound as follows:

(A) (−) - 2-(4-Methoxy-5-phenyl-3-thienyl)propionic acid: The racemate of 2-(4-methoxy-5-phenyl-3-thienyl) propionic acid is dissolved in a 12-fold quantity of acetone, and the calculated amount of cinchonidine is added. After 3 hours, the crystalline precipitate, which contains the cinchonidine salt of (−) - 2 - (4-methoxy-5-phenyl-3-thienyl)propionic acid in strongly concentrated form, is filtered off and recrystallized several times from ethanol. M.P. of the cinchonidine salt: 131–134°. $[\alpha]_D = -97°$ (in ethanol, c.=1).

The free acid produced from the cinchonidine salt forms a tough resin, $[\alpha]_D = -76°$ (in chloroform, c.=1).

M.P. of the sodium salt of (−)-2-(4-methoxy-5-phenyl-3-thienyl)propionic acid: 200–202° (from ethanol). $[\alpha]_D = -19.5°$ (in water, c.=1).

(B) (+) - 2-(4-Methoxy-5-phenyl-3-thienyl)propionic acid: The mother liquors obtained after filtering off the cinchonidine salt crystallized above, are acidified with 2 N sulphuric acid and extracted with ether. The residue obtained after concentrating the ether phase, and which contains (+) - 2 - (4-methoxy-5-phenyl-3-thienyl) propionic acid in strongly concentrated form, is converted into a salt with the calculated amount of (−)-α-methylbenzylamine, and this salt is recrystallized several times from ethanol. M.P. of the α-methylbenzylamine salt: 154–157°. $[\alpha]_D = +26°$ (in ethanol, c.=1).

The free acid produced from the α-methylbenzylamine salt forms a tough resin. $[\alpha]_D = +76°$ (in chloroform, c.=1).

M.P. of the sodium salt of (+)-2-(4-methoxy-5-phenyl-3-thienyl)propionic acid: 201–203° (from ethanol). $[\alpha]_D = +19.5°$ (in water, c.=1).

The starting material may be obtained as follows:

(a) An ethereal solution of 11.5 g. of 4-methoxy-5-phenyl-3-thiophene acetonitrile is added to 5.6 g. of potassium tert.butylate in 80 cc. of ether in an atmosphere of nitrogen. 7.8 g. of methyl iodide are then slowly added dropwise, the mixture is stirred at room temperature for 1 hour and is subsequently extracted with ice water and dried over magnesium sulphate. After evaporating the solvent, crude 2 - (4 - methoxy-5-phenyl-3-thienyl) propionitrile is obtained and is used as such for the next reaction.

The following compounds may be produced in a manner analogous to that described in Example 1 or 16.

Ex. No.	Substance	Produced analog. to Ex. No.	Physical constants, observations
17	2-[4-methoxy-5-(4-methoxyphenyl)-3-thienyl] propionic acid	16	M.P. 99–101° (ether/petroleum ether).
	Starting material: 2-[4-methoxy-5-(4-methoxyphenyl)-3-thienyl]propionitrile	16a	Unpurified.
18	2-[5-(4-chlorophenyl)-4-methoxy-3-thienyl]propionic acid	16	M.P. 82° (ether/petroleum ether).
	Starting material: 2-[5-(4-chlorophenyl)-4-methoxy-3-thienyl]propionitrile	16a	Unpurified.
19	2-[5-(4-fluorophenyl)-4-methoxy-3-thienyl]propionic acid	16	M.P. 101–103° (ether/petroleum ether).
	Starting material: 2-[5-(4-fluorophenyl)-4-methoxy-3-thienyl]propionitrile	16a	Unpurified.
20	2-[5-(3-chlorophenyl)-4-methoxy-3-thienyl]propionic acid	16	M.P. 77–78° (petroleum ether/ether).
	Starting material: 2-[5-(3-chlorophenyl)-4-methoxy-3-thienyl]propionitrile	16a	Unpurified.
21	2-(4-methoxy-5-phenyl-3-thienyl) hexanoic acid	16	M.P. 68–69° (ether/petroleum ether).
	Starting material: 2-(4-methoxy-5-phenyl-3-thienyl) hexanoic acid nitrile	16a	Unpurified.
22	2-(4-methoxy-5-*o*-tolyl-3-thienyl) propionic acid	1B	M.P. 71–72° (pentane).
	Starting material: 2-(4-methoxy-5-*o*-tolyl-3-thienyl)propionitrile	16a	Unpurified.
23	2-(4-methoxy-5-*m*-tolyl-3-thienyl)propionic acid	22	M.P. 82–85° (pentane).
	Starting material: 2-(4-methoxy-5-*m*-tolyl-3-thienyl)propionitrile	16a	Unpurified.
24	2-(4-methoxy-5-*p*-tolyl-3-thienyl)propionic acid	1B	M.P. 86–88° (pentane).
	Starting material: 2-(4-methoxy-5-*p*-tolyl-3-thienyl)propionitrile	16a	Unpurified.
25	2-[5-(2-chlorophenyl)-4-methoxy-3-thienyl]propionic acid	1B	M.P. 108–110° (ether/pentane).
	Starting material: 2-[5-(2-chlorophenyl)-4-methoxy-3-thienyl]propionitrile	16a	Unpurified.
26	2-[5-(2,4-dichlorophenyl)-4-methoxy-3-thienyl] propionic acid	16	M.P. 75–77° (ether/pentane).
	Starting material: 2-[5-(2,4-dichlorophenyl)-4-methoxy-3-thienyl] propionitrile	16a	
27	2-[5-(3-fluorophenyl)-4-methoxy-3-thienyl] propionic acid	16	M.P. 78–80° (ether/pentane).
	Starting material: 2-[5-(3-fluorophenyl)-4-methoxy-3-thienyl] propionitrile	16a	
28	2-[5-(3,4-dimethoxyphenyl)-4-methoxy-3-thienyl] propionic acid	16	M.P. of the sodium salt 245–247° (acetone), produced with 1 N NaOH in methanolic solution,
	Starting material: 2-[5-(3,4-dimethoxyphenyl)-4-methoxy-3-thienyl] propionitrile.	16a	dried at 70° in a high vacuum.
29	2-(4-isopropoxy-5-phenyl-3-thienyl) propionic acid	28	M.P. of the sodium salt 213–215° (acetone).
	Starting material: 2-(4-isopropoxy-5-phenyl-3-thienyl)propionitrile	16a	
30	2-(4-ethoxy-5-phenyl-3-thienyl)propionic acid	28	M.P. of the potassium salt 218° (acetone/ether).
	Starting material: 2-(4-ethoxy-5-phenyl-3-thienyl)propionitrile	16a	
31	2-(4-methoxy-5-phenyl-3-thienyl)butyric acid	16	M.P. of the potassium salt 208–210° (acetone/ether).
	Starting material: 2-(4-methoxy-5-phenyl-3-thienyl)butyronitrile	16a	
32	4-methoxy-5-(*m*-trifluoromethylphenyl)-3-thiophene acetic acid	1A	M.P. 98–100° (ether/petroleum ether).
	Starting material:		
	(a) α-Bromo-*m*-trifluoromethylphenyl acetic acid ethyl ester	10c	Unpurified oil, $B.P._{.12}$ 133°.
	(b) α-[2-(carbethoxy)ethylthio]-*m*-trifluoromethyl-phenyl acetic acid ethyl ester.	5a	Unpurified oil, $B.P._{0.01}$ 130–140°.
	(c) 5-(*m*-trifluoromethylphenyl)tetrahydro-4-oxo-3-thiophene carboxylic acid ethyl ester.	5b	Unpurified.
	(d) 5-(*m*-trifluoromethylphenyl)-4-hydroxy-3-thiophene carboxylic acid ethyl ester.	5c	M.P. 98–99° (aqueous ethanol).
	(e) 4-methoxy-5-(*m*-trifluoromethylphenyl)-3-thiophene carboxylic acid ethyl ester.	1a	$B.P._{0.03}$ 121–124°, n_D^{25} 1.5395.
	(f) 4-methoxy-5-(*m*-trifluoromethylphenyl)-3-thenyl alcohol	6e	$B.P._{0.07}$ 129°, n_D^{25} 1.5612.
	(g) 4-methoxy-5-(*m*-trifluoromethylphenyl)-3-thenyl chloride	1c	$B.P._{0.05}$ 121–123°, n_D^{25} 1.5620.
	(h) 4-methoxy-5-(*m*-trifluoromethylphenyl)-3-thiophene acetonitrile	1d	Distillation in an air bath at 130–140°/0.01 mm. of Hg.
33	4-methoxy-5-(2-methoxyphenyl)-3-thiophene acetic acid	1A	M.P. 93–95° (ether/petroleum ether).
	Starting material:		
	(a) α-Chloro-*o*-methoxyphenyl acetic acid ethyl ester		$B.P._{0.04}$ 103–105°, produced from *o*-methoxy-mandelic acid ethyl ester and thionyl chloride.
	(b) 2-[2-(carbethoxy)ethylthio]-*o*-methoxyphenyl acetic acid ethyl ester	6a	Unpurified.
	(c) 5-(2-methoxyphenyl)tetrahydro-4-oxo-3-thiophene carboxylic acid ethyl ester.	5b	Do.
	(d) 4-hydroxy-5-(2-methoxyphenyl)-3-thiophene carboxylic acid ethyl ester	5c	M.P. 95–97° (ethanol).
	(e) 4-methoxy-5-(2-methoxyphenyl)-3-thiophene carboxylic acid ethyl ester	1a	M.P. 53–55°.
	(f) 4-methoxy-5-(2-methoxyphenyl)-3-thenyl alcohol	6e	$B.P._{0.02}$ 160–170°.
	(g) 4-methoxy-5-(2-methoxyphenyl)-3-thenyl chloride	1c	Unpurified, $B.P._{0.02}$ 170–190°.
	(h) 4-methoxy-5-(2-methoxyphenyl)-3-thiophene acetonitrile	1d	$B.P._{0.05}$ 170–180°.
34	5-(2,5-dichlorophenyl)-4-methoxy-3-thiophene acetic acid	1A	M.P. 93–96° (ether/petroleum ether).
	Starting material:		
	(a) 2,5-dichloromandelic acid ethyl ester		$B.P._{0.3}$ 116–117°, produced from 2,5-dichloromandelic acid and ethanol.
	(b) α-Chloro-2,5-dichlorophenyl acetic acid ethyl ester		$B.P._{0.3}$ 108°, produced from 2,5-dichloromandelic acid ethyl ester and phosphorus pentachloride.
	(c) α-[2-(carbethoxy)ethylthio]-2,5-dichlorophenyl acetic acid ethyl ester	5a	Unpurified, $B.P._{0.01}$ 155–165°.
	(d) 5-(2,5-dichlorophenyl)tetrahydro-4-oxo-3-thiophene carboxylic acid ethyl ester.	5b	M.P. 84–86° (ethanol/water).
	(e) 5-(2,5-dichlorophenyl)-4-hydroxy-3-thiophene carboxylic acid ethyl ester.	5c	M.P. 113–115° (80% ethanol).
	(f) 5-(2,5-dichlorophenyl)-4-methoxy-3-thiophene carboxylic acid ethyl ester.	1a	M.P. 78–80°.
	(g) 5-(2,5-dichlorophenyl)-4-methoxy-3-thenyl alcohol	6e	$B.P._{0.05}$ 155–160°.
	(h) 5-(2,5-dichlorophenyl)-4-methoxy-3-thenyl chloride	1c	$B.P._{0.07}$ 137°.
	(i) 5-(2,5-dichlorophenyl)-4-methoxy-3-thiophene acetonitrile	1d	$B.P._{0.03}$ 158°.
35	2-[5-(*m*-trifluoromethylphenyl)-4-methoxy-3-thienyl] propionic acid	16	M.P. 106–109° (ether/petroleum ether).
	Starting material: 2-[5-(*m*-trifluoromethylphenyl)-4-methoxy-3-thienyl]propionitrile.	16a	Unpurified.
36	2-[5-(2-methoxyphenyl)-4-methoxy-3-thienyl]propionic acid	16	M.P. 113–115° (ether/petroleum ether).
	Starting material: 2-[5-(2-methoxyphenyl)-4-methoxy-3-thienyl]propionitrile.	16a	Unpurified.
37	2-[5-(2,5-dichlorophenyl)-4-methoxy-3-thienyl] propionic acid	16	M.P. 108–112° (ether/petroleum ether).
	Starting material: 2-[5-(2,5-dichlorophenyl)-4-methoxy-3-thienyl] propionitrile	16a	Unpurified.
38	2-methyl-2-(4-methoxy-5-phenyl-3-thienyl) propionic acid	16	M.P. 134–137° (ether/petroleum ether).
	Starting material: 2-methyl-2-(4-methoxy-5-phenyl-3-thienyl) propionitrile	16a	Unpurified.
39	2-methyl-2-(4-methoxy-5-phenyl-3-thienyl) hexanoic acid	16	M.P. 126–127° (ether/petroleum ether).
	Starting material: 2-methyl-2-(4-methoxy-5-phenyl-3-thienyl) hexanoic acid nitrile.	16a	Unpurified, from 2-(4-methoxy-5-phenyl-3-thienyl)-propionitrile and butyl iodide.

Example 40: 4-Hydroxy-5-phenyl-3-thiophene acetic acid

2.5 g. of 4-hydroxy-5-phenyl-3-thiophene acetonitrile are boiled at reflux for 24 hours in 12.5 cc. of a 2 N caustic soda solution. The dark solution is rendered acid to Congo red with 2 N sulphuric acid and is extracted with ether. After concentrating the ether phase by evaporation, the title compound is obtained as dark viscous oil and is characterized by its infrared spectrum. Cyclization of the title compound yields 2,3-dihydro-6-phenylthieno [3,4-b]furan-2-one which has a M.P. of 104–106° (from benzene/petroleum ether).

The starting material may be obtained as follows:

(a) A solution of 15.2 g. of 4-methoxy-5-phenyl-3-thiophene acetonitrile is added dropwise while stirring to a sodium ethylate mercaptide solution produced from 3.2 g. of a 50% sodium hydride dispersion and 4.2 g. of ethyl mercaptan in 120 cc. of dimethyl formamide in an atmosphere of nitrogen, the dark solution is heated to 100° for 5 hours, is cooled, is poured on a mixture of ice/2 N hydrochloric acid and is extracted with benzene. The benzene extracts are extracted with ice-cooled 2 N caustic soda solution, the alkaline extracts are rendered acid and again extracted with benzene. Upon concentrating the benzene phase which has been washed with a saturated sodium chloride solution, 4-hydroxy-5-phenyl-3-thiophene acetonitrile crystallizes. M.P. of the crude product: 85–92°.

The following compounds may be produced in a manner analogous to that described in Example 1 or Example 40 and may be characterized by the melting point of the lactone obtained therefrom by cyclization.

Ex. No.	Substance	Produced analog. Ex. No.	Observations	M.P. of the lactone
41	5-(4-fluorophenyl)-4-hydroxy-3-thiophene acetic acid	40	Oily	134–136° (sinters frob 130°, benzene/petroleum ether).
	Starting material: 5-(4-fluorophenyl)-4-hydroxy-3-thiophene acetonitrile	40a	Unpurified oil	
42	5-(4-chlorophenyl)-4-hydroxy-3-thiophene acetic acid	40	Oily	159–160° (decomp., benzene).
	Starting material: 5-(4-chlorophenyl)-4-hydroxy-3-thiophene acetonitrile	40a	Unpurified oil	
43	2-[5-(4-fluorophenyl)-4-hydroxy-3-thienyl] propionic acid	40		84–85° (benzene/petroleum ether).
	Starting material: 2-[5-(4-fluorophenyl)-4-hydroxy-3-thienyl] propionitrile	40a	Unpurified oil	
44	4-hydroxy-5-*o*-tolyl-3-thiophene acetic acid	1B	Oily	88–89° (pentane).
	Starting material: 4-hydroxy-5-*o*-tolyl-3-thiophene acetonitrile	40a	Unpurified oil	
45	5-(2-chlorophenyl)-4-hydroxy-3-thipohene acetic acid	1B	Oily	112–113° (pentane).
	Starting material: 5-(2-chlorophenyl)-4-hydroxy-3-thiophene acetonitrile	40a	Unpurified oil	

Example 46: 2-(4-Hydroxy-5-phenyl-3-thienyl)propionic acid

2 - (4 - hydroxy-5-phenyl-3-thienyl)propionitrile (produced in a manner analogous to that described in Example 40(a) is reacted in accordance with the process described in Example 40. A solution of 2.1 g. of potassium hydroxide in 50 cc. of methanol is added to 9.2 g. of the crude title compound, the mixture is evaporated to dryness and dried in a high vacuum at 60° for 18 hours. The residue is boiled with a mixture of ether and a small amount of acetone, whereby the potassium salt of the title compound crystallizes. M.P. approx. 100°; the salt is strongly hygroscopic.

Example 47: 4-Methoxy-5-phenyl-3-thiophene acetic acid amide

2 g. of 4-methoxy-5-phenyl-3-thiophene acetonitrile are boiled at reflux for 90 minutes in 100 cc. of 0.5 N caustic soda solution with the addition of a small amount of ethanol. The reaction solution is concentrated to approx. one third of its original volume, and the solution is divided between benzene and water. Upon concentrating the benzene phase which has been dried over magnesium sulphate, the title compound crystallizes. M.P. 112–114° (from benzene/ether).

Example 48: 2-(4-Methoxy-5-phenyl-3-thienyl)propionic acid amide

2 g. of 2 - (4-methoxy-5-phenyl-3-thienyl)propionitrile are boiled at reflux for approx. sixty minutes in 100 cc. of 1.5 N caustic soda solution with the addition of a small amount of ethanol. The reaction is discontinued as soon as an ammonia evolution is observed, and the reaction mixture is worked up as described in Example 47. M.P. of the title compound: 134–137° (from benzene/petroleum ether).

Example 49: 4-Methoxy-5-phenyl-3-thiophene acetic acid ethyl ester

A solution of 64 g. of 4-methoxy-5-phenyl-3-thiophene acetonitrile in 600 cc. of ethanol is saturated with hydrogen chloride gas while cooling with ice water, and is subsequently heated at reflux for 24 hours. The solution is then evaporated to dryness, 11 cc. of water and 500 cc. of ethanol are added, the mixture is again boiled at reflux for 2½ hours, is evaporated to dryness, and the residue is divided between chloroform and water. The title compound, obtained after concentrating the chloroform layer which has been washed with sodium hydrogen carbonate solution and dried over magnesium sulphate, is distilled in a Hickmann flask. B.P. 144–145°/0.08 mm. Hg, yellow oil.

M.P. of 4-methoxy-5-phenyl-3-thiophene acetic acid, obtained by hydrolysis of the title compound: 88–94°.

The following compounds may be produced in a manner analogous to that described in Example 49 and may be characterized by the melting points of the acids obtained therefrom by hydrolysis.

Ex. No.	Substance	Physical constants, observations	M.P. of the acid
50	5-(4-fluorophenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	B.P.$_{0.25}$ 165–171°	114–116° (ether/petroleum ether).
51	5-(4-chlorophenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	B.P.$_{0.05}$ 154–156°	85–87° (ether/petroleum ether).
52	4-methoxy-5-(4-methoxyphenyl)-3-thiophene acetic acid ethyl ester	B.P.$_{0.09}$ 170–173°	101–104° (ether/petroleum ether).
53	5-(3-chlorophenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	B.P.$_{0.09}$ 179°	101–103° (ether/petroleum ether).
54	4-methoxy-5-*o*-tolyl-3-thiophene acetic acid ethyl ester	Oily	60–62° (pentane).
55	4-methoxy-5-*m*-tolyl-3-thiophene acetic acid ethyl ester	do	89–90° (ether/pentane).
56	4-methoxy-5-*p*-tolyl-3-thiophene acetic acid ethyl ester	do	88–90° (ether/pentane).
57	5-(2-chlorophenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	do	97–100° (pentane).
58	5-(2, 4-dichlorophenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	do	107–109° (ether/pentane).
59	5-(3-fluorophenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	do	90–92° (ether/pentane).
60	5-(3, 4-dichlorophenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	do	125–127° (ether/pentane).
61	5-(3, 4-dimethoxyphenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	B.P.$_{0.09}$ 198°	123–126° (benzene/petroleum ether).
62	4-isopropoxy-5-phenyl-3-thiophene acetic acid ethyl ester	B.P.$_{0.15}$ 140–145°	63° (ether/petroleum ether).
63	4-ethoxy-5-phenyl-3-thiophene acetic acid methyl ester	B.P.$_{0.07}$ 150°, n_D^{23} 1.5812.	53–57° (pentane).

TABLE—Continued

Ex. No.	Substance	Physical constants, observations	M.P. of the acid
64	2-(4-methoxy-5-phenyl-3-thienyl) propionic acid methyl ester	B.P.$_{0.1}$ 156–158°, n_D^{21} 1.5695.	101–102° (ether/petroleum ether).
65	2-[4-methoxy-5-(4-methoxyphenyl)-3-thienyl] propionic acid ethyl ester	B.P.$_{0.07}$ 173–175°	99–101° (ether/petroleum ether).
66	2-[5-(4-chlorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	B.P.$_{0.8}$ 192°	61–62° (petroleum ether).
67	2-[5-(4-fluorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	B.P.$_{0.1}$ 164°	101–103° (ether/petroleum ether).
68	2-[5-(3-chlorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	B.P.$_{0.1}$ 159–161°	77–78° (petroleum ether/ether).
69	2-(4-methoxy-5-phenyl-3-thienyl) hexanoic acid ethyl ester	B.P.$_{0.08}$ 146°, n_D^{24} 1.552.	68–69° (ether/petroleum ether).
70	2-(4-methoxy-5-*o*-tolyl-3-thienyl) propionic acid ethyl ester	Oily	71–72° (pentane).
71	2-(4-methoxy-5-*m*-tolyl-3-thienyl) propionic acid ethyl ester	do	82–85° (pentane).
72	2-(4-methoxy-5-*p*-tolyl-3-thienyl) propionic acid ethyl ester	do	86–88° (pentane).
73	2-[5-(2-chlorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	do	108–110° (ether/pentane).
74	2-[5-(2, 4-dichlorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	do	75–77° (ether/pentane).
75	2-[5-(3-fluorophenyl)-4-methoxy-3-thienyl] propionic aicd ethyl ester	do	78–80° (ether/pentane).
76	2-[5-(3,4-dimethoxyphenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	do	M.P. of the sodium salt 245–247° (acetone).
77	2-(4-isopropoxy-5-phenyl-3-thienyl) propionic acid ethyl ester	B.P.$_{0.01}$ 140°	M.P. of the sodium salt 213–215° (acetone).
78	2-(4-ethoxy-5-phenyl-3-thienyl)propionic acid methyl ester	Oily	218° (acetone/ether).
79	2-(4-methoxy-5-phenyl-3-thienyl) butyric acid ethyl ester	B.P.$_{0.07}$ 135°	79–81° (ether/petroleum ether).
80	4-methoxy-5-(*m*-trifluoromethylphenyl)-3-thiophene acetic acid ethyl ester	B.P.$_{0.01}$ 160–180°, n_D^{24} 1.5332.	98–103° (ether/petroleum ether).
81	4-methoxy-5-(2-methoxyphenyl)-3-thiophene acetic acid ethyl ester	B.P.$_{0.08}$ 130–140° n_D^{22} 1.5808.	93–95° (ether/petroleum ether).
82	5-(2,5-dichlorophenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	B.P.$_{0.04}$ 149°, n_D^{22} 1.5868.	93–96° (ether/petroleum ether).
83	2-[5-(*m*-trifluoromethylphenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester.	B.P. $_{0.08}$ 127–130°	106–109° (ether/petroleum ether).
84	2-[5-(2-methoxyphenyl)-4-methoxy-3-thienyl]propionic acid ethyl ester	B.P.$_{0.1}$ 152°, n_D^{22} 1.5704.	113–115° (ether/petroleum ether).
85	2-[5-(2,5-dichlorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	B.P.$_{0.08}$ 160–170° n_D^{26} 1.5771.	108–112° (ether/petroleum ether).
86	2-methyl-2-(4-methoxy-5-phenyl-3-theinyl) propionic acid ethyl ester	B.P.$_{0.1}$ 140–142°, M.P. 68–70° (ether/petroleum ether).	
87	2-methyl-2-(4-methoxy-5-phenyl-3-thienyl) hexanoic acid ethyl ester	Oily	126–127° (ether/petroleum ether).
88	4-methoxy-5-phenyl-3-thiophene acetic acid isopropyl ester	B.P.$_{0.05}$ 148° M.P. 53–58°.	
89	2-(4-methoxy-5-phenyl-3-thienyl) propionic acid methyl ester	B.P.$_{01}$ 145°, n_D^{21} 1.5822.	101–102°.
90	2-(4-methoxy-5-phenyl-3-thienyl) propionic acid isopropyl ester	B.P.$_{0.05}$ 135°	101–102°.
91	2-(4-methoxy-5-phenyl-3-thienyl) propionic acid cyclopentyl ester	B.P.$_{0.05}$ 152°	101–102°.
92	2-(4-methoxy-5-phenyl-3-thienyl) propionic acid cyclohexyl ester	B.P.$_{0.05}$ 175°	101–102°.
93	2-(4-methoxy-5-phenyl-3-thienyl) propionic acid n-octyl ester	B.P.$_{01}$ 170°	101–102°.
94	2-(4-methoxy-5-phenyl-3-thienyl) propionic acid (2-cyclohexylethyl) ester	B.P.$_{0.05}$ 188°	101–102°.

Example 95: 4-Hydroxy-5-phenyl-3-thiophene acetic acid ethyl ester

A solution of 6 g. of 4-hydroxy-5-phenyl-3-thiophene acetonitrile in 35 cc. of ethanol is saturated with hydrogen chloride gas while cooling with ice, 1.2 cc. of water are subsequently added, and the mixture is boiled at reflux for 24 hours. The reaction mixture is evaporated to dryness, the residue is taken up in ether, is washed with water, the residue obtained after concentrating the ether phase by evaporation is again taken up in ethanol, and the solution is saturated with hydrogen chloride gas and again boiled at reflux for 18 hours. The ethanol is then evaporated, the residue is taken up in ether, washed with water, the ether phase is concentrated, and the resulting crude oily title compound is purified by distillation in a bulb tube. B.P. 165°/0.01 mm. Hg.

The following compounds may be obtained in a manner analogous to that described in Example 95.

Ex. No.	Substance	Produced analog. to Ex. No.	Observations
96	5-(4-fluorophenyl)-4-hydroxy-3-thiophene acetic acid ethyl ester.	95	Oily.
97	5-(4-chlorophenyl)-4-hydroxy-3-thiophene acetic acid ethyl ester.	95	Do.
98	2-[5-(4-fluorophenyl)-4-hydroxy-3-thienyl] propionic acid ethyl ester.	95	Do.
99	4-hydroxy-5-*o*-tolyl-3-thiophene acetic acid ethyl ester.	95	Do.
100	5-(2-chlorophenyl)-4-hydroxy-3-thiophene acetic acid ethyl ester.	95	Do.
101	2-(4-hydroxy-5-phenyl-3-thienyl) propionic acid ethyl ester.	95	Do.

Example 102: 4-Methoxy-5-phenyl-3-thiophene acetic acid

68.5 g. of 4 - methoxy - 5 - phenyl-3-thiophene acetic acid ethyl ester are boiled for a short time in a solution of 15.3 g. of potassium hydroxide in 250 cc. of water and 250 cc. of methanol, and the mixture is subsequently stirred at room temperature for 24 hours. The methanol is then removed by evaporation, the reaction mixture is rendered acid with 2 N hydrochloric acid, and extraction is effected with ether. Upon concentrating the ether phase, which has been washed with saturated sodium chloride solution and dried over magnesium sulphate, the title compound crystallizes. M.P. 88–94° (from ether/petroleum ether).

The following compounds may be produced in a manner analogous to that described in Example 102.

Ex. No.	Substance	Physical constants, observations
103	5-(4-fluorophenyl)-4-methoxy-3-thiophene acetic acid	M.P. 114–116° (ether/petroleum ether).
104	5-(4-chlorophenyl)-4-methoxy-3-thiophene acetic acid	M.P. 85–87° (ether/petroleum ether).
105	4-methoxy-5-(4-methoxyphenyl)-3-thiophene acetic acid	M.P. 100–104° (ether/petroleum ether, sinters from 80°).
106	5-(3-chlorophenyl)-4-methoxy-3-thiophene acetic acid	M.P. 101–103° (acetone/petroleum ether).
107	4-methoxy-5-*m*-tolyl-3-thiophene acetic acid	M.P. 89–90°.
108	4-methoxy-5-*p*-tolyl-3-thiophene acetic acid	M.P. 88–90°.
109	4-methoxy-5-*o*-tolyl-3-thiophene acetic acid	M.P. 60–62° (pentane).
110	5-(2-chlorophenyl)-4-methoxy-3-thiophene acetic acid	M.P. 97–100° (pentane).
111	5-(2,4-dichlorophenyl)-4-methoxy-3-thiophene acetic acid	M.P. 107–109° (diethyl ether/pentane).
112	5-(3-fluorophenyl)-4-methoxy-3-thiophene acetic acid	M.P. 90–92° (ether/pentane).
113	5-(3,4-dichlorophenyl)-4-methoxy-3-thiophene acetic acid	M.P. 125–127° (diethyl ether/pentane).
114	5-(3,4-dimethoxyphenyl)-4-methoxy-3-thiophene acetic acid	M.P. 123–126° (benzene/petroleum ether).

TABLE—Continued

Ex. No.	Substance	Physical constants, observations
115	4-isopropoxy-5-phenyl-3-thiophene acetic acid	M.P. 63° (ether/petroleum ether).
116	4-ethoxy-5-phenyl-3-thiophene acetic acid	M.P. 53–57° (pentane).
117	2-(4-methoxy-5-phenyl-3-thienyl) propionic acid	M.P. 101–102° (ether/petroleum ether). M.P. of the sodium salt 236–238° (decomp.) The racemate may be separated into the optical antipodes as described in Ex. 16A. M.P. of the soidum salt of the (−) acid 200–202°, $[\alpha]_D=-19.5°$. M.P. of the sodium salt of the (+) acid 201–203°, $[\alpha]_D=+19.5°$.
118	2-[4-methoxy-5-(4-methoxyphenyl)-3-thienyl] propionic acid	M.P. 99–101° (ether/petroleum ether).
119	2-[5-(4-chlorophenyl)-4-methoxy-3-thienyl] propionic acid	M.P. 82° (ether/petroleum ether).
120	2-[5-(4-fluorophenyl)-4-methoxy-3-thienyl] propionic acid	M.P. 101–103° (ether/petroleum ether).
121	2-[5-(3-chlorophenyl)-4-methoxy-3-thienyl] propionic acid	M.P. 77–78° (petroleum ether/ether).
122	2-(4-methoxy-5-phenyl-3-thienyl) hexanoic acid	M.P. 68–69° (ether/petroleum ether).
123	2-(4-methoxy-5-*o*-tolyl-3-thienyl) propionic acid	M.P. 71–72° (pentane).
124	2-(4-methoxy-5-*m*-tolyl-3-thienyl) propionic acid	M.P. 82–85° (pentane).
125	2-(4-methoxy-5-*p*-tolyl-3-thienyl) propionic acid	M.P. 86–88° (pentane).
126	2-[5-(2-chlorophenyl)-4-methoxy-3-thienyl] propionic acid	M.P. 108–110° (ether/pentane).
127	2-[5-(2,4-dichlorophenyl)-4-methoxy-3-thienyl] propionic acid	M.P. 75–77° (ether/pentane).
128	2-[5-(3-fluorophenyl)-4-methoxy-3-thienyl] propionic acid	M.P. 78–80° (ether/pentane).
129	2-[5-(3,4-dimethoxyphenyl)-4-methoxy-3-thienyl] propionic acid.	M.P. of the sodium salt 245–247° (acetone), produced with 1 N NaOH in methanolic solution, dried at 70° in a high vacuum.
130	2-(4-isopropoxy-5-phenyl-3-thienyl) propionic acid	M.P. of the sodium salt 213–215° (acetone/ether).
131	2-(4-ethoxy-5-phenyl-3-thienyl) propionic acid	M.P. of the potassium salt 218° (acetone/ether).
132	2-(4-methoxy-5-phenyl-3-thienyl) butyric acid	M.P. 79–81° (ether/petroleum ether).
133	4-methoxy-5-(*m*-trifluoromethylphenyl)-3-thiophene acetic acid.	M.P. 98–100° (ether/petroleum ether).
134	4-methoxy-5-(2-methoxyphenyl)-3-thiophene acetic acid	M.P. 93–95° (ether/petroleum ether).
135	5-(2,5-dichlorophenyl)-4-methoxy-3-thiophene acetic acid	M.P. 93–96° (ether/petroleum ether).
136	2-[5-(*m*-trifluoromethylphenyl)-4-methoxy-3-thienyl] propionic acid.	M.P. 106–109° (ether/petroleum ether).
137	2-[5-(2,5-dichlorophenyl)-4-methoxy-3-thienyl] propionic acid	M.P. 108–112° (ether/petroleum ether).
138	2-[5-(2-methoxyphenyl)-4-methoxy-3-thienyl] propionic acid	M.P. 113–115° (ether/petroleum ether).
139	2-methyl-2-(4-methoxy-5-phenyl-3-thienyl) propionic acid	M.P. 134–137° (ether/petroleum ether).

Example 140: 2-Methyl-2-(4-methoxy-5-phenyl-3-thienyl) hexanoic acid

10 g. of 2 - methyl-2-(4-methoxy-5-phenyl-3-thienyl) hexanoic acid ethyl ester are boiled at reflux for 48 hours with 10 g. of potassium hydroxide in 3 cc. of water and 25 cc. of methanol. The methanol is subsequently removed by evaporation, the residue is diluted with a small amount of water, is washed with ether, is then rendered acid to Congo red with sulphuric acid and extracted with ether. Upon concentrating the ether phase by evaporation the title compound is obtained. M.P. 126–127° (from ether/petroleum ether).

Example 141: 4-Hydroxy-5-phenyl-3-thiophene acetic acid

(A) 4 - hydroxy - 5 - phenyl - 3 - thiophene acetic acid ethyl ester is reacted in accordance with the process described in Example 102. The crude title compound obtained as viscous oil is purified by distillation in a bulb tube in a high vacuum. B.P. 140–145°/0.08 mm. Hg. The compound is obtained as yellow oil.

(B) 1 g. of 4 - hydroxy - 5-phenyl-3-thiophene acetic acid ethyl ester is boiled at reflux for 24 hours in 6 cc. of 2 N caustic soda solution. The solution is subsequently rendered acid with 2 N sulphuric acid and is extracted with ether. The title compound is isolated from the ether phase as described in section A.

The 2,3 - dihydro - 6-phenylthieno[3,4-b]furan-2-one, obtained by cyclization of the title compound, has a M.P. of 104–106° (from benzene/petroleum ether).

The following compounds may be produced in a manner analogous to that described in Example 141 and may be characterized by the melting points of the lactones obtained therefrom by cyclization.

Ex. No.	Substance	Observations	M.P. of the lactone
142	5-(4-fluorophenyl)-4-hydroxy-3-thiophene acetic acid.	Oily	134–136° (benzene/petroleum ether).
143	5-(4-chlorophenyl)-4-hydroxy-3-thiophene acetic acid.	do	159–160° (decomp., benzene).
144	2-[5-(4-fluorophenyl)-4-hydroxy-3-thienyl] propionic acid.	do	84–85° (benezne/petroleum ether).
145	4-hydroxy-5-o-tolyl-3-thiophene acetic acid.	do	88–89° (pentane).
146	5-(2-chlorophenyl)-4-hydroxy-3-thiophene acetic acid.	do	112–113° (pentane).

Example 147: 2-(4-Hydroxy-5-phenyl-3-thienyl) propionic acid

2 - (4-hydroxy-5-phenyl-3-thienyl)propionic acid ethyl ester is reacted in accordance with the process described in Example 102. A solution of 2.1 g. of potassium hydroxide in 50 cc. of methanol is added to 9.2 g. of the oily crude title compound, the solution is evaporated to dryness, and the resulting crude potassium salt of the title compound is dried in a high vacuum at 60° for 18 hours and is then boiled with a small amount of acetone and a large quantity of ether, whereby the strongly hydroscopic potassium salt of the title compound is obtained in crystalline form. M.P. approx. 100°.

Example 148: 4-Methoxy-5-phenyl-3-thiophene acetic acid

68.5 g. of 4-methoxy-5-phenyl-3-thiophene acetic acid ethyl ester are stirred at 80° for 16 hours in a mixture of 250 cc. of water and 100 cc. of dimethyl sulphoxide with the addition of 300 cc. of concentrated hydrochloric acid. The reaction mixture is then diluted with a large quantity of water and is extracted with chloroform. Upon concentrating the chloroform phase which has been washed with saturated sodium chloride solution and dried over magnesium sulphate, the title compound crystallizes. M.P. of the title compound: 88–94° (from ethyl/petroleum ether).

Example 149: 2-(4-Methoxy-5-phenyl-3-thienyl) propionic acid methyl ester

119 g. of 2 - (4-methoxy-5-phenyl-3-thienyl)propionic acid chloride are added dropwise at 10° to a mixture of 80 cc. of pyridine and 120 cc. of methyl alcohol in 250 cc. of chloroform, and the mixture is stirred at room temperature for 3 hours. The reaction solution is then successively extracted with 1 N hydrochloric acid, with sodium hydrogen carbonate solution and with saturated aqueous sodium chloride solution and is concentrated. The resulting crude oily title compound is purified by distillation in a Hickmann flask. B.P. 145°/0.1 mm. Hg. $n_D^{21}=1.5822$.

The starting material may be obtained as follows:

(a) 18 g. of thionyl chloride are poured over 20 g. of 2-(4-methoxy-5-phenyl-3-thienyl)propionic acid, and this is allowed to stand at room temperature for 18 hours. The resulting 2-(4-methoxy-5-phenyl-3-thienyl)propionic acid chloride is purified by distillation in a Hickmann flask and forms a yellow viscous oil. B.P. 159°/0.2 mm. Hg.

The following compounds may be obtained in a manner analogous to that described in Example 149.

Ex. No.	Substance	Physical constants
150	2-(4-methoxy-5-phenyl-3-thienyl) propionic acid isopropyl ester.	B.P.$_{0.05}$ 135°.
151	2-(4-methoxy-5-phenyl-3-thienyl) propionic acid cyclopentyl ester.	B.P.$_{0.05}$ 152°.
152	2-(4-methoxy-5-phenyl-3-thienyl) propionic acid cyclohexyl ester.	B.P.$_{0.05}$ 175°.
153	2-(4-methoxy-5-phenyl-3-thienyl) propionic acid n-octyl ester.	B.P.$_{0.1}$ 170°.
154	2-(4-methoxy-5-phenyl-3-thienyl) propionic acid (2-cyclohexylethyl) ester.	B.P.$_{0.05}$ 188°.
155	4-methoxy-5-phenyl-3-thiophene acetic acid isopropyl ester.	M.P. 53–58°.

tion is allowed to stand at room temperature for 24 hours. The reaction mixture is subsequently concentrated, and the residue is divided between water and ether, the ether phase is successively washed with sodium hydrogen carbonate solution and with saturated sodium chloride solution, is dried and concentrated. The resulting crude title compound is purified by distillation in a Hickmann flask in a high vacuum. B.P. 156–158°/0.1 mm. Hg. n_D^{25}=1.5695.

The following compounds may be produced in a manner analogous to that described in Example 157.

Ex. No.	Substance	Physical constants, observations
158	4-methoxy-5-phenyl-3-thiophene acetic acid ethyl ester	B.P.$_{0.08}$ 144–145°.
159	5-(4-fluorophenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	B.P.$_{0.25}$ 165–171°.
160	5-(4-chlorophenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	B.P.$_{0.05}$ 154–156°.
161	4-methoxy-5-(4-methoxyphenyl)-3-thiophene acetic acid ethyl ester	B.P.$_{0.09}$ 170–173°.
162	5-(3-chlorophenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	B.P.$_{0.09}$ 179°.
163	4-methoxy-5-*o*-tolyl-3-thiophene acetic acid ethyl ester	Oily, R_f value 0.29 (adsorbent: silica gel, eluant: chloroform).
164	4-methoxy-5-*m*-tolyl-3-thiophene acetic acid ethyl ester	Oily, R_f value 0.22 (adsorbent: silica gel, eluant: toluene, repeat twice).
165	4-methoxy-5-*p*-tolyl-3-thiophene acetic acid ethyl ester	Oily.
166	5-(2-chlorophenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	Do.
167	5-(2, 4-dichlorophenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	Oily, R_f value 0.5 (adsorbent: silica gel, eluant: chloroform).
168	5-(3-fluorophenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	Oily, R_f value 0.3 (adsorbent: silica gel, eluant: chloroform).
169	5-(3, 4-dichlorophenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	Oily, R_f value 0.7 (adsorbent: silica gel, eluant: acetic acid ethyl ester).
170	5-(3, 4-dimethoxyphenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	B.P.$_{0.09}$ 198°.
171	4-isopropoxy-5-phenyl-3-thiophene acetic acid ethyl ester	B.P.$_{0.15}$ 140–145°.
172	4-ethoxy-5-phenyl-3-thiophene acetic acid methyl ester	B.P.$_{0.07}$ 150°, n_D^{23} 1.5812.
173	2-(4-methoxy-5-phenyl-3-thienyl) propionic acid methyl ester	B.P.$_{0.1}$ 145°, n_D^{21} 1.5822.
174	2-4-[methoxy-5-(4-methoxyphenyl)-3-thienyl] propionic acid ethyl ester	B.P.$_{0.07}$ 173–175°.
175	2-5-[(4-chlorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	B.P.$_{0.8}$ 192° (M.P. 61–62°, petroleum ether).
176	2-5-[(4-fluorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	B.P.$_{0.1}$ 164°.
177	2-5-[(3-chlorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	B.P.$_{0.1}$ 159–161°.
178	2-(4-methoxy-5-phenyl-3-thienyl) hexanoic acid ethyl ester	B.P.$_{0.08}$ 146°, n_D^{24} 1.552.
179	2-(4-methoxy-5-*o*-tolyl-3-thienyl) propionic acid ethyl ester	Oily, R_f value 0.18 (adsorbent: silica gel, eluant: toluene, repeat twice).
180	2-(4-methoxy-5-*m*-tolyl-3-thienyl) propionic acid ethyl ester	Oily, R_f value 0.24 (adsorbent: silica gel, eluant: toluene, repeat twice).
181	2-(4-methoxy-5-*p*-tolyl-3-thienyl) propionic acid ethyl ester	Oily.
182	2-[5-(2-chlorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	Do.
183	2-[5-(2, 4-dichlorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	Oily, R_f value 0.55 (adsorbent: silica gel, eluant chloroform).
184	2-[5-(3-fluorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	Oily, R_f value 0.7 (adsorbent: silica gel, eluant: chloroform).
185	2-[5-(3, 4-dimethoxyphenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	Oily.
186	2-(4-isopropoxy-5-phenyl-3-thienyl) propionic acid ethyl ester	B.P.$_{0.01}$ 140°.
187	2-(4-ethoxy-5-phenyl-3-thienyl) propionic acid methyl ester	Oily.
188	2-(4-methoxy-5-phenyl-3-thienyl) butyric acid ethyl ester	B.P.$_{0.07}$ 135°.
189	4-methoxy-5-(*m*-trifluoromethylphenyl)-3-thiophene acetic acid ethyl ester	B.P.$_{0.01}$ 160–180°, n_D^{24} 1.5332.
190	4-methoxy-5-(2-methoxyphenyl)-3-thiophene acetic acid ethyl ester	B.P.$_{0.08}$ 130–140°, n_D^{22} 1.5808.
191	5-(2, 5-dichlorophenyl)-4-methoxy-3-thiophene acetic acid ethyl ester	B.P.$_{0.04}$ 149°, n_D^{22} 1.5863.
192	2-[5-(*m*-trifluoromethylphenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	B.P.$_{0.08}$ 127–130°.
193	2-[5-(2-methoxyphenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	B.P.$_{0.1}$ 152°, n_D^{22} 1.5704.
194	2-[5-(2, 5-dichlorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	B.P.$_{0.08}$ 160–170°, n_D^{25} 1.5771.
195	2-methyl-2-(4-methoxy-5-phenyl-3-thienyl) propionic acid ethyl ester	B.P.$_{0.1}$ 140–142°, M.P. 68–70° (ether/petroleum ether).

Example 156: 2-(4-Methoxy-5-phenyl-3-thienyl) propionic acid tert.butyl ester

2.7 g. of tert.butyl alcohol are added dropwise at room temperature to a Grignard compound produced from 0.86 g. of magnesium shavings and 5.1 g. of methyl iodide in ether, and a solution of 10.0 g. of 2-(4-methoxy-5-phenyl-3-thienyl)propionic acid cholride in 15 cc. of chloroform is subsequently added dropwise, and the reaction mixture is boiled at reflux for 18 hours. The reaction mixture is then poured on ice water, the ether layer is separated, washed with saturated sodium chloride solution, dried and concentrated. The title compound obtained as a viscous oil is purified by distillation in a bulb tube. B.P. 170–175°/0.01 mm. Hg (air bath).

Example 157: 2-(4-Methoxy-5-phenyl-3-thienyl) propionic acid ethyl ester

A solution of 10 g. of 2-(4-methoxy-5-phenyl-3-thienyl) propionic acid in 40 cc. of ethanol is saturated with hydrogen chloride gas while cooling with ice, and the solu-

Example 196: 2-(4-Methoxy-5-phenyl-3-thienyl) propionic acid ethyl ester

A solution of 29.2 g. of 4-methoxy-5-phenyl-3-thiophene acetic acid ethyl ester in 100 cc. of absolute ether is added dropwise at −40 to −50° to a suspension of sodium amide in liquid ammonia, produced from 2.43 g. of sodium, 150 cc. of liquid ammonia and a small amount of iron III nitrate, the reaction mixture is stirred at the same temperature for ½ hour, and a solution of 16.6 g. of methyl iodide in 50 cc. of ether is subsequently added dropwise within 50 minutes, and stirring is continued for a further hour. 6.3 g. of ammonium chloride are then carefully added, the ammonia is evaporated at room temperature and is simultaneously replaced by the addition of ether. The ammonia-free ethereal suspension is stirred at room temperature for a further 1½ hours and is then divided between 2 N hydrochloric acid and ether. The oily title compound, obtained after concentrating the ether phase which has been washed with aqueous sodium hydrogen carbonate solution and with water and dried, is purified by distillation in a Hickmann flask. B.P. 156–158°/0.1 mm. Hg. n_D^{25}=1.5695.

The 2-(4-methoxy-5-phenyl-3-thienyl) propionic acid, obtained by hydrolysis of the title compound, has a M.P.

of 103–104° (sintering from 95°, from ether/petroleum ether).

The following compounds may be produced in a manner analogous to that described in Example 196.

Ex. No.	Substance	Physical constants, observations	M.P. of the acid
197	2-[5-(4-chlorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	$B.P._{0.8}$ 192°	61–62° (petroleum ether).
198	2-[5-(4-fluorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	$B.P._{0.1}$ 164°	101–103° (ether/petroleum ether).
199	2-[5-(3-chlorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	$B.P._{0.1}$ 159–161°	77–78° (petroleum ether/ether).
200	2-(4-methoxy-5-phenyl-3-thienyl] hexanoic acid ethyl ester	$B.P._{0.08}$ 146°, n_D^{24} 1.552.	68–69° (ether/petroleum ether).
201	2-(4-methoxy-5-*o*-tolyl-3-thienyl) propionic acid ethyl ester	Oily	71–72° (pentane).
202	2-(4-methoxy-5-*m*-tolyl-3-thienyl) propionic acid ethyl ester	do	82–85° (pentane).
203	2-(4-methoxy-5-*p*-tolyl-3-thienyl) propionic acid ethyl ester	do	86–88° (pentane).
204	2-[5-(2-chlorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	do	108–110° (ether/pentane).
205	2-[5-(2,4-dichlorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	do	75–77° (ether/pentane).
206	2-[5-(3-fluorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	do	78–80° (ether/pentane).
207	2-[5-(3,4-dimethoxyphenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	do	M.P. of the sodium salt 245–247° (acetone).
208	2-(4-Isopropoxy-5-phenyl-3-thienyl) propionic acid ethyl ester	$B.P._{0.01}$ 140°	M.P. of the sodium salt 213–215° (acetone).
209	2-(4-ethoxy-5-phenyl-3-thienyl) propionic acid methyl ester	Oily	218° (acetone/ether).
210	2-(4-methoxy-5-phenyl-3-thienyl) butyric acid ethyl ester	$B.P._{0.07}$ 135°	79–81° (ether/petroleum ether).
211	2-[4-methoxy-5-(4-methoxyphenyl)-3-thienyl] propionic acid ethyl ester	$B.P._{0.07}$ 173–175°	99–101° (ether/petroleum ether).
212	2-[5-(*m*-trifluoromethylphenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	$B.P._{0.08}$ 127–130°	106–109° (ether/petroleum ether).
213	2-[5-(2-methoxyphenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	$B.P._{0.1}$ 152°, n_D^{23} 1.5704.	113–115° (ether/petroleum ether).
214	2-[5-(2,5-dichlorophenyl)-4-methoxy-3-thienyl] propionic acid ethyl ester	$B.P._{0.08}$ 160–170° n_D^{25} 1.5771.	108–112° (ether/petroleum ether).
215	2-(4-methoxy-5-phenyl-3-thienyl) propionic acid isopropyl ester	$B.P._{0.05}$ 135°	103–104° (ether/petroleum ether).

Example 216: 2-Methyl-2-(4-methoxy-5-phenyl-3-thienyl) hexanoic acid ethyl ester

10 g. of 2-(4-methoxy-5-phenyl-3-thienyl) propionic acid ethyl ester are added at room temperature, in a atmosphere of nitrogen, to 0.85 g. of finely dispersed sodium hydride suspended in dimethyl formamide, the mixture is heated to 60° for 30 minutes, is cooled, and 5 cc. of butyl iodide are added dropwise. The mixture is stirred at room temperature for 2 hours, is heated to 60° for a short time, is cooled, a 3-fold quantity of ice water and approx. 2 N hydrochloric acid are added, and extraction is effected with ether. After concentrating the ether phase which has been washed with sodium hydrogen carbonate solution and with water and dried, the title compound is obtained as an oil.

The 2 - methyl - 2-(4-methoxy-5-phenyl-3-thienyl)hexanoic acid, obtained by hydrolysis of the title compound, has a M.P. of 126–127° C. from ether/petroleum ether).

Example 217: 2-Methyl-2-(4-methoxy-5-phenyl-3-thienyl)propionic acid ethyl ester

2 - (4-methoxy-5-phenyl-3-thienyl)propionic acid ethyl ester is reacted with methyl iodide in accordance with the process described in Example 216. The title compound is purified by distillation. B.P. 140–142°/0.1 mm. Hg. The compound is obtained as yellow oil which gradually solidifies in crystalline form. M.P. 68–70° (from ether/petroleum ether).

Example 218: 2-(4-Methoxy-5-phenyl-3-thienyl) propionic acid amide

40 cc. of a 25% aqueous ammonia solution are added dropwise within 30 minutes to 20 g. of 2-(4-methoxy-5-phenyl-3-thienyl)propionic acid chloride, and the reaction mixture is allowed to stand at room temperature for 2 hours. The mixture is then extracted with chloroform, the chloroform layer is washed with 2 N hydrochloric acid, water, saturated sodium carbonate solution and water, is dried and concentrated. The title compound obtained in crystalline form is recrystallized from benzene/petroleum ether. M.P. 134–137°.

Example 219: 4-Methoxy-5-phenyl-3-thiophene acetic acid amide

4-methoxy-5-phenyl-3-thiophene acetic acid chloride [produced in a manner analogous to that described in Example 149(a)] is reacted with ammonia in accordance with the process described in Example 218. M.P. of the title compound: 112–114° (from benzene/ether).

Example 220: 2-(4-Methoxy-5-phenyl-3-thienyl) propionic acid methyl amide

2-(4-methoxy-5-phenyl-3-thienyl)propionic acid chloride is reacted with a 33% aqueous monomethyl amine solution in accordance with the process described in Example 218. M.P. of the title compound: 102–104° (from benzene/petroleum ether).

Example 221: 2-(4-Methoxy-5-phenyl-3-thienyl) propionic acid dimethyl amide

2-(4-methoxy-5-phenyl-3-thienyl)propionic acid chloride is reacted with a 40% aqueous dimethyl amine solution in accordance with the process described in Example 218. The title compound is purified by distillation and is obtained as a yellow viscous oil. B.P. 195–200°/0.05 mm. Hg.

Example 222: 4-Hydroxy-5-phenyl-3-thiophene acetic acid ethyl ester

A solution of 10.5 g. of ethyl mercaptan in 100 cc. of dimethyl formamide is added dropwise at room temperature in an atmosphere of nitrogen to 8.2 g. of sodium hydride in 100 cc. of dimethyl formamide. A solution of 46.6 g. of 4-methoxy-5-phenyl-3-thiophene acetic acid ethyl ester in 150 cc. of dimethyl formamide is then added dropwise, and the reaction mixture is heated to 100° for 2½ hours. The reaction mixture is then cooled, water is added, the mixture is rendered acid to Congo red with 2 N hydrochloric acid, the separated oil is extracted with benzene, the benzene phase is extracted with 2 N caustic soda solution while cooling with ice, and the caustic soda solution phase is again rendered acid to Congo red by the addition of 4 N hydrochloric acid, is extracted with benzene, and the dried benzene phase is concentrated. The resulting title compound is purified by chromatography and distilled.

The following compounds may be produced in a manner analogous to that described in Example 222.

Ex. No.	Substance	Produced analog. to Ex. No.	Observations
223	5-(4-fluorophenyl)-4-hydroxy-3-thiophene acetic acid ethyl ester.	222	Oily.
224	5-(4-chlorophenyl)-4-hydroxy-3-thiophene acetic acid ethyl ester.	222	Do.
225	2-[5-(4-fluorophenyl)-4-hydroxy-3-thienyl] propionic acid ethyl ester.	222	Do.

Example 226: 4-Hydroxy-5-*o*-tolyl-3-thiophene acetic acid

A solution of 2.50 g. of ethyl mercaptan in 20 cc. of dimethyl formamide is added dropwise at room temperature to a suspension of 1.92 g. of a 50% sodium hydride dispersion in 20 cc. of dimethyl formamide, in an atmosphere of nitrogen. A solution of 5.8 g. of 4-methoxy-5-*o*-

tolyl-3-thiophene acetic acid ethyl ether in 15 cc. of dimethyl formamide is then added dropwise, and the reaction mixture is subsequently heated to 100° for 2½ hours. The cooled reaction mixture is then rendered acid with 70 cc. of ice-cold 1 N hydrochloric acid, the separated oil is extracted with toluene, the toluene layer is extracted at 0° with a 1 N caustic soda solution, and the caustic soda solution extract is subsequently rendered acid to Congo red with hydrochloric acid while cooling with ice. The acid solution is again extracted with toluene, and the toluene phase, which has been washed with aqueous sodium chloride solution and dried, is concentrated by evaporation, whereby the title compound is obtained as an oil. The 2,3 - dihydro-6-*o*-tolylthieno[3,4-b]furan-2-one, obtained by cyclization of the title compound, has a M.P. of 88–89° (from pentane).

Example 227: 5-(2-Chlorophenyl)-4-hydroxy-3-thiophene acetic acid

A solution of 1.24 g. of ethyl mercaptan in 12 cc. of dimethyl formamide is added dropwise at room temperature in an atmosphere of nitrogen to a suspension of 0.96 g. of a 50% sodium hydride dispersion in 12 cc. of dimethyl formamide, a solution of 6.2 g. of 5-(2-chlorophenyl)-4-methoxy-3-thiophene acetic acid ethyl ester is then added dropwise, the reaction mixture is heated to 100° for 3½ hours and is worked up as described in Example 226, whereby the title compound is obtained as an oil.

The 6-(2-chlorophenyl)-2,3-dihydrothieno [3,4-b] furan-2-one, obtained by cyclization of the title compound, has a M.P. of 112–113° (from pentane).

Example 228: 2-(4-Hydroxy-5-phenyl-3-thienyl) propionic acid

6.5 g. of ethyl mercaptan are added dropwise in an atmosphere of nitrogen to a suspenion of 2.6 g. of sodium hydride in 75 cc. of dimethyl formamide, a solution of 15.3 g. of 2-(4-methoxy-5-phenyl-3-thienyl)propionic acid ethyl ester in 25 cc. of dimethyl formamide is then added dropwise, the reaction mixture is heated to 100° for 3 hours and is worked up as described in Example 223. A solution of 2.1 g. of potassium hydroxide in 50 cc. of methanol is added to 9.2 g. of the crude title compound obtained as an oil, the mixture is evaporated to dryness and the resulting crude potassium salt of the title compound is dried in a high vacuum at 60° for 18 hours, whereupon it is boiled with a mixture of ether and a small amount of acetone, whereby the strongly hygroscopic potassium salt of the title compound crystallizes. M.P. approx. 100°.

Example 229: 2,3-Dihydro-6-phenylthieno [3,4-b] furan-2-one

29.3 g. of 4-hydroxy-5-phenyl-3-thiophene acetic acid are boiled at reflux for 3 hours in 300 cc. of benzene with 14.3 g. of acetic anhydride in an atmosphere of nitrogen. The mixture is then concentrated and the crude title compound, obtained as dark, crystallizing residue, is taken up in chloroform, filtered through 50 g. of silica gel, concentrated and the resulting title compound recrystallized from benzene/petroleum ether. The title compound has a M.P. of 104–106°.

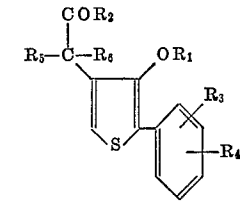
The following compounds may be produced in a manner analogous to that described in Example 229.

Ex. No.	Substance	Physical constants, observations
230	6-(4-fluorophenyl)-2,3-dihydrothieno[3,4-b]furan-2-one.	M.P. 134–136° (benzene/petroleum ether, sinters from 130°).
231	6-(4-chlorophenyl)-2,3-dihydrothieno[3,4-b]furan-2-one.	M.P. 159–160° (decomp., benzene).
232	6-(4-fluorophenyl)-2,3-dihydro-3-methylthieno[3,4-b]furan-2-one.	M.P. 84–85° (benzene/petroleum ether).
233	2,3-dihydro-6-*o*-tolylthieno[3,4-b]furan-2-one.	M.P. 88–89° (pentane).
234	6-(2-chlorophenyl)-2,3-dihydrothieno[3,4-b]furan-2-one.	M.P. 112–113° (pentane).

The compounds of the Examples that possess an asymmetric centre, e.g. the acids of Examples 17, 21 to 27, may be obtained in optically pure form thereof in manner known *per se*. Determination of the relative configuration thereof with respect to (+)-2-(4-methoxy-5-phenyl-3-thienyl) propionic acid may also be effected in manner known *per se*, e.g. by O.R.D. (optical rotary dispersion) complemented, if necessary, by C.D. (circular dichroism).

What is claimed is:

1. A compound of the formula:



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wherein R_1 is hydrogen or alkyl of 1 to 4 carbon atoms,
R_2 is hydroxy, alkoxy of 1 to 4 carbon atoms, cycloalkyloxy of 3 to 6 carbon atoms, cycloalkylalkoxy of 3 to 6 ring carbon atoms and 1 to 4 alkoxy carbon atoms, amino, monoalkylamino of 1 to 4 carbon atoms or dialkylamino, each alkyl substituent having 1 to 4 carbon atoms,
or R_1 and R_2 together denote a single bond, R_3 is hydrogen, chlorine or alkyl of 1 to 4 carbon atoms,
or when R_1 is hydrogen, or when R_1 and R_2 together denote a single bond, then R_3 may be hydroxy,
or when R_1 is alkyl of 1 to 4 carbon atoms, then R_3 may be alkoxy of 1 to 4 carbon atoms,
R_4 is hydrogen, chlorine, bromine or alkyl of 1 to 4 carbon atoms,
or when R_1 is hydrogen or when R_1 and R_2 together denote a single bond, then R_4 may be hydroxy,
or when R_1 is alkyl of 1 to 4 carbon atoms, then R_4 may be alkoxy of 1 to 4 carbon atoms,
or when R_3 is hydrogen, then R_4 may be fluorine or trifluoromethyl,
R_5 is hydrogen or alkyl of 1 to 4 carbon atoms, and
R_6 is hydrogen or methyl.

2. A compound of Claim **1**, wherein R_5 is hydrogen or alkyl of 1 to 3 carbon atoms.

3. A compound according to Claim **1**, wherein R_1 is hydrogen.

4. A compound of Claim **1**, wherein R_1 is methyl.

5. A compound of Claim **1**, wherein R_2 is hydroxy.

6. A compound of Claim **1**, wherein R_5 is different to R_6.

7. A compound of Claim **6**, in optically pure isomeric form.

8. A compound of Claim **7**, in "D' form."

9. The compound of Claim **1**, which is 2-(4-methoxy-5-phenyl-3-thienyl) propionic acid.

10. The compound of Claim **1**, which is 4-methoxy-5-phenyl-3-thiophene acetic acid.

11. The compound of Claim **1**, which is 2,3-dihydro-6-phenylthieno[3,4-b] furan-2-one.

12. The compound of Claim **1**, which is 5-(4-fluorophenyl)-4-methoxy-3-thiophene acetic acid.

13. The compound of Claim **1**, which is 5-(4-chlorophenyl)-4-methoxy-3-thiophene acetic acid.

14. The compound of Claim **1**, which is 2-[5-(4-fluorophenyl)-4-methoxy-3-thienyl] propionic acid.

15. The compound of Claim **1**, which is 4-methoxy-5-(4-methoxyphenyl)-3-thiophene acetic acid.

16. The compound of Claim **1**, which is 2-[4-methoxy-5-(4-methoxyphenyl)-3-thienyl] propionic acid.

17. The compound of Claim **1**, which is 2-[5-(4-chlorophenyl)-4-methoxy-3-thienyl] propionic acid.

18. The compound of Claim **1**, which is 2-[5-(3- chlorophenyl)-4-methoxy-3-thienyl] propionic acid.

19. The compound of Claim **1**, which is 2-(4-methoxy-5-*m*-tolyl-3-thienyl) propionic acid.

20. The compound of Claim 1, which is 5-(2-chlorophenyl)-4-methoxy-3-thiophene acetic acid.

21. The compound of Claim 1, which is 2-(4-methoxy-5-*o*-tolyl-3-thienyl) propionic acid.

22. The compound of Claim 1, which is 2,3-dihydro-6-*o*-tolylthieno[3,4-b]furan-2-one.

23. The compound of Claim 1, which is 2-(4-methoxy-5-phenyl-3-thienyl) propionic acid amide.

24. The compound of Claim 1, which is 4-methoxy-5-phenyl-3-thiophene acetic acid amide.

25. The compound of Claim 1, which is 2-(4-ethoxy-5-phenyl-3-thienyl) propionic acid.

26. The compound of Claim 1, which is 2-(4-hydroxy-5-phenyl-3-thienyl) propionic acid.

27. The compound of Claim 1, which is (+)-2-(4-methoxy-5-phenyl-3-thienyl) propionic acid.

28. A compound of Claim 1, wherein R_2 is hydroxy and/or R_1 is hydrogen, in pharmaceutically acceptable salt form.

29. A compound of Claim 28, in sodium or potassium salt form.

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