

PATENT SPECIFICATION

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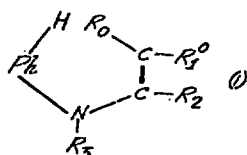
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(54) ESTERS OF α -1-AMINO-1,1-ALKYLIDENE MALONIC ACIDS

- (71) We, CIBA-GEIGY A.G. (formerly known as Ciba Limited), a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—
 10 The present invention relates to starting materials used in the process for the preparation of 3 - quinoline - carboxylic acids as described in British Patent Application No. 30403/69 (Serial No. 1270412). These starting materials are di-lower alkyl esters of α - (1 - phenylamino - 1,1 - alkylidene) - malonic acids, in which the phenyl residue contains a cycloaliphatyloxy or cycloaliphatylmercapto group and a higher aliphatyloxy or aliphatylmercapto group, and in which one of the positions of the phenyl nucleus adjacent to the amino group is unsubstituted, or tautomers of such compounds in which the amino group is unsubstituted, particularly compounds of the formula I



- in which Ph is a 1,2-phenylene radical substituted by a group of the formula $-X_1-A-R^I$ and a group of the formula $-X_2-R^{II}$, in which R^I is a cycloaliphatic

radical, A represents a direct bond between X_1 and R^I or a bivalent aliphatic radical, each of X_1 and X_2 is oxygen or sulfur, and R^{II} is a higher aliphatic radical, each of R_0 and R_1 stands for a carbo-lower alkoxy group, R_1 stands for hydrogen or a lower alkyl group, and R_2 is a hydrogen atom, an optionally substituted aliphatic or cycloaliphatic hydrocarbon radical, or tautomers of such compound in which R_2 is a hydrogen atom.

In the present specification and unless otherwise specified, the term "lower" denotes an organic group, radical or compound as having up to 7, preferably up to 4 carbon atoms, whereas the term "higher" denotes an organic group, radical or compound as having from 8 to 20, preferably from 8 to 16, carbon atoms.

A cycloaliphatic residue R^I is primarily a cycloaliphatic hydrocarbon radical which may be mono-, di- or polysubstituted, for example, by an optionally substituted aliphatic, aromatic or araliphatic hydrocarbon, particularly by a lower alkyl group and/or by a free, etherified or esterified hydroxy group (for example a halogen atom), especially a cycloalkyl radical containing preferably 3 to 8 ring-carbon atoms, which may be substituted by one or more lower alkyl groups, and/or halogen atoms, primarily a cycloalkyl radical with 3 to 6 ring carbon atoms, which may be substituted by up to 4 lower alkyl groups. These radicals are, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl radicals, or corresponding cycloalkyl radicals mono-, di- or poly-substituted by optionally substituted aliphatic, aromatic

or araliphatic hydrocarbon, for example lower alkyl, e.g. methyl or ethyl, groups, as well as by free, etherified or esterified hydroxy groups, particularly halogen atoms.

- 5 An optionally substituted aliphatic hydrocarbon residue is primarily a lower alkyl, e.g. methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*.-butyl, *tert*.-butyl, *n*-pentyl, isopentyl, *n*-hexyl, isohexyl, *n*-heptyl or isohexyl group. An optionally substituted aromatic or araliphatic hydrocarbon residue is, for example, an R_a -phenyl residue or an R_a -phenyl-lower alkyl, e.g. R_a -benzyl group, in which R_a stands for hydrogen, lower alkyl for example, one of the groups mentioned above), lower alkoxy (e.g. methoxy, ethoxy, *n*-propyloxy, isopropoxy, *n*-butoxy or isobutoxy), trifluoromethyl, nitro, di-lower alkylamino (e.g. dimethylamino or diethylamino), or halogeno (e.g. fluoro, chloro or bromo). An etherified hydroxy group is, for example, a lower alkoxy group, for example the groups mentioned above, as well as an aryloxy or aryl-lower alkoxy, e.g. R_a -phenyloxy or R_a -phenyl-lower alkoxy, for example R_a -benzyloxy, group, in which R_a has the previously given meaning, whereas an esterified hydroxy group is, for example, a hydroxy group esterified by an organic carboxylic acid, for example a lower alkanoyloxy, e.g. acetyloxy or propionyl-oxy, group, or primarily a halogen, e.g. fluorine or chlorine, atom.

- Other cycloaliphatic hydrocarbon radicals R^I are cycloalkenyl radicals containing at most 2 double bonds and preferably 3 to 8 ring-carbon atoms, which may be substituted as the above cycloalkyl radicals, for example, by optionally substituted aliphatic, aromatic or araliphatic hydrocarbon residues, for example lower alkyl groups, as well as by free, etherified or esterified hydroxy groups, particularly halogen atoms, primarily cycloalkenyl groups with 5 to 6 ring-carbon atoms, which may be substituted by up to 4 lower alkyl groups. These radicals are, for example, 1-, 2- or 3-cyclopentenyl, 2,4-cyclopentadienyl, 1-, 2- or 3-cyclohexenyl or 2,5-cyclohexadienyl, as well as 2-cyclopropenyl, 1-, 2- or 3-cycloheptenyl, 2,6-cycloheptadienyl, or 2-cyclooctenyl radicals or corresponding cycloalkenyl radicals mono-, di- or poly-substituted by optionally substituted aliphatic, aromatic or araliphatic hydrocarbon residues, for example lower alkyl, e.g. methyl, groups, and/or by free, etherified or esterified hydroxy groups, particularly halogen atoms.

- A bivalent aliphatic residue A is a bivalent aliphatic hydrocarbon radical, primarily a lower alkylene radical, which has preferably up to 4 carbon atoms and may be mono- or polysubstituted by optionally substituted aliphatic, aromatic or araliphatic hydrocarbon residues, for example lower alkyl groups, and/or by free, etherified or esterified hydroxy groups, particularly halogen

atoms. It represents primarily a methylene group, but may also stand for a 1,1- or 1,2-ethylene, 1,1-, 1,2-, 2,2- or 1,3-propylene, 2-methyl-1,3- or 1,4-butylene radical.

A higher aliphatic residue R^{II} is above all a higher aliphatic hydrocarbon residue, which may be substituted for example, as the above cycloaliphatic hydrocarbon residue R^I , particularly a higher alkyl, as well as a higher alkenyl residue, which contains 8 to 20, particularly 8—16 carbon atoms. It may be straight or branched and may be linked with the oxygen or sulfur X_2 through any carbon atom. Higher alkyl residues of this type are, for example, 1- or 2-*n*-octyl, 1- or 2-*n*-nonyl, 1- or 2-*n*-decyl, 1- or 2-*n*-undecyl, 1- or 2-*n*-dodecyl, 1- or 2-*n*-tridecyl, 1- or 2-*n*-tetradecyl, 1- or 2-*n*-pentadecyl, 1- or 2-*n*-hexadecyl, 1- or 2-*n*-heptadecyl, 1- or 2-*n*-octadecyl or 1- or 2-*n*-icosyl, as well as groups of this type substituted by lower alkyl, particularly methyl groups, for example 3,7-dimethyl-1-*n*-octyl, 3,7-dimethyl-3-*n*-octyl, 3,7,11-trimethyl-1-*n*-dodecyl or 3,7,11-trimethyl-3-*n*-dodecyl. Higher alkenyl residues are, for example, citronellyl, geranyl, neryl, linalyl, farnesyl, *n*-9-octadecenyl or phytlyl residues.

In the compounds of the present invention, the cycloaliphatyloxy or cycloaliphatylmercapto group of the formula $-X_1-A-R^I$ and the higher aliphatyloxy- or aliphatylmercapto group of the formula $-X_2-R^{II}$ advantageously occupy the 4- or the 5-position of the 1,2-phenylene residue Ph.

Apart from the cycloaliphatyloxy or cycloaliphatylmercapto group of the formula $-X_1-A-R^I$ and the higher aliphatyloxy or aliphatylmercapto group of the formula $-X_2-R^{II}$, the group Ph may contain one or two additional substituents, for example lower alkyl, e.g. the previously mentioned groups, higher alkyl, e.g. the previously mentioned groups, lower alkenyl, e.g. allyl or methallyl groups, higher alkenyl, e.g. the previously mentioned groups, aryl-lower alkyl, for example R_a -phenyl-lower alkyl, e.g. benzyl or 1- or 2-phenylethyl groups, free hydroxy or mercapto groups, etherified hydroxy or mercapto groups, for example lower alkoxy, lower alkenyloxy, halogeno-lower alkoxy, aryloxy or aryl-lower alkoxy groups, or lower alkyl-mercapto, lower alkenyl-mercapto, halogeno-lower alkylmercapto, arylmercapto or aryl-lower alkyl-mercapto groups, e.g. the previously mentioned lower alkoxy groups; allyloxy or methallyloxy; 2-chloroethoxy or 3,3,3-trifluoropropoxy; phenyloxy; benzyloxy or 1- or 2-phenyl-ethoxy; methylmercapto or ethylmercapto; allylmercapto; 3-bromopropylmercapto; phenylmercapto, benzylmercapto or phenylethylmercapto groups, or etherified hydroxy or mercapto groups having one of the formulae $-X_1-A-R^I$ and $-X_2-R^{II}$, in which X_1 , X_2 , A, R^I and R^{II} have the previously given meaning but need not have the

saine meanings as the respective symbols in the formulæ mentioned at the beginning of this paragraph, esterified hydroxy groups, for example halogen, e.g. fluorine, chlorine or bromine atoms, lower alkanoyloxy, e.g. acetyloxy or propionyloxy groups, aryl-lower alkanoyloxy, for example R_4 -phenyl-lower alkanoyloxy-, e.g. benzoyloxy or phenylacetyloxy groups, esterified mercapto groups, trifluoromethyl groups, nitro groups, or amino groups, for example di-lower alkyl-amino, e.g. the previously mentioned di-lower alkyl-amino groups, or lower alkanoylamino-, e.g. acetylamino or propionylamino groups. In the above groups with a phenyl residue, the latter may represent, for example, an R_4 -phenyl group, R_4 having the previously given meaning.

Each of the groups R_4 and R_4' is above all an esterified carboxyl group, in which the esterifying portion is a lower alkyl group, which in the group R_4' may be e.g. methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl or isobutyl group, and in the group R_4 may be e.g. methyl, ethyl, *n*-propyl or *n*-butyl.

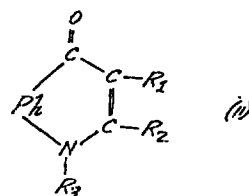
The group R_3 , apart from being primarily hydrogen, may also stand for lower alkyl, e.g. as defined above.

An aliphatic hydrocarbon radical represented by R_3 , which primarily stands for hydrogen, is, for example, a lower alkyl group, as well as lower alkenyl, as defined above, where as a cycloaliphatic radical R_3 may be one of the above defined cycloalkyl or cycloalkenyl groups represented by R^I . A substituted aliphatic hydrocarbon radical is, for example, a lower alkyl radical (as represented, for example, by the above lower alkylene group A) substituted for example, by hydroxy groups, etherified hydroxy, for example lower alkoxy groups, esterified hydroxy groups, for example halogen atoms, free or esterified carboxyl groups, for example carbonyl lower alkoxy, e.g. carbomethoxy or carbethoxy groups, amino groups, for example free amino groups, mono-lower alkylamino or di-lower alkyl-amino groups, e.g. methylamino, ethylamino, *n*-propylamino, dimethylamino or diethylamino, lower alkylencamino, as well as mono-aza-, mono-oxa- or mono-thia-lower alkylencamino groups, in which ring heteroatoms are separated from another by at least two carbon atoms, for example ethylenecamino, pyrrolidino, piperidino, piperazino, 4-methylpiperazino, 4-ethylpiperazino, morpholino or thiamorpholino groups, or cycloalkyl or cycloalkenyl groups, which may be optionally substituted, e.g. by lower alkyl groups and/or halogen atoms, for example those having the meaning given above for the corresponding group R^I , or aryl, for example phenyl, for example, R_4 -phenyl groups.

As indicated above, the present invention also comprises the tautomers of the com-

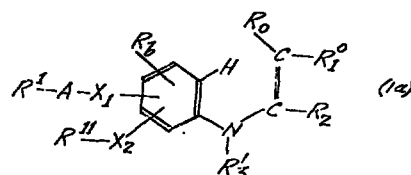
pounds of the above formula I in which R_3 is hydrogen.

The compounds of the invention are valuable as key intermediates in the manufacture of compounds of the formula II



in which R_4 , R_4' , R_3 , and R_3 have the meanings defined above. Compounds of the formula II are important as growth promoting agents, particularly in poultry and especially in animals which are diseased with bacteria or protozoa infections, especially with coccidiosis producing parasites. These compounds are readily obtained by the ring-closure of the compounds of the present invention; their manufacture and properties are described in detail in British Patent Application No. 30403/69 (Serial No. 1270412).

Especially valuable as intermediates are the formula

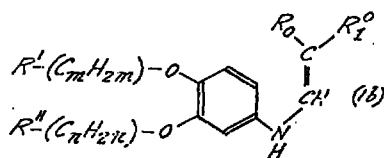


in which R^I , R_4' , R_4 , X_1 , X_2 and R_2 have the previously given meanings, a represents a direct bond between R^I and X_1 or a lower alkylene residue, R^I being a cycloalkyl or cycloalkenyl radical, which may be optionally substituted, for example, as indicated above, primarily by lower alkyl groups and/or halogen atoms, R^{II} stands for a higher alkyl or a higher alkenyl group, R_3' is hydrogen, a lower alkyl or lower alkenyl group, a free, esterified or etherified hydroxy-lower alkyl group, a free or esterified carboxyl-lower alkyl group, an amino-lower alkyl group, an aryl-lower alkyl group or a radical having the meaning given to the group R^I-A- , and R_4 stands for hydrogen, a lower alkyl or aryl-lower alkyl group, a free, etherified or esterified hydroxy or mercapto group, a trifluoromethyl group, a nitro group or an optionally substituted amino group, and the tautomers of such compounds in which R_3' stands for hydrogen.

Particularly useful compounds of the above type are those of the formula Ia, in which each of R_4 and R_4' is a carbo-lower alkoxy group, R^I is a 3- or 8-membered $(R_4)_n$ -cycloalkyl radical, A represents a direct bond or a lower alkylene radical, each of X_1 and X_2

stands for an oxygen atom, R^u is a higher alkyl group, R_b is a hydrogen atom, a lower or higher alkyl group, a R_b -phenyl-lower alkyl group, a lower or higher alkoxy group, a halogeno-lower alkoxy group with 2-7 carbon and at most 3 halogen atoms, an R_b -phenyl-lower alkoxy group, an R_b -phenyloxy group, a group of the formula R^1-A-X_1 , R^1 , A and X_1 having the previously given meaning, a halogen atom, a trifluoromethyl, nitro or di-lower alkyl-amino group, R_2 represents a hydrogen atom or a lower alkyl group, and R_3 stands for a hydrogen atom, a lower alkyl group, or a hydroxy-lower alkyl or di-lower alkyl-amino-lower alkyl group, in which the hetero atoms are separated from the nitrogen atom by at least 2 carbon atoms, and wherein R_a has the previously given meaning, R_c is a hydrogen atom, a lower alkyl group or a halogen atom, and n represents 1 or 2, and above all their tautomers in which R_3' represents hydrogen. Advantageously, R_b represents hydrogen and each of the groups of the formulae R^1-A-X_1 and R^u-X_2 occupies the 4- or the 5-position.

Useful compounds of the above type are primarily those of the formula



in which one of the groups R' and R'' , particularly R'' , is hydrogen and the other is a cycloalkyl group having 3 to 6 ring carbon atoms and being optionally substituted by lower alkyl, and in which the one residue of the formulae $-(C_mH_{2m})-$ and $-(C_nH_{2n})-$, which carries the cycloalkyl group—particularly the group of the formula $-(C_mH_{2m})-$, contains 1-4 carbon atoms and the other 8-16 carbon atoms, and each of R^c and R_3' is a carbo-lower alkoxy group.

Preferred are compounds of the formula (Ib), in which one of the groups R' and R'' , especially R'' , is hydrogen and the other is the cyclopropyl group, and in which the one group of the formula $-(C_mH_{2m})-$ and $-(C_nH_{2n})-$, which carries the cyclopropyl group, particularly the group of the formula $-(C_mH_{2m})-$, contains 1 carbon atom and the other 8-16 carbon atoms, and each of R^c and R_3' is a carbo-lower alkoxy group.

Of special value are the di-lower alkyl, especially dimethyl or diethyl, N - (4 - cyclopropylmethoxy - 3 - [n - octyloxy-, n-decyloxy-, n-dodecyloxy or n-tetra-decyloxy]) - aminomethylene-malonates, as well as the di-lower alkyl, e.g. dimethyl or diethyl, N - (3 - cyclopropylmethoxy - 4 - n - decyloxy) - aminomethylene-malonates.

The compounds of the present invention are

prepared according to known methods, for example, by condensing an aniline compound, which contains as substituents of the phenyl nucleus a cycloaliphatyloxy or cycloaliphatylmercapto group and a higher aliphatyloxy or aliphatylmercapto group, with a di-lower alkyl ester of an α -(1-lower alkoxy-1,1-lower alkylidene)malonic acid.

The above-mentioned reaction is carried out under standard conditions, for example, in the presence or absence of solvents or diluents, preferably those inert towards the reaction components and in the presence or absence of catalysts and/or condensing agents, if necessary, while cooling or heating, under increased pressure, and/or in the atmosphere of an inert gas.

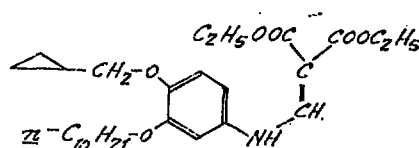
In the above reaction, it may be that in the preparation of the starting material the latter may not be isolated and may be used without purification. Thus, the aniline starting material, which contains as substituents of the phenyl nucleus a cycloaliphatyloxy or cycloaliphatylmercapto group and a higher aliphatyloxy or aliphatylmercapto group, may be obtained by reduction of the corresponding aromatic nitro compound, and, without isolation, condensed with a di-lower alkyl ester of an α -(1-lower alkoxy-1,1-lower alkylidene)malonic acid to form the compounds of the invention.

The starting materials are known or can be prepared by known methods.

The following Examples illustrate the invention; temperatures are given in degrees Centigrade.

EXAMPLE 1

A mixture of 10.5 g of 4-cyclopropylmethoxy - 3 - n - decyloxy - nitrobenzene, 100 ml of anhydrous ethanol and 0.5 g of platinum oxide is hydrogenated at a pressure of 3 atmospheres and room temperature until the hydrogen uptake has ceased. To the mixture, 6.5 g of diethyl ethoxymethylene-malonate are added and the whole is refluxed for 3 hours, then filtered hot. The filtrate is evaporated under reduced pressure, to yield the diethyl N - (4 - cyclopropylmethoxy - 3 - n - decyloxy - phenyl) - aminomethylene - malonate of the formula



In an analogous manner are prepared the dimethyl N - (4 - cyclopropylmethoxy - 3 - n - decyloxy - phenyl) - amino - methylene - malonate and the diethyl N - (4 - cyclopropylmethoxy - 3 - n - tetra - decyloxy -

phenyl) - aminomethylene - malonate, m.p. 56—7°.

The starting material is prepared as follows: To a solution of 55 g of pyrocatechol in 250 ml of anhydrous ethanol, 20 g of sodium hydroxide are added while stirring, followed by 86.9 g of cyclopropylmethyl bromide; the latter is added dropwise during one hour. The mixture is stirred and refluxed for 24 hours, then concentrated to about 1/3 of the original volume. The concentrate is diluted with water and the mixture is extracted with methylene chloride; the organic extract is washed with water, dried, filtered and evaporated. The residue is distilled; the fraction boiling at 90—94°/0.4 mm Hg represents the pyrocatechol mono-cyclopropylmethyl ether.

A mixture of 28.3 g of pyrocatechol mono-cyclopropylmethyl ether, 6.8 g of sodium hydroxide and 100 ml of benzene is stirred and refluxed for 30 minutes. After cooling, the resulting precipitate is filtered off and resuspended in 300 ml of benzene; to the ice cooled mixture, 23.9 g of benzoyl chloride are added during 1/2 hour while stirring. The mixture is stirred for 4 hours at 25°, then washed with 200 ml of a 2% aqueous sodium hydroxide solution and 200 ml of water. The organic layer is separated, dried, filtered and evaporated and the residue is distilled. The fraction boiling at 173—175°/0.3 mm Hg represents the 2-cyclopropylmethoxy-phenyl benzoate.

To a solution of 25 g of 2 - cyclopropylmethoxyphenyl benzoate in 210 ml of glacial acetic acid, 25.2 ml of fuming nitric acid are added during 1/4 hour while stirring at room temperature. The mixture is heated at 100° for 20 minutes, then poured into 200 ml of ice-water. The resulting precipitate is filtered off and recrystallized from isopropanol to yield the 2 - cyclopropylmethoxy - 5 - nitro - phenyl benzoate, m.p. at 96—99°.

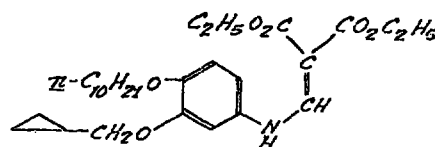
A mixture of 40 g of 2 - cyclopropylmethoxy - 5 - nitrophenyl benzoate, 150 ml of 95% aqueous ethanol and 11.5 g of a 50% aqueous sodium hydroxide solution is refluxed for 2 hours and evaporated under reduced pressure. The residue is taken up in 300 ml of water, the solution is acidified with 40 ml of concentrated hydrochloric acid and extracted with 300 ml of methylene chloride. The organic extract is stirred with 500 ml of a 10% aqueous sodium hydrogen carbonate solution for 2 hours. The organic layer is separated; the aqueous layer is extracted with methylene chloride, and the combined organic solutions are dried, filtered and evaporated. The residue is triturated with hexane to yield the 4 - cyclopropylmethoxy-3-hydroxy-nitrobenzene, m.p. 104—105°.

The mixture of 18 g of 4 - cyclopropylmethoxy - 3 - hydroxy - nitrobenzene, 130 ml of toluene and 3.44 g of sodium hydroxide

is stirred and refluxed for 1 hour, then evaporated under reduced pressure. The residue is taken up in 130 ml of dimethylformamide, 0.4 g of sodium iodide and 19 g of *n*-decyl bromide are added and the mixture is stirred under a nitrogen atmosphere for 17 hours at room temperature, then diluted with 500 ml of water and extracted with methylene chloride. The organic extract is washed with water, dried, filtered and evaporated. The residue is recrystallized from *n*-hexane to yield the 4-cyclopropylmethoxy-3 - *n* - decyloxy - nitrobenzene, m.p. 59—61°.

EXAMPLE 2

A mixture of 12 g of 3 - cyclopropyloxy - 4 - *n* - decyloxynitrobenzene, 200 ml of anhydrous ethanol and 0.8 g of platinum oxide is hydrogenated under a pressure of 3 atmospheres and at room temperature until the hydrogen uptake has ceased. The mixture is combined with 7.4 g of diethyl ethoxymethylene-malonate and refluxed for 3 hours while stirring, then filtered hot. The filtrate is evaporated under reduced pressure to yield the diethyl *N* - (3 - cyclopropylmethoxy - 4 - *n* - decyloxy - phenyl) - aminomethylene - malonate of the formula



The starting material is prepared as follows: To a mixture of 22 g of pyrocatechol, 200 ml of acetone and 50 g of anhydrous potassium carbonate, 46.4 g of *n*-decyl bromide are added while stirring. The mixture is refluxed under a nitrogen atmosphere for 36 hours, then filtered. The filtrate is evaporated under reduced pressure, the residue is distilled. The fraction boiling at 140—144°/0.4 mm Hg represents the pyrocatechol mono-*n*-decyl ether. About the same amount of pyrocatechol di-*n*-decyl ether is also obtained, b.p. 198—200°/0.3 mm Hg.

A mixture of 12 g of pyrocatechol mono-*n*-decyl ether, 1.9 g of sodium hydroxide and 50 ml of benzene is stirred and refluxed for 30 minutes and evaporated. To the residue, the mixture of 7.7 g of benzoyl chloride and 150 ml of benzene is slowly added while cooling; the mixture is stirred at room temperature for 4 hours, then washed with 200 ml of a 2% aqueous sodium hydroxide solution and water, dried, filtered and evaporated under reduced pressure. The residue is distilled; the fraction boiling at 175—180°/0.1 mm Hg represents the 2 - *n* - decyloxy - phenyl benzoate.

A total of 11.8 g of 2 - *n* - decyloxy-phenyl

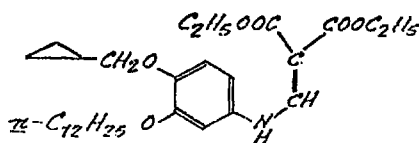
benzoate is dissolved in 100 ml of glacial acetic acid; 12 ml of fuming nitric acid are added dropwise while stirring and the mixture is heated on the steam bath for 20 minutes, then cooled to 30° and slowly added to 125 ml ice-water. The aqueous mixture is extracted with methylene chloride; the organic extract is washed with water, dried, filtered and evaporated to yield the 2 - *n* - decyloxy - 5 - nitro - phenyl benzoate.

A mixture of 78 g of 2 - *n* - decyloxy - 5 - nitro - phenyl benzoate, 235 ml of ethanol and 18 g of a 50% aqueous sodium hydroxide solution is refluxed for 2½ hours and evaporated under reduced pressure. The residue is taken up in 200 ml of water; the solution is acidified with 50 ml of concentrated hydrochloric acid and extracted with methylene chloride. The organic extract is washed with a 10% aqueous sodium hydrogen carbonate solution and water, dried, filtered and evaporated to yield the 4 - *n* - decyloxy - 3 - hydroxy - nitrobenzene, m.p. 53—54°.

A mixture of 12.5 g of 4 - *n* - decyloxy - 3 - hydroxy - nitrobenzene, 85 ml of toluene, 1.7 g of sodium hydroxide, 0.18 g of sodium iodide and 85 ml of dimethylformamide is refluxed for 1 hour while stirring. A total of 10.2 g of cyclopropylmethyl bromide (85%) is then added dropwise while stirring; the mixture is stirred at 120° for 24 hours, then diluted with water and extracted with methylene chloride. The organic extract is washed with water, dried, filtered and evaporated. The residue is recrystallized from *n*-hexane to yield the 3 - cyclopropylmethoxy - 4 - *n* - decyloxy - nitrobenzene, m.p. 61—62°.

EXAMPLE 3

A mixture of 9 g of 4 - cyclopropylmethoxy - 3 - *n* - dodecyloxy - nitrobenzene, 150 ml of anhydrous ethanol and 0.5 g of platinum oxide is hydrogenated under a pressure of 3 atmospheres and room temperature until the hydrogen uptake has ceased. 5 g of Diethyl ethoxymethylene-malonate are then added and the mixture is refluxed for 5 hours under a nitrogen atmosphere, then filtered. The filtrate is evaporated under reduced pressure to yield the diethyl N - (4 - cyclopropylmethoxy - 3 - *n* - dodecyloxy - phenyl) - aminomethylene-malonate, m.p. 67°, of the formula

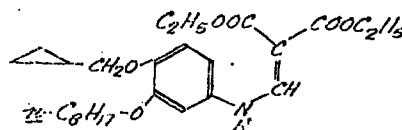


The starting material is prepared as follows: A mixture of 5 g of 4-cyclopropylmethoxy - 3 - hydroxy - nitrobenzene, 35 ml of toluene and 0.92 g of sodium hydroxide is stirred and refluxed for 1 hour under a

nitrogen atmosphere and evaporated under reduced pressure. The residue is taken up in 35 ml of dimethylformamide, 0.1 g of sodium iodide and 5.73 g of *n*-dodecyl bromide are then added and the mixture is stirred for 40 hours under a nitrogen atmosphere at 120°. It is cooled, diluted with 100 ml of water and extracted with methylene chloride. The organic extract is dried, filtered and evaporated to yield the 4-cyclopropylmethoxy - 3 - *n* - dodecyloxy - nitrobenzene.

EXAMPLE 4

A mixture of 9 g of 4 - cyclopropylmethoxy - 3 - *n* - octyl - oxy - nitrobenzene, 100 ml of anhydrous ethanol and 0.5 g of platinum oxide is hydrogenated under a pressure of 3 atmospheres and at room temperature until the hydrogen uptake ceases. To the mixture, 6.1 g of diethyl ethoxy-methylene-malonate are added; the mixture is refluxed for 3 hours, then filtered hot. The filtrate is evaporated under reduced pressure to yield the diethyl N - (4 - cyclopropyl - methoxy - 3 - *n* - octyloxy - phenyl) - aminomethylene - malonate of the formula



In an analogous manner is prepared the dimethyl N - (4 - cyclopropylmethoxy - 3 - *n* - octyloxy - phenyl) - aminomethylene - malonate.

The starting material is prepared as follows: A mixture of 36 g of 4 - cyclopropylmethoxy - 3 - hydroxy - nitrobenzene, 260 ml of toluene and 6.88 g of sodium hydroxide is stirred and refluxed for one hour and evaporated under reduced pressure. The residue is taken up in 260 ml of dimethylformamide, 0.15 g of sodium iodide and 38 g of *n*-octyl bromide are added and the mixture is heated at 120° bath temperature for 29 hours while stirring under a nitrogen atmosphere. The mixture is diluted with 500 ml of water and extracted with methylene chloride. The organic extract is washed with water, dried, filtered and evaporated. The residue is recrystallized from *n*-hexane, to yield the 4 - cyclopropylmethoxy - 3 - *n* - octyloxy - nitrobenzene, m.p. 48—49°.

EXAMPLE 5

A mixture of 93 g of 2 - cyclopropylmethoxy - 3 - *n* - decyloxy - nitrobenzene, 300 ml of isopropanol and 1.5 g of platinum oxide is hydrogenated until the hydrogen uptake ceases. After filtering, the filtrate is combined with 47.5 g of diethyl ethoxymethylene-malonate; the mixture is stirred for 16 hours and evaporated under reduced pressure to

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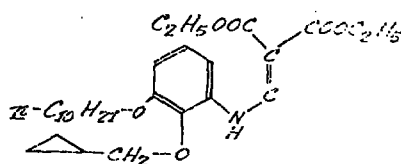
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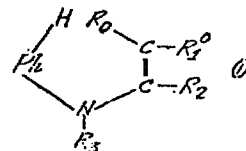
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yield the diethyl N - (2 - cyclopropylmethoxy - 3 - n - decyloxy - phenyl) - aminomethylene - malonate, of the formula

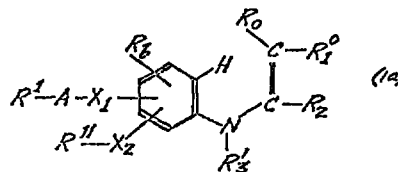


WHAT WE CLAIM IS:—
1. A compound of the formula



in which Ph is a 1,2-phenylene residue substituted by a group of the formula $-X_1-A-R^I$ and a group of the formula $-X_2-R^{II}$, in which R^I is a cycloaliphatic radical, A represents a direct bond between X_1 and R^I or a bivalent aliphatic radical, each of X_1 and X_2 is oxygen or sulfur, and R^{II} is a higher aliphatic radical, each of R_0 and R_1 stands for a carbo-lower alkoxy group, R_2 stands for hydrogen or a lower alkyl group, and R_3 is hydrogen atom, an optionally substituted aliphatic or cycloaliphatic hydrocarbon radical, or a tautomer of such a compound in which R_3 is a hydrogen atom.

2. A compound of the formula



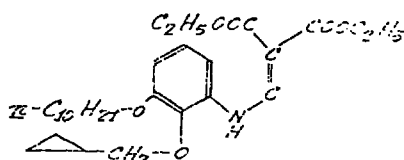
in which R_1' and R_0 have the meanings given in claim 1, R^I is a cycloalkyl or cycloalkenyl residue, which may be optionally substituted by one or more optionally substituted aliphatic, aromatic, or araliphatic hydrocarbon residues and/or by one or more free, etherified or esterified hydroxy groups, A represents a direct bond between R^I and X_1 or a lower alkylene residue, each of X_1 and X_2 represents an oxygen or sulfur atom, R^{II} stands for a higher alkyl or a higher alkenyl group, R_2 is a hydrogen atom or a lower alkyl radical, R_3 is a hydrogen atom, a lower alkyl or lower alkenyl group, a lower alkyl group substituted by a free, etherified or esterified hydroxy group, a free or esterified carboxyl group, an amino group or an aryl group, or R_3 is a group of the formula R^I-A- , R^I and A have the previously given meaning, and R_0 represents a hydrogen atom, a lower alkyl group, an aryl-lower alkyl group, a free, etherified or esterified hydroxy or mercapto group, a trifluoromethyl group, a nitro group or an optionally substituted amino group, or

The starting material is prepared as follows: To a mixture of 100 g of 2 - cyclopropylmethoxyphenyl benzoate, 2400 ml of acetic acid and 150 ml of acetic anhydride, 220 ml of nitric acid (95%) are added within 2 minutes while stirring. The mixture is stirred for 10 minutes at 62°, then diluted with 800 ml of water and stirred for 1 hour at 25°. The resulting precipitate is filtered off and washed with 100 ml of water to yield the 2-cyclopropylmethoxy - 5 - nitrophenyl benzoate, m.p. 97—100°. The combined filtrate is cooled to 20° and stirred at this temperature for 2 hours. The resulting precipitate is filtered off, washed with water and dried under reduced pressure to yield the 2 - cyclopropylmethoxy - 3 - nitrophenyl benzoate, m.p. 50—52°.

A mixture of 80 g of 2 - cyclopropylmethoxy - 3 - nitrophenyl benzoate, 300 ml of 95% aqueous ethanol and 40 g of 50% aqueous sodium hydroxide is refluxed for 1 hour, then diluted with 150 ml of water and concentrated under reduced pressure. The concentrate is diluted with 150 ml of water and acidified with 25 ml of concentrated hydrochloric acid. The mixture is extracted with 300 ml of methylene chloride; the organic extract is washed with 100 ml of water, stirred for 2 hours with 100 ml of 10% aqueous sodium hydrogen carbonate and finally twice with 100 ml of water, dried, filtered, and evaporated under reduced pressure. The residue is taken up in 100 ml of toluene; 10 g of sodium hydroxide and 1 g of sodium iodide are added, and the mixture is refluxed until all the water has been removed via a water-trap. After diluting with 100 ml of dimethylformamide, the mixture is distilled until the vapor temperature reaches 120°. To the hot concentrate, 55.6 g of n-decyl bromide are added dropwise; the mixture is stirred for 1½ hours at 110—118°, then cooled to 20°, diluted with 300 ml of water and extracted with 300 ml of methylene chloride. The organic extract is washed with 100 ml of water, dried, filtered and evaporated, to yield the 2 - cyclopropylmethoxy - 3 - n - decyloxy - nitrobenzene.

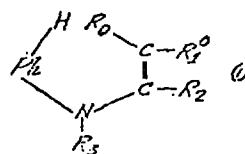


yield the diethyl N - (2 - cyclopropylmethoxy - 3 - n - decyloxy - phenyl) - aminomethylene - malonate, of the formula



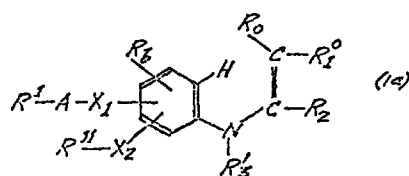
WHAT WE CLAIM IS:—

1. A compound of the formula



in which Ph is a 1,2-phenylene residue substituted by a group of the formula $-X_1-A-R^I$ and a group of the formula $-X_2-R^{II}$, in which R^I is a cycloaliphatic radical, A represents a direct bond between X_1 and R^I or a bivalent aliphatic radical, each of X_1 and X_2 is oxygen or sulfur, and R^{II} is a higher aliphatic radical, each of R_1 and R_2 stands for a carbo-lower alkoxy group, R_3 stands for hydrogen or a lower alkyl group, and R_3 is hydrogen atom, an optionally substituted aliphatic or cycloaliphatic hydrocarbon radical, or a tautomer of such a compound in which R_3 is a hydrogen atom.

2. A compound of the formula



in which R_1 and R_2 have the meanings given in claim 1, R^I is a cycloalkyl or cycloalkenyl residue, which may be optionally substituted by one or more optionally substituted aliphatic, aromatic, or araliphatic hydrocarbon residues and/or by one or more free, etherified or esterified hydroxy groups, A represents a direct bond between R^I and X_1 or a lower alkylene residue, each of X_1 and X_2 represents an oxygen or sulfur atom, R^{II} stands for a higher alkyl or a higher alkenyl group, R_1 is a hydrogen atom or a lower alkyl radical, R_2 is a hydrogen atom, a lower alkyl or lower alkenyl group, a lower alkyl group substituted by a free, etherified or esterified hydroxy group, a free or esterified carboxyl group, an amino group or an aryl group, or R_3 is a group of the formula R^I-A- , R^I and A have the previously given meaning, and R_4 represents a hydrogen atom, a lower alkyl group, an aryl-lower alkyl group, a free, etherified or esterified hydroxy or mercapto group, a trifluoromethyl group, a nitro group or an optionally substituted amino group, or

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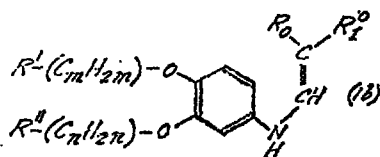
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- 5 The starting material is prepared as follows: To a mixture of 100 g of 2 - cyclopropylmethoxyphenyl benzoate, 2400 ml of acetic acid and 150 ml of acetic acid anhydride, 220 ml of nitric acid (95%) are added within 2 minutes while stirring. The mixture is stirred for 10 minutes at 62°, then diluted with 800 ml of water and stirred for 1 hour at 25°. The resulting precipitate is filtered off and washed with 100 ml of water to yield the 2-cyclopropylmethoxy - 5 - nitrophenyl benzoate, m.p. 97--100°. The combined filtrate is cooled to 20° and stirred at this temperature for 2 hours. The resulting precipitate is filtered off, washed with water and dried under reduced pressure to yield the 2 - cyclopropylmethoxy - 3 - nitrophenyl benzoate, m.p. 50--52°.
- 10 A mixture of 80 g of 2 - cyclopropylmethoxy - 3 - nitro phenyl benzoate, 300 ml of 95% aqueous ethanol and 40 g of 50% aqueous sodium hydroxide is refluxed for 1 hour, then diluted with 150 ml of water and concentrated under reduced pressure. The concentrate is diluted with 150 ml of water and acidified with 25 ml of concentrated hydrochloric acid. The mixture is extracted with 300 ml of methylene chloride; the organic extract is washed with 100 ml of water, stirred for 2 hours with 100 ml of 10% aqueous sodium hydrogen carbonate and finally twice with 100 ml of water, dried, filtered, and evaporated under reduced pressure. The residue is taken up in 100 ml of toluene; 10 g of sodium hydroxide and 1 g of sodium iodide are added, and the mixture is refluxed until all the water has been removed via a water-trap. After diluting with 100 ml of dimethylformamide, the mixture is distilled until the vapor temperature reaches 120°. To the hot concentrate, 55.6 g of n-decyl bromide are added dropwise; the mixture is stirred for 1½ hours at 110--118°, then cooled to 20°, diluted with 300 ml of water and extracted with 300 ml of methylene chloride.
- 15 The organic extract is washed with 100 ml of water, dried, filtered and evaporated, to yield the 2 - cyclopropylmethoxy - 3 - n - decyloxy - nitrobenzene.

- a tautomer of such a compound in which R_3' stands for hydrogen.
3. A compound of the formula Ia given in claim 2, in which each of the R_0 and R_1^0 is a carbo-lower alkoxy group, R^I stands for a 3- to 8-membered $(R_0)_n$ -cycloalkyl residue, A is a direct bond between R^I and X_1 or a lower alkylene residue, each of X_1 and X_2 stands for an oxygen atom, R^{II} is a higher alkyl group, R_0 is a hydrogen atom, a lower alkyl residue, an R_0 -phenyl-lower alkyl residue, a lower alkoxy group, a halogeno-lower alkoxy group with 2 to 7 carbon atoms and at most 3 halogen atoms, an R_0 -phenyl-lower alkoxy group, an R_0 -phenyloxy group, a group of the formula R^I-A-X_1 in which R^I , A and X_1 have the above given meaning, a halogen atom, a trifluoromethyl group, a nitro group or a di-lower alkyl-amino group, R_2 is a hydrogen atom or a lower alkyl group and R_3' is a hydrogen atom, a lower alkyl group, or a hydroxy-lower alkyl or di-lower alkyl-amino-lower alkyl group in which the hetero atoms are separated from the nitrogen atom by at least 2 carbon atoms, and in which R_0 is a hydrogen atom, a lower alkyl, a lower alkoxy, a trifluoromethyl, a nitro or a di-lower alkylamino group or a halogen atom, R_0 is a hydrogen atom, a lower alkyl group or a halogen atom, and n is 1 or 2, or a tautomer of such a compound in which R_3' represents hydrogen.
4. A compound of the formula Ia given in claim 2, in which R^I , A, X_1 , X_2 , R^{II} , R_2 , R_3' , R_0 and R_1^0 have the meaning given in claim 3 and R_0 is hydrogen and the group of the formulae R^I-A-X_1 and $R^{II}-X_2$ occupy the 4- or 5-position in either order, or a tautomer thereof in which R_3' is hydrogen.
5. A compound of the formula



- in which one of the groups R^I and R^{II} is hydrogen and the other is a cycloalkyl group having 3 to 6 ring carbon atoms and being optionally substituted by lower alkyl, and in which the one group of the formulae $-(C_nH_{2n})-$ and $-(C_nH_{2n})-$ which carries the cycloalkyl group has 1 to 4 carbon atoms and the other has 8 to 16 carbon atoms, and each of R_0 and R_1^0 is a carbo-lower alkoxy group.
6. A compound of the formula Ia given in claim 5, in which one of the groups R^I and R^{II} is hydrogen and the other cyclopropyl, and in which the one group of the formulae $-(C_nH_{2n})-$ and $-(C_nH_{2n})-$ which carries the cyclopropyl group has one carbon atom and the other has 8 to 16 carbon atoms, and each of R_0 and R_1^0 is a carbo-lower alkoxy group.
7. Diethyl N - (4 - cyclopropylmethoxy - 3 - n - decyloxyphenyl) - aminomethylene - malonate.
8. Dimethyl N - (4 - cyclopropylmethoxy - 3 - n - decyloxyphenyl) - aminomethylene - malonate.
9. Diethyl N - (4 - cyclopropylmethoxy - 3 - n - tetradecyloxyphenyl) - amino - methylene - malonate.
10. Diethyl N - (3 - cyclopropylmethoxy - 4 - n - decyloxyphenyl) - amino - methylene - malonate.
11. Diethyl N - (4 - cyclopropylmethoxy - 3 - n - dodecyloxyphenyl) - amino - methylene - malonate.
12. Diethyl N - (4 - cyclopropylmethoxy - 4 - n - octyloxyphenyl) - amino - methylene - malonate.
13. Dimethyl N - (4 - cyclopropylmethoxy - 3 - n - octyloxyphenyl) - amino - methylene - malonate.

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