

PATENT SPECIFICATION

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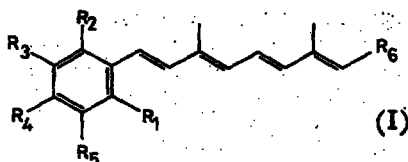


(54) POLYENE DERIVATIVES

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

The present invention relates to polyene derivatives. More particularly, the invention is concerned with polyene derivatives, a process for the manufacture thereof and pharmaceutical preparations containing same.

The polyene derivatives provided by the present invention are compounds of the general formula



wherein R₁ and R₂ each represent a lower alkyl group, R₃ represents a hydrogen or halogen atom or a lower alkyl, lower alkoxy, lower alkenoxy, nitro, amino, mono(lower alkyl)-amino, di(lower alkyl)amino, lower alkanoyl-amino or N-heterocyclic group, R₄ represents a hydrogen atom or a lower alkyl, lower alkenyl, lower alkoxy, lower alkenoxy, nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, lower alkanoyl-amino or N-heterocyclic group and R₅ represents a hydrogen or halogen atom or a lower alkyl, lower alkenyl, lower alkoxy, lower alkenoxy, nitro, amino, mono(lower alkyl)amino, di(lower

alkyl)amino, lower alkanoyl-amino or N-heterocyclic group (provided that at least one of R₃, R₄ and R₅ represents other than a hydrogen atom and, when R₃ or R₅ represents a halogen atom, R₄ represents other than a lower alkoxy group) and R₆ represents a formyl, hydroxymethyl, alkoxymethyl, alkanoyloxymethyl, carboxyl, alkoxycarbonyl, alkenoxycarbonyl, alkynoxycarbonyl, carbamoyl, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl or N-heterocyclic carbonyl group, and salts thereof.

The aforementioned lower alkyl and lower alkenyl groups contain up to 6 carbon atoms such as the methyl, ethyl, propyl, isopropyl or 2-methylpropyl group and the vinyl, allyl or butenyl group. The lower alkoxy and lower alkenoxy groups likewise contain up to 6 carbon atoms such as the methoxy, ethoxy or isopropoxy group and the vinyloxy or allyloxy group.

Of the halogen atoms, fluorine and chlorine are preferred.

The amino group can be monosubstituted or disubstituted by straight-chain or branched-chain lower alkyl groups (e.g. methyl, ethyl, isopropyl etc).

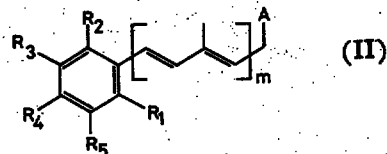
The lower alkanoylamino groups contain residues which are derived from lower alkane-carboxylic acids containing up to 6 carbon atoms (e.g. acetic acid, propionic acid or pivalic acid).

The N-heterocyclic groups are preferably 5-membered or 6-membered groups which, in addition to the nitrogen atom, may also contain an oxygen or sulphur atom or a further nitrogen atom. Examples of such groups are the

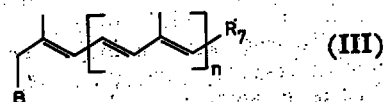
- 2 pyrrolidino, piperidino, morpholino and thio-morpholino groups.
- 5 The alkoxyethyl and alkoxyethyl groups preferably contain alkoxy moieties having up to 6 carbon atoms. These can be straight-chain or branched-chain such as, for example, the methoxy, ethoxy and isopropoxy groups. However, the alkoxy moiety can also be a higher alkoxy group containing from 7 to 10 20 carbon atoms, especially the cetyloxy group.
- 10 The alkenoxycarbonyl and alkynoxycarbonyl groups preferably contain alkenoxy and alkynoxy moieties having up to 6 carbon atoms such as, for example, the allyloxy or propargyloxy group.
- 15 The alkanoyloxymethyl groups are preferably derived from lower alkanecarboxylic acids containing from 1 to 6 carbon atoms (e.g. acetic acid, propionic acid or pivalic acid). They may, however, also be derived from 20 higher alkanecarboxylic acids containing from 7 to 20 carbon atoms (e.g. palmitic acid or stearic acid).
- 25 The carbamoyl group can be monosubstituted or disubstituted by straight-chain or branched-chain lower alkyl groups (e.g. methyl, ethyl or isopropyl). Examples of such substituted carbamoyl groups are the methyl-carbamoyl, dimethylcarbamoyl and diethyl-carbamoyl groups.
- 30 The N-heterocyclyl moieties of the N-heterocyclyl-carbonyl groups are preferably 5-membered or 6-membered heterocyclic moieties which, in addition to the nitrogen atom, may contain an oxygen or sulphur atom or a further nitrogen atom. Examples of such moieties are piperidino, morpholino, thio-morpholino or pyrrolidino.
- 35 Examples of compounds of formula I are:
- 40 9 - (2,3,6 - trimethyl - phenyl) - 3,7-dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid,
9 - (2,4,6 - trimethyl - phenyl) - 3,7-dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid,
45 9 - (2,4,6 - triisopropyl - phenyl) - 3,7-dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid,
9 - (2,3,4,6 - tetramethyl - phenyl) - 3,7-dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid,
50 9 - (4 - methoxy - 2,6 - dimethyl - phenyl) - 3,7 - dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid,
9 - (4 - methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid,
55 9 - (3 - methoxy - 2,4,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid,
9 - (4 - methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid ethyl ester,
60 9 - (4 - methoxy - 2,3,6 - trimethyl-

- phenyl) - 3,7 - dimethyl - nona - 2 - trans,4-cis,6 - trans,8 - trans - tetraen - 1 - oic acid ethyl ester,
9 - (4 - methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid isopropyl ester,
9 - (4 - methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid amide,
9 - (4 - methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid ethyl amide,
9 - (4 - methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid allyl ester,
9 - (4 - methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid propargyl ester,
9 - (4 - methoxy - 3 - allyl - 2,6 - dimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid,
9 - (4 - methoxy - 3 - nitro - 2,6 - dimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid ethyl ester,
9 - (3 - dimethylamino - 2,4,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid ethyl ester,
9 - (4 - isopropoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid,
9 - (4 - allyloxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid,
9 - (3 - chloro - 2,4,6 - trimethyl - phenyl) - 3,7 - dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid and
9 - (3 - nitro - 2,4,6 - trimethyl - phenyl) - 3,7 - dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid.

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



with a compound of the general formula

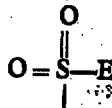


wherein m stands for zero and n stands for 1 or m stands for 1 and n stands for zero; one of the two symbols A and B represents an oxo group and the other symbol represents a triarylphosphonium group of the formula $-P[X]_3^+Y^-$, in which X represents an aryl group and Y represents the anion of an in-

organic or organic acid, or a dialkoxyphosphinyl group of the formula —P[Z]_2 ,



in which Z represents an alkoxy group, or one of the two symbols A and B represents a sulphone group of the formula



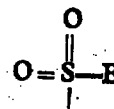
in which E represents an aryl or aralkenyl group which may be substituted by one or more electron-releasing to weakly electron-withdrawing substituents, and the other symbol represents a halogen atom or an alkanesulphonyloxy or arylsulphonyloxy group, R_1 , R_2 , R_3 , R_4 and R_5 have the significance given earlier and R_7 represents a carboxy, alkoxy-carbonyl, alkenoxycarbonyl, alkynoxycarbonyl, di(lower alkyl)carbamoyl or heterocyclal-carbonyl group, or, when B represents an oxo group, R_7 can also represent an alkoxymethyl or alkanoyloxymethyl group, or, when B represents a halogen atom or an alkanesulphonyloxy or arylsulphonyloxy group, R_7 can also represent a formyl, alkoxymethyl or alkanoyloxymethyl group, or, when B represents a triarylphosphonium group or a dialkoxyphosphinyl group or a sulphone group, R_7 can also represent a formyl group, and cleaving off any sulphone group which may be present in the reaction product with the formation of an additional carbon-carbon bond and, if desired, converting an acid or amine into a salt; or transforming a carboxylic acid of formula I into a carboxylic acid ester of formula I or into an amide of formula I; or transforming a carboxylic acid ester of formula I into a carboxylic acid of formula I or into an amide of formula I; or reducing a carboxylic acid of formula I or a carboxylic acid ester of formula I to the corresponding alcohol of formula I and optionally etherifying or esterifying said alcohol; or saponifying an alcohol ester of formula I; or oxidising an alcohol or alcohol ester of formula I to the corresponding carboxylic acid.

The aryl groups denoted by X in the triarylphosphonium groups of the formula $\text{—P[X]}_3\text{OY}^\ominus$ include all generally known aryl groups, but especially mononuclear aryl groups such as phenyl, lower alkyl-substituted phenyl or lower alkoxy-substituted phenyl (e.g. tolyl, xylyl, mesityl and *p*-methoxyphenyl). Of the inorganic acid anions denoted by Y, the chloride, bromide, iodide and hydrosulphate ions are preferred and, of the organic acid anions, the tosyloxy ion is preferred.

The alkoxy groups denoted by Z in the dialkoxyphosphinyl groups of the formula —P[Z]_2 are preferably lower alkoxy groups

containing from 1 to 6 carbon atoms, especially methoxy and ethoxy.

Examples of aryl and aralkenyl groups, which may be substituted by one or more electron-releasing to weakly electron-withdrawing substituents, denoted by E in the sulphone group of the formula



are phenyl and styryl which may be substituted in the *o*-, *m*- or *p*-position by methoxy, phenoxy, acetoxy, dimethylamino, phenylmethylamino, acetylamino, methylthio, phenylthio, thioacetyl, chloro, bromo or cyano or in the *m*-position by nitro.

The starting materials of formulae II and III are, in part, novel compounds. Triaryl phosphonium compounds of formula II, except those in which R_4 is a hydrogen atom or a lower alkyl group, are described and claimed in our copending application No. 9185/76 which is divided out of the present application (Serial No. 1,468,402). They can be prepared, for example, in the following manner:

Compounds of formula II in which m stands for zero and A represents a triarylphosphonium group [IIa] or a dialkoxyphosphinyl group [IIc] can be prepared, for example, by treating a corresponding $(\text{R}_1\text{—}\text{R}_5)$ -benzene with formaldehyde in the presence of a hydrohalic acid (e.g. concentrated hydrochloric acid), if desired in a solvent (especially glacial acetic acid), and reacting the resulting $(\text{R}_1\text{—}\text{R}_5)$ -benzyl halide of formula II in which m stands for zero and A for a halogen atom [IIIi] in a manner known per se with a triaryl phosphine in a solvent, preferably with triphenyl phosphine in toluene or benzene, or with a trialkyl phosphite, especially with triethyl phosphite.

An alkoxy group present in the aforementioned $(\text{R}_1\text{—}\text{R}_5)$ -benzene can be introduced, for example, by alkylation of a hydroxy group present. For example, the corresponding phenol can be reacted, preferably in a solvent (e.g. an alkanol) and in the presence of a base (e.g. potassium carbonate), with an alkyl halide (e.g. methyl iodide) or dimethyl sulphate.

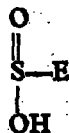
Compounds of formula II in which m stands for 1 and A represents a triarylphosphonium group [IIb] or a dialkoxyphosphinyl group [IId] can be prepared, for example, in the following manner: The corresponding $(\text{R}_1\text{—}\text{R}_5)$ -benzene is initially subjected to a formylating reaction; for example, by allowing a formylating agent to react with the substituted-benzene. This can be carried out, for example, by formylating the substituted-benzene in the presence of a Lewis acid. As the formylating agent there can be used, in particular, an orthoformic acid ester, formyl

chloride and dimethylformamide. Especially suitable Lewis acids are the halides of zinc, aluminium, titanium, tin and iron such as zinc chloride, aluminium trichloride, titanium tetrachloride, tin tetrachloride and iron trichloride as well as the halides of inorganic and organic acids such as, for example, phosphorus oxychloride and methane sulphonyl chloride.

If the formylating agent is present in excess, the formylation may be carried out without the addition of a further solvent. In general, however, it is recommended to carry out the formylation in an inert solvent (e.g. nitrobenzene or in a chlorinated hydrocarbon such as methylene chloride). The formylation can be carried out at a temperature between 0° C and the boiling point of the mixture.

A resulting (R₁—R₅)-benzaldehyde can subsequently be chain-lengthened in a manner known per se by condensation with acetone in the cold (i.e. at a temperature of about 0°—30° C) in the presence of alkali (e.g. dilute aqueous sodium hydroxide) to give a 4 - [(R₁—R₅) - phenyl] - but - 3 - en - 2 - one which can be converted into the corresponding 5 - [(R₁—R₅) - phenyl] - 3 - methyl - 3 - hydroxy - penta - 4 - en - 1 - yne in a manner known per se by means of an organometallic reaction (e.g. by means of a Grignard reaction by the addition of acetylene). The resulting tertiary acetylenic carbinol is subsequently partially hydrogenated in a manner known per se using a partially deactivated noble metal catalyst (Lindlar catalyst). The resulting tertiary ethylenic carbinol can subsequently be converted, under allyl rearrangement, into the desired phosphonium salt of formula IIb in which *m* stands for 1 by treatment with a triaryl phosphine, especially with triphenyl phosphine, in the presence of a hydrohalide such as hydrogen chloride or hydrogen bromide in a solvent (e.g. in benzene). The tertiary ethylenic carbinol can, moreover, be halogenated to give a halide of formula II in which *m* stands for 1 and A for a halogen atom [IIk] and this halide can be reacted with a trialkyl phosphite (e.g. triethyl phosphite) to give a corresponding phosphonate of formula IId.

Compounds of formula II in which *m* stands for zero and A represents a sulphone group [IIf] can be prepared, for example, by dissolving a (R₁—R₅)-benzyl alcohol or a corresponding benzyl halide in a polar solvent such as an alcohol (e.g. methanol, ethanol or isopropanol) or in tetrahydrofuran or dimethylformamide or in glacial acetic acid and treating the solution at room temperature with a sulphonic acid of the formula



wherein E has the significance given earlier, or with an alkali salt thereof. The sulphone can be isolated, for example, by making the reaction mixture neutral by adding an aqueous sodium hydrogen carbonate solution and extracting the sulphone with an organic solvent (e.g. ethyl acetate or ether).

Compounds of formula II in which *m* stands for 1 and A represents a sulphone group [IIf] can be prepared in an analogous manner by reacting a 5 - [(R₁—R₅) - phenyl] - 3 - methyl - penta - 2,4 - dien - 1 - ol or a halide thereof with a sulphonic acid as formulated earlier or with an alkali salt thereof.

Compounds of formula II in which *m* stands for zero and A represents an oxo group [IIg] can be prepared, for example, by formylating in the previously described manner a (R₁—R₅)-benzene. In this manner, a (R₁—R₅)-benzaldehyde is directly obtained from the (R₁—R₅)-benzene.

Compounds of formula II in which *m* stands for 1, and A represents an oxo group [IIh] can be prepared, for example, by submitting a 4 - [(R₁—R₅) - phenyl] - but - 3 - en - 2 - one, described hereinbefore in connection with the preparation of compounds of formula IIb, to a Wittig reaction with ethoxycarbonylmethylene-triphenylphosphorane or with diethyl-phosphonoacetic acid ethyl ester. The resulting 5 - [(R₁—R₅) - phenyl] - 3 - methyl - penta - 2,4 - dien - 1 - oic acid ethyl ester is subsequently reduced in the cold with a mixed metal hydride, especially lithium aluminium hydride, in an organic solvent (e.g. ether or tetrahydrofuran) to give a 5 - [(R₁—R₅) - phenyl] - 3 - methyl - penta - 2,4 - dien - 1 - ol. This alcohol is then oxidised by treatment with an oxidising agent, for example, with manganese dioxide in an organic solvent such as acetone or methylene chloride at a temperature between 0° C and the boiling point of the mixture to give the desired 5 - [(R₁—R₅) - phenyl] - 3 - methyl - penta - 2,4 - dien - 1 - al of formula IIh.

The compounds of formula III are also, in part, novel.

Compounds of formula III in which *n* stands for zero, R' is for instance COOH, and B represents a triarylphosphonium group [IIIa] or a dialkoxyphosphinyl group [IIIc] can be readily prepared, for example, by reacting an etherified 3-halomethyl-crotyl alcohol or an optionally esterified 3-halomethyl-crotonic acid with a triaryl phosphine in a solvent, preferably with triphenyl phosphine in toluene or benzene, or with a trialkyl phosphite, especially with triethyl phosphite, this reaction being supplemented as necessary by treatment giving the desired R'.

Compounds of formula III in which *n* stands for 1, R' is for instance COOH, and B represents a triarylphosphonium group [IIIb] or a dialkoxyphosphinyl group [IIId] can be prepared, for example, by reducing the formyl

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group of an aldehyde of formula III in which n stands for 1, R' is for instance COOH , and B is an oxo group [IIh] to the hydroxymethyl group using a metal hydride such as sodium borohydride in an alkanol (e.g. ethanol or isopropanol). The resulting alcohol can be halogenated using a conventional halogenating agent (e.g. phosphorus oxychloride) and the resulting halide, e.g. 8-halo-3,7-dimethyl-octa-2,4,6-triene-1-carboxylic acid (a compound of formula III in which n stands for 1, R' is for instance COOH , and B is halogen [IIIk]), or a derivative thereof, can be reacted either with a triaryl phosphine in a solvent, preferably with triphenyl phosphine in toluene or benzene, to give a desired phosphonium salt of formula IIIb or with a trialkyl phosphite, especially with triethyl phosphite, to give a desired phosphonate of formula IIId.

Compounds of formula III in which n stands for zero, R' is for instance CHO and B represents a sulphone group [IIIe] can be prepared, for example, by reacting 4-hydroxy-3-methyl-but-2-en-1-al or the corresponding acetate or bromide of this alcohol in a polar solvent (e.g. isopropanol or n-butanol) in the manner previously described with one of the sulphinic acids defined hereinbefore or with an alkali metal salt thereof, this reaction being supplemented as necessary by treatment giving the desired R' .

Compounds of formula III in which n stands for 1, R' is for instance COOH , and B represents a sulphone group [IIIf] can be prepared in a manner analogous to that described earlier by the reaction of, for example, 8-hydroxy-3,7-dimethyl-octa-2,4,6-trien-1-oic acid or the corresponding acetate or bromide of this alcohol with a sulphinic acid as hereinbefore defined or with an alkali metal salt thereof.

Compounds of formula III in which n stands for zero, R' is for instance COOH , and B represents an oxo group [IIig] can be prepared, for example, by oxidatively cleaving an optionally esterified tartaric acid; for example, using lead tetraacetate at room temperature in an organic solvent such as benzene. The glyoxylic acid derivative resulting from the medial cleavage of the tartaric acid structure is subsequently condensed in a manner known per se, conveniently in the presence of an amine, with propionaldehyde at an elevated temperature (e.g. at a temperature between 60°C and 110°C) with water cleavage to give the desired 3-formyl-crotonic acid derivative.

Compounds of formula III in which n stands for 1, R' is for instance COOH , and B represents an oxo group [IIih] can be prepared, for example, by reacting 4,4-dimethoxy-3-methyl-but-1-en-3-ol with phosgene in the cold, preferably at -10°C to -20°C , in the presence of a tertiary amine such as pyridine and condensing the resulting

2-formyl-4-chloro-but-2-ene under the conditions of a Wittig reaction with an esterified or etherified 3-formyl-crotyl alcohol or with an optionally esterified 3-formyl-crotonic acid to give the desired aldehyde of formula IIIh.

According to the process provided by the present invention, the following reactions are effected:

phosphonium salts of formula IIa or IIb are reacted with aldehydes of formula IIIh or IIIg,

or

phosphonium salts of formula IIIa or IIIb are reacted with aldehydes of formula IIIh or IIg,

or

phosphonates of formula IIc or IId are reacted with aldehydes of formula IIIh or IIIg,

or

phosphonates of formula IIIc or IIId are reacted with aldehydes of formula IIIh or IIg,

or

sulphones of formula IIe or IIf are reacted with halides of formula IIIk or IIIi, the latter being a formula III in which n stands for zero and B represents a halogen atom,

or

sulphones of formula IIIe or IIIf are reacted with halides of formula IIk or IIi, the latter being a formula II in which n stands for zero and A represents a halogen atom.

According to the Wittig procedure, the reaction components are reacted with one another in the presence of an acid binding agent, for example, in the presence of an alkali metal alcoholate such as sodium methylate or in the presence of an epoxide, which may be an optionally lower-alkyl-substituted ethylene oxide, e.g. 1,2-butylene oxide, if desired in a solvent (e.g. in a chlorinated hydrocarbon such as methylene chloride or in dimethylformamide) at a temperature between room temperature and the boiling point of the reaction mixture.

According to the Horner procedure, the reaction components are reacted with one another with the aid of a base and preferably in the presence of an inert organic solvent; for example, with the aid of sodium hydride in benzene, toluene, dimethylformamide, tetrahydrofuran, dioxan or 1,2-dimethoxyethane or with the aid of an alkali metal alcoholate in an alkanol (e.g. sodium methylate in methanol) at a temperature between 0°C and boiling point of the reaction mixture.

According to the Julia procedure, the reaction components are reacted with one another with the aid of a condensation agent, conveniently in the presence of a polar solvent. Suitable solvents are, for example, dimethylformamide, dimethyl sulphoxide, dimethylacetamide, tetrahydrofuran and hexamethyl-

phosphonic acid triamide as well as alkanols such as methanol, isopropanol or tertbutanol. Examples of strong bases which are preferably used as the condensation agent are alkali metal carbonates (especially sodium carbonate), alkaline earth metal carbonates, alkali metal hydroxides (e.g. sodium hydroxide or potassium hydroxide), alkali metal alcoholates (e.g. sodium methylate and, especially, potassium tertbutylate), alkaline earth metal alcoholates, alkali metal hydrides (e.g. sodium hydride), alkyl-magnesium halides (e.g. methyl-magnesium bromide) and alkali metal amides (e.g. sodium amide). The reaction is expediently carried out at a low temperature, especially at a temperature below the freezing point (e.g. between -50°C and -80°C).

It has been shown to be convenient in certain cases to carry out the reactions described hereinbefore *in situ*, i.e. without isolating the phosphonium salt, phosphonate or sulphone from the medium in which it is prepared.

A carboxylic acid of formula I can be converted in a manner known *per se* (e.g. by treatment with thionyl chloride, preferably in pyridine) into an acid chloride which can be converted by treatment with ammonia into an amide and by reaction with an alkanol into an ester.

A carboxylic acid ester of formula I can be hydrolysed in a manner known *per se* (e.g. by treatment with an alkali, especially aqueous-alkalcoholic sodium hydroxide or potassium hydroxide) at a temperature between room temperature and the boiling point of the mixture and then amidated either via an acid halide or as described hereinafter.

A carboxylic acid ester of formula I can be converted directly into a corresponding amide, for example, by treatment with lithium amide. The lithium amide is advantageously treated with the ester at room temperature.

A carboxylic acid or a carboxylic acid ester of formula I can be reduced in a manner known *per se* to give a corresponding alcohol of formula I. The reduction is advantageously carried out using a metal hydride or alkyl metal hydride in an inert solvent. The preferred hydrides are the mixed metal hydrides such as lithium-aluminium hydride or bis-[methoxy-ethylenoxy]-sodium aluminium hydride. Suitable solvents are, *inter alia*, ether, tetrahydrofuran or dioxan when lithium aluminium hydride is used and ether, hexane, benzene or toluene when diisobutyl aluminium hydride or bis[methoxy-ethylenoxy]-sodium aluminium hydride is used.

An alcohol of formula I can be etherified with an alkyl halide (e.g. ethyl iodide), for example, in the presence of a base, preferably sodium hydride, in an organic solvent such as dioxan, tetrahydrofuran, 1,2-dimethoxyethane, dimethylformamide or in the presence of an alkali metal alcoholate in an alkanol at a temperature between 0°C and room temperature.

An alcohol of formula I can also be esterified by treatment with an alkanoyl halide or anhydride, expediently in the presence of a base (e.g. pyridine or triethylamine) at a temperature between room temperature and the boiling point of the mixture.

An alcohol ester can be saponified in a manner known *per se*; for example, in the manner previously described in connection with the hydrolysis of a carboxylic acid ester.

An alcohol of formula I or an ester thereof can be oxidised in a manner known *per se* to give a corresponding acid of formula I. The oxidation is advantageously carried out with silver (I) oxide and alkali in water or in an organic water-miscible solvent at a temperature between room temperature and the boiling point of the mixture.

An amine of formula I forms addition salts with inorganic and organic acids. Examples of such salts are those formed with hydrohalic acids (especially with hydrochloric or hydrobromic acid), with other mineral acids (e.g. with sulphuric acid) and with organic acids (e.g. with benzoic acid, acetic acid, citric acid or lactic acid).

A carboxylic acid of formula I forms salts with bases, especially with alkali metal hydroxides and especially with sodium hydroxide or potassium hydroxide.

The compounds of formula I can occur as *cis/trans* mixtures which, if desired, can be separated into the *cis* and *trans* components or isomerised to the all-*trans* compounds in a manner known *per se*.

As specific examples of the reactions which may be made to take place in the process provided by the present invention, we may mention those reactions in which:—

(a) a 4-methoxy-2,3,6-trimethyl-benzyl-triphenylphosphonium halide is reacted with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid or with the ethyl ester thereof;

(b) a 5-(4-methoxy-2,3,6-trimethyl-phenyl)-3-methyl-penta-2,4-diene-1-triphenylphosphonium halide is reacted with 3-formyl-crotonic acid or with the ethyl ester thereof;

(c) 4-methoxy-2,3,6-trimethyl-benzaldehyde is reacted with a 1-(carboxy or ethoxycarbonyl)-2,6-dimethyl-hepta-1,3,5-trien-7-triphenylphosphonium halide;

(d) 5-(4-methoxy-2,3,6-trimethyl-phenyl)-3-methyl-penta-2,4-dien-1-al is reacted with a 3-methyl-crotonic acid 4-triphenylphosphonium halide or with the ethyl ester thereof;

(e) 4-methoxy-2,3,6-trimethyl-benzyl-diethylphosphonate is reacted with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid or with the ethyl ester thereof;

(f) 5-(4-methoxy-2,3,6-trimethyl-phenyl)-3-methyl-penta-2,4-dien-1-diethylphosphonate is reacted with 3-formyl-

crotonic acid or with the ethyl ester thereof;
(g) 4 - methoxy - 2,3,6 - trimethyl - benzaldehyde is reacted with 1-(carboxy or ethoxycarbonyl) - 2,6 - dimethyl - hepta - 1,3,5-trien-7-diethylphosphonate;

5 (h) 5 - (4 - methoxy - 2,3,6 - trimethylphenyl) - 3 - methyl - penta - 2,4 - dien - 1 - al is reacted with 3-methyl-crotonic acid 4-diethyl-phosphonate or with the ethyl ester thereof;

10 (i) 1 - (phenylsulphonyl)methyl - 4-methoxy - 2,3,6 - trimethyl - benzene is reacted with 8-bromo-3,7-dimethyl-octa-2,4,6-trien-1-oic acid or with the ethyl ester thereof;

15 (j) 1 - phenylsulphonyl - 5 - (4 - methoxy-2,3,6 - trimethyl - phenyl) - 3 - methyl-penta-2,4-diene is reacted with 4-bromo-3-methyl-crotonic acid;

20 (k) 4 - methoxy - 2,3,6 - trimethyl - benzyl chloride is reacted with 1-(carboxy or ethoxycarbonyl) - 7 - phenylsulphonyl - 2,6 - dimethyl-hepta-1,3,5-triene; or

25 (l) 1 - bromo - 5 - (4 - methoxy - 2,3,6-trimethyl - phenyl) - 3 - methyl - penta - 2,4-diene is reacted with 4-phenylsulphonyl-3-methyl-crotonic acid or with the ethyl ester thereof.

The polyene derivatives provided by this invention are pharmacodynamically valuable. They can be used for the topical and systemic therapy of benign and malignant neoplasms and of premalignant lesions as well as for the systemic and topical prophylaxis of the said conditions. They are also suitable for the topical and systemic therapy of acne, psoriasis and other dermatoses associated with an intensified or pathologically altered cornification, as well as inflammatory and allergic dermatological conditions. They can moreover be used for the control of disorders of the mucous membranes associated with inflammatory or degenerative or metaplastic alterations.

The toxicity of the compounds of formula I is slight. For example, as will be evident from the following Table, the acute toxicity [LD₅₀] of 9 - (4 - methoxy - 2,3,6 - trimethyl - phenyl) - 3,7 - dimethyl - nona-2,4,6,8-tetraen-1-oic acid [A] and of 9-(4-methoxy - 2,3,6 - trimethyl - phenyl) - 3,7-dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid ethyl ester [B] in the mouse after intraperitoneal administration in rape-oil lies at 700 or 1000 mg/kg.

TABLE

Acute toxicity

Substance A	LD ₁₀ mg/kg	LD ₅₀ mg/kg	LD ₉₀ mg/kg
after 1 day	>4000	>4000	>4000
after 10 days	580	700	890
after 20 days	580	700	890
Substance B	LD ₁₀ mg/kg	LD ₅₀ mg/kg	LD ₉₀ mg/kg
after 1 day	>4000	>4000	>4000
after 10 days	1400	1900	2600
after 20 days	710	1000	1400

55 The tumour-inhibiting activity of the present polyene derivatives is significant. In the papilloma test, tumours induced with dimethylbenzanthracene and croton oil regress. The diameters of the papillomae decline within 2 weeks on intraperitoneal administration. In the case of substance A, the decline is by 38% at 50 mg/kg/week and by 69% at 100 mg/kg/week and in the case of substance B the decline is by 45% at 25 mg/kg/week and by 63% at 50 mg/kg/week.

65 The polyene derivatives provided by this invention can accordingly be used as medicaments; for example, in the form of pharmaceutical preparations which contain them in

association with a compatible pharmaceutical carrier.

The pharmaceutical preparations suitable for systemic administration can be prepared, for example, by adding a compound of formula I as the active ingredient to non-toxic, inert, solid or liquid carriers which are conventional in such preparations.

The pharmaceutical preparations can be administered enterally or parenterally. For enteral administrations, the pharmaceutical preparations suitably take the form of, for example, tablets, capsules, dragées, syrups, suspensions, solutions and suppositories. For parenteral administration, the pharmaceutical

preparations suitably take the form of infusion or injection solutions.

The dosages in which the present polyene derivatives are administered can vary according to the particular pharmaceutical dosage form and mode of administration as well as according to the requirements of the patient.

The polyene derivatives can be administered in amounts of 5 mg to 200 mg daily in one or more dosages. A preferred form of administration comprises capsules containing ca 10 mg to ca 100 mg of active ingredient.

The pharmaceutical preparations can contain inert and also pharmacodynamically active additives. Tablets or granulates, for example, can contain binding agents, filling agents, carrier materials or diluents. Liquid preparations take the form of, for example, sterile solutions which are miscible with water. Capsules can contain, in addition to the active ingredient, a filling material or thickening agent. Furthermore, flavour-improving additives, materials normally used as preservatives, stabilisers, moisture-retainers or emulsifiers and salts for varying the osmotic pressure, buffers and other additives may also be present.

The aforementioned carrier substances and diluents can be organic or inorganic in nature; for example, water, gelatin, lactose, starch, magnesium stearate, talc, gum arabic, polyalkyleneglycols and the like. A prerequisite is that all adjuvants used in the preparation of the pharmaceutical preparations are non-toxic.

For topical administration, the pharmaceutical preparations are expediently provided in the form of ointments, tinctures, creams, solutions, lotions, sprays, suspensions and the like. Ointments, creams and solutions are preferred. These pharmaceutical preparations for topical administration can be prepared by mixing the polyene derivatives with non-toxic, inert, solid or liquid carriers which are suitable for topical administration and which are common per se in such preparations.

For topical administration, there are expediently used ca 0.01 to ca 0.3%, preferably 0.02 to 0.1% solutions and ca 0.05 to ca 5%, preferably ca 0.1 to ca 2.0% ointments or creams.

The pharmaceutical preparations may contain an anti-oxidant (e.g. tocopherol, N-methyl- γ -tocopheramine, butylated hydroxyanisole or butylated hydroxytoluene).

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

Example 1.

228 g of 5-(4-methoxy-2,3,6-trimethylphenyl)-3-methyl-penta-2,4-diene-1-triphenylphosphonium bromide are introduced under nitrogen gassing into 910 ml of dimethylformamide and treated with cooling at 5°—10° C within 20 minutes with 17.5 g of a suspension of sodium hydride (ca 50%) in mineral oil. The mixture is stirred for 1 hour

at about 10° C, treated dropwise at 5°—8° C with 61.8 g of 3-formylcrotonic acid butyl ester, heated for 2 hours at 65° C and subsequently introduced into 8 litres of ice-water. After the addition of 300 g of sodium chloride, the mixture is thoroughly extracted with a total of 18 litres of hexane. The extract is washed five times with 1 litre of methanol/water (6:4) each time and twice with 1.5 litres of water each time, dried over sodium sulphate and evaporated under reduced pressure. There is obtained 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester of melting point 80°—81° C, which can be converted into the free acid as follows:

125.8 g of 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester are introduced into 2000 ml of absolute ethanol and treated with a solution of 125.8 g of potassium hydroxide in 195 ml of water. The mixture is heated to boiling under nitrogen gassing for 30 minutes, cooled, introduced into 10 litres of ice/water and, after the addition of ca 240 ml of concentrated hydrochloric acid (pH 2—4), thoroughly extracted with a total of 9 litres of methylene chloride. The extract is washed to neutrality with about 6 litres of water, dried over calcium chloride and evaporated under reduced pressure. The residue is taken up in 700 ml of hexane. The 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid that separates has a melting point of 228°—230° C.

The 5-(4-methoxy-2,3,6-trimethylphenyl)-3-methyl-penta-2,4-diene-1-triphenylphosphonium bromide employed as the starting compound can be prepared, for example, as follows:

500 g of 2,3,5-trimethylphenol are introduced into 1840 ml of ethanol and 184 ml of water and treated under gentle stirring with 240 g of potassium hydroxide. To the resulting, clear solution, 626 g of methyl iodide are added dropwise at 0°—5° C within 30—45 minutes. The mixture is stirred for 2 hours at room temperature, subsequently stirred under reflux conditions for 12 hours at 60° C, then treated with 5 litres of water and thoroughly extracted with a total of 6 litres of ether. The extract is washed first with 3 litres of 3-N sodium hydroxide, then washed twice with 1 litre of water each time, dried over sodium sulphate and evaporated under reduced pressure. There is obtained 2,3,5-trimethylanisole which boils at 88°—90° C/10 Torr after rectification.

184 g of phosphorus oxychloride are added dropwise during 20—30 minutes to 87.1 g of dimethylformamide with stirring at 10°—20° C. The temperature should rise to 25° C towards the end of the addition. Into the obtained mixture, 150 g of 2,3,5-trimethyl-

anisole are introduced during 20 minutes with cooling at 10°—20° C. The mixture is slowly heated to a maximum 115° C, stirred for 6 hours at 100° C in order to complete the reaction and then poured after cooling into 2 kg of ice/water (1:1). After the addition of 1500 ml of benzene, the mixture is treated with 500 g of sodium acetate. The aqueous phase that forms is separated after stirring for 1 hour and again extracted with 1000 ml of benzene. The combined benzene extracts are washed successively with 480 ml of 1.5-N hydrochloric acid and 500 ml of water, dried over sodium sulphate and filtered over 20 g of decoloring carbon. The filtrate is evaporated under reduced pressure. There is obtained 2,3,6-trimethyl-*p*-anisaldehyde which melts at 65°—66° C after recrystallisation from hexane.

260 g of 2,3,6-trimethyl-*p*-anisaldehyde are introduced into a mixture of 3500 ml of acetone and 1400 ml of water and treated during ca 30 minutes with 730 ml of sodium hydroxide (10% by weight) with stirring at 0°—5° C. The mixture is stirred for 3 days at room temperature and after lowering the pH value to 4—5 by the addition of acetic acid, subsequently concentrated under reduced pressure. The concentrate is extracted with a total of 3000 ml of ether. The ether extract is washed successively with 700 ml of an aqueous 5% sodium bicarbonate solution and 700 ml of water, dried over sodium sulphate and evaporated under reduced pressure. There is obtained oily 4-(4-methoxy-2,3,6-trimethylphenyl)-but-3-en-2-one which boils at 120°—127° C/0.05 Torr after rectification.

36.45 g of magnesium are superficially corroded with a small amount of iodine, introduced into 1000 ml of tetrahydrofuran and treated dropwise under nitrogen during 45 minutes with 162.5 g of ethyl bromide. In so doing, the temperature should come initially to 8°—10° C. It can rise to 25° C towards the end of the introduction. The mixture is stirred, optionally with a further addition of 5—10 ml of alkyl bromide, until the magnesium has gone completely into solution. The Grignard solution obtained is subsequently added dropwise at 0° C to a saturated acetylene/tetrahydrofuran solution which has been prepared from 650 ml of tetrahydrofuran by gassing for 3 hours with acetylene at -10° C to -5° C. The reagent is stirred for 1 hour at 0° C and then treated dropwise during 30—45 minutes with acetylene gassing at 0° C, with a solution of 218 g of 4-(4-methoxy-2,3,6-trimethylphenyl)-but-3-en-2-one in 250 ml of tetrahydrofuran. The mixture is stirred for 24 hours at 0° C and subsequently for 12 hours at room temperature, then introduced into 4.5 kg of ice/water (3.5:1), adjusted to a pH of ca 4 by the addition of 700 ml of 3-N hydrochloric acid and thoroughly extracted with a total of

3 litres of ether. The ether extract is washed to neutrality with a total of 2 litres of water, dried over sodium sulphate and filtered over 20 g of decoloring carbon. The filtrate is evaporated under reduced pressure. There is obtained 5-(4-methoxy-2,3,6-trimethylphenyl)-3-methyl-3-hydroxy-penta-4-en-1-yne, which melts at 58°—60° C after rectification at 125°—135° C/0.04 Torr.

244 g of 5-(4-methoxy-2,3,6-trimethylphenyl)-3-methyl-3-hydroxy-penta-4-en-1-yne are dissolved in 400 ml of hexane and, after the addition of 45 g of a partially poisoned palladium catalyst, hydrogenated at room temperature and atmospheric pressure. The hydrogenation is stopped after about 40—60 minutes after the uptake of the amount of hydrogen necessary for the saturation of the acetylene to ethylene bond (25 litres). The hydrogenation solution is filtered. The filtrate is washed with 300 ml of ethyl acetate and evaporated under reduced pressure. There is obtained 5-(4-methoxy-2,3,6-trimethylphenyl)-3-methyl-3-hydroxy-penta-1,4-diene which melts at 46°—47° C.

246 g of 5-(4-methoxy-2,3,6-trimethylphenyl)-3-methyl-3-hydroxy-penta-1,4-diene are dissolved in 2400 ml of benzene. The solution is treated with 343 g of triphenylphosphonium hydrobromide, stirred for 24 hours at 60° C, then cooled and the benzene separated. The sediment is digested four times with 500 ml of benzene each time and, after separation of the benzene washings, dissolved in 700 ml of methylene chloride. The solution is evaporated under reduced pressure. There is obtained 5-(4-methoxy-2,3,6-trimethylphenyl)-3-methyl-penta-2,4-diene-1-triphenylphosphonium bromide which is dried in vacuo before processing further.

The 3-formylcrotonic acid butyl ester used as the reaction component can be prepared, for example, as follows:

1775 g of lead tetraacetate (90%) are gradually introduced within 30 minutes at 25°—30° C into a solution of 1000 g of L(+)-tartaric acid dibutyl ester in 3850 ml of benzene. The mixture is subsequently stirred for 1 hour at room temperature. The sediment is filtered off and extracted with 500 ml of benzene. The benzene extract is evaporated under reduced pressure. There is obtained glyoxylic acid butyl ester which boils at 50°—65° C/12 Torr after rectification.

836 g of the glyoxylic acid butyl ester obtained are introduced into 376 g of propionaldehyde. The mixture is treated dropwise at 60° C with 40.8 g of *n*-dibutylamine. In so doing, the temperature should not rise above 106° C. The mixture is then stirred for 2 hours at 106°—111° C, cooled and taken up in ether. The ether extract is washed successively with 500 ml of 1-N sulphuric acid, 700 ml of water, 1000 ml of a 5% aqueous sodium bicarbonate solution and subsequently with

1000 ml of water, dried over sodium sulphate and evaporated under reduced pressure. There is obtained 3-formyl-crotonic acid butyl ester which boils at 93°—105° C/14 Torr after rectification.

Example 2.

In a manner analogous to that described in Example 1 9 - (4 - allyloxy - 2,3,6 - trimethyl - phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid ethyl ester is manufactured from 5 - (4 - allyloxy - 2,3,6-trimethyl - phenyl) - 3 - methyl - penta - 2,4-diene-1-triphenylphosphonium bromide by reaction with 3-formyl-crotonic acid ethyl ester. From this product there is manufactured 9 - (4 - allyloxy - 2,3,6 - trimethyl - phenyl) - 3,7 - dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid of melting point 198°—200° C.

The 5 - (4 - allyloxy - 2,3,6 - trimethyl-phenyl) - 3 - methyl - penta - 2,4 - diene-1-triphenylphosphonium bromide employed as the starting material can be prepared in a manner analogous to that described in Example 1 by alkylation of 2,3,5-trimethyl-phenol with allyl bromide to give 2,3,5-trimethyl-phenyl allyl ether (boiling point 76°/80° C/0.05 Torr), by formylation of the ether obtained to give 4-allyloxy-2,3,6-trimethyl-benzaldehyde (boiling point 90°—102° C/0.15 Torr), by condensation of the aldehyde obtained with acetone to give 4-(4-allyloxy - 2,3,6 - trimethyl - phenyl) - but-3-en-2-one (boiling point 135°—138° C/0.05 Torr), by reaction of the ketone obtained with acetylene to give 5-(4-allyloxy-2,3,6-trimethyl - phenyl) - 3 - methyl - 3 - hydroxy-penta-4-en-1-yne, by partial hydrogenation of the tertiary acetylene carbinol obtained to give 5 - (4 - allyloxy - 2,3,6 - trimethyl - phenyl) - 3 - methyl - 3 - hydroxy - penta - 1,4 - diene and by reaction of the tertiary ethylene carbinol obtained with triphenylphosphine hydrobromide. There is obtained 5-(4-allyloxy-2,3,6 - trimethyl - phenyl) - 3 - methyl - penta - 2,4 - diene - triphenylphosphonium bromide which melts at 114°—116° C.

Example 3.

28.5 g of 5-(4-methoxy-2,3,6-trimethyl-phenyl) - 3 - methyl - penta - 2,4 - diene-1-triphenylphosphonium bromide are introduced under nitrogen gassing into 240 ml of isopropyl alcohol. After the addition of 0.12 g of butylated hydroxytoluene, the mixture is cooled to -35° C and treated at this temperature under strong stirring during 5 minutes with 7.50 g of 3-formyl-crotyl acetate. The mixture is subsequently mixed with 7.2 g of potassium hydroxide solution (50% by weight) while maintaining the temperature below -25° C and, after stirring for 1 hour at -30° C, introduced into a mixture of 110 g of water, 90 g of ice and 90 ml of hexane. The hexane layer is separated. The aqueous

phase is shaken out five times with 90 ml of hexane each time. The combined hexane extracts are shaken out five times with 180 ml of methanol/water (80:20) each time. The hexane phase is washed with water, dried over sodium sulphate and evaporated under reduced pressure. There is obtained 1-acetoxy-9-(4-methoxy - 2,3,6 - trimethyl - phenyl) - 3,7-dimethyl - nona - 2,4,6,8 - tetraene as an oil which can be purified by adsorption on silica gel using hexane/ether (80:20) as the eluent.

Example 4.

59 g of 2,3,6-trimethyl-benzyl-triphenylphosphonium bromide and 28 g of 7-formyl-3 - methyl - octa - 2,4,6 - trien - 1 - oic acid butyl ester are introduced into 280 ml of absolute ethanol. The mixture is treated dropwise between 0° C and 10° C with a solution of 2.72 g of sodium in 160 ml of absolute ethanol, subsequently stirred for 48 hours at room temperature, then introduced into 800 ml of water and thoroughly extracted with a total of 3000 ml of hexane. The hexane extract is shaken out three times with 1000 ml of methanol/water (60:40) each time, then dried over sodium sulphate and evaporated under reduced pressure. There is obtained 9 - (2,3,6 - trimethyl - phenyl) - 3,7 - dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid butyl ester as an oil which can be converted into the free acid as follows:

10 g of 9-(2,3,6-trimethyl-phenyl)-3,7-dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid butyl ester are introduced into 100 ml of absolute ethanol and, after the addition of a solution of 10 g of potassium hydroxide in 20 ml of water, heated to boiling under nitrogen gassing. The initially cloudy solution which becomes clear with boiling is cooled after 30 minutes and introduced into ice/water. After acidification with concentrated hydrochloric acid, the solution is thoroughly extracted with methylene chloride. The extract is washed to neutrality with water, dried over calcium chloride and evaporated under reduced pressure. There is obtained 9-(2,3,6-trimethyl - phenyl) - 3,7 - dimethyl - nona-2,4,6,8-tetraen-1-oic acid which melts at 191°—192° C after recrystallisation from ethyl acetate.

The 2,3,6-trimethyl-benzyl-triphenylphosphonium bromide employed as the starting material can be prepared, for example, as follows:

300 g of pseudocumol are treated dropwise with 700 ml of concentrated sulphuric acid. In so doing, the temperature can rise to 40° C. The mixture is subsequently cooled to 20° C and, after the addition of 450 g of bromine, stirred for 1 hour at room temperature. Thereafter, 700 ml of water are added dropwise. In so doing, the temperature rises to 50° C. The precipitated mixture of solid materials is

filtered off and dissolved in 3000 ml of hot water. The insoluble 3,5,6-tribromo-1,2,4-trimethylbenzene is separated and rejected. The aqueous solution is slowly introduced into 1000 ml of sulphuric acid (80% by weight) which is being heated at 180° C and blown through with steam. The 1-bromo-2,3,6-trimethylbenzene coming over with the steam boils at 86° C/6 Torr.

250 g of 1-bromo-2,3,6-trimethylbenzene are dissolved in 400 ml of ether. The solution is added dropwise at 20°—30° C with slight cooling into a suspension of 66.5 g of magnesium (activated with iodine) and 200 ml of ether. The mixture is treated dropwise at 20°—30° C with a solution of 135 g of ethyl bromide in 250 ml of ether and subsequently heated to boiling under reflux conditions for 3—4 hours. As soon as the magnesium has gone into solution, 385 g of orthoformic acid ethyl ester dissolved in 250 ml of absolute ether are introduced. The mixture is heated to boiling for 5 hours. After evaporation of the ether, the mixture is poured onto ice, treated with 1000 ml of 5-N hydrochloric acid and heated to boiling for 30 minutes under carbon dioxide gassing. The distillate obtained by water distillation is extracted with methylene chloride. The methylene chloride phase is evaporated under reduced pressure. There is obtained 2,3,6-trimethylbenzaldehyde which boils at 70°—72° C/1.2 Torr.

129.6 g of 2,3,6-trimethylbenzaldehyde are dissolved in 300 ml of methanol and, after the addition of 70 ml of water, cooled to 0° C. The mixture is treated portionwise with 18.25 g of sodium borohydride, stirred for 1 hour, subsequently poured onto ice and thoroughly extracted with ether. The ether extract is dried over sodium sulphate and evaporated under reduced pressure. There is obtained 2,3,6-trimethylbenzyl alcohol.

75 g of 2,3,6-trimethylbenzyl alcohol are dissolved in 175 ml of low-boiling petroleum ether. The solution is treated dropwise at -10° C during 2 hours with a solution of 51 g of phosphorus tribromide in 60 ml of low-boiling petroleum ether. The mixture is stirred for 12 hours at room temperature, then poured onto ice and extracted with ether. The ether extract is washed first with an ice-cold, saturated, aqueous sodium bicarbonate solution, then with a saturated common salt solution, dried over sodium sulphate and evaporated under reduced pressure. There is obtained 2,3,6-trimethylbenzyl bromide which boils at 75°—80° C/0.05 Torr after rectification.

73.3 g of 2,3,6-trimethylbenzyl bromide are dissolved in 170 ml of benzene. The solution is treated with 90.0 g of triphenylphosphine. In so doing, the temperature rises to 40° C. The mixture is stirred for 12 hours at room temperature. The precipitated 2,3,6-trimethylbenzyl-triphenylphosphonium brom-

ide melts at 240°—242° C after washing with low-boiling petroleum ether and drying.

The 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester employed as the reaction component can be prepared, for example, as follows:

After the addition of a small amount of iron (III) nitrate, 2700 ml of liquid ammonia are treated portionwise under stirring and cooling with 169.5 g of potassium. As soon as the initially blue coloration has disappeared (i.e. after about 30—45 minutes) acetylene gas is led in at a rate of 3 litres/minute until the dark coloration of the mixture becomes lighter. Then, the gas stream is reduced to 2 litres/minute and the mixture treated dropwise with a solution of 500 g of methylglyoxal-dimethyl-acetal in 425 ml of absolute ether. The gassing with acetylene is continued for 1 hour with stirring. The mixture is subsequently treated portionwise with 425 g of ammonium chloride, gradually warmed to 30° C during 12 hours under evaporation of ammonia and then extracted with 1600 ml of ether. The ether extract is dried over sodium sulphate and evaporated under reduced pressure. There is obtained 4,4-dimethoxy-3-methyl-but-1-en-3-ol which boils at 33° C/0.03 Torr after rectification; $n_D^{25} = 1.4480$.

198 g of 4,4-dimethoxy-3-methyl-but-1-en-3-ol are dissolved in 960 ml of high-boiling petroleum ether and, after the addition of 19.3 g of 5% palladium catalyst and 19.3 g of quinoline, hydrogenated under normal conditions. After the uptake of 33.5 litres of hydrogen, the hydrogenation is stopped. The catalyst is filtered off. The filtrate is evaporated under reduced pressure. There is obtained 4,4-dimethoxy-3-methyl-but-1-en-3-ol which boils at 70°—72° C/18 Torr after rectification.

195 ml of phosgene are led into 1570 ml of carbon tetrachloride at -10° C. After the addition of 213 g of pyridine, the solution is treated dropwise at -10° C to -20° C with 327 g of 4,4-dimethoxy-3-methyl-but-1-en-3-ol. The mixture is slowly warmed to 25° C under stirring, stirred for a further 3 hours at room temperature, cooled to 15° C and treated with 895 ml of water. The aqueous phase is separated and rejected. After standing for 12 hours in the cold, the organic phase is treated with 448 ml of 5% sulphuric acid, stirred for 5 hours, washed with water, dried over sodium sulphate and evaporated under reduced pressure. There is obtained 2-formyl-4-chloro-but-2-ene which boils at 37°—40° C/1.8 Torr after rectification; $n_D^{25} = 1.4895$.

165.7 g of 2-formyl-4-chloro-but-2-ene are dissolved in 840 ml of benzene and treated with 367 g of triphenylphosphine. The mixture is heated to boiling under reflux conditions for 12 hours with nitrogen gassing and then cooled to 20° C. The precipitated 2-formyl-but-2-ene-4-triphenylphosphonium chloride melts at

250°—252° C after washing with benzene and drying.

212.6 g of 2-formyl-but-2-ene-4-triphenylphosphonium chloride and 95 g of 3-formylcrotonic acid butyl ester are introduced into 1100 ml of butanol and treated at 5° C with a solution of 57 g of triethylamine in 60 ml of butanol. The mixture is subsequently stirred for 6 hours at 25° C, then cooled, introduced into water and thoroughly extracted with hexane. The hexane phase is first washed repeatedly with methanol/water (6:4) and then with water, dried over sodium sulphate and filtered. The filtrate is isomerised for 12 hours by shaking with iodine. The iodine is removed by the addition of sodium thiosulphate. The filtrate is washed again with water, dried and evaporated under reduced pressure. There is obtained 7-formyl-3-methylocta-2,4,6-trien-1-oic acid butyl ester which boils at 102°—105° C/0.09 Torr after rectification.

Example 5.

In a manner analogous to that described in Example 4, 9-(2,4,6-triisopropyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester (oil) is manufactured from 2,4,6-triisopropyl-benzyl-triphenylphosphonium bromide by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester. From this product, there is manufactured 9-(2,4,6-triisopropyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid of melting point 221° C.

The 2,4,6-triisopropyl-benzyl-triphenylphosphonium chloride employed as the starting material can be prepared, for example, as follows:

136 g of 1,3,5-triisopropyl-benzene, 228 ml of acetic acid, 420 ml of concentrated hydrochloric acid and 55 g of formaldehyde (35%) are heated to 60° C. The mixture is stirred at this temperature firstly for 3 hours and then after a further addition of 21 g of formaldehyde (35%) for a further 12 hours. The mixture is cooled to room temperature and thoroughly extracted with benzene. The benzene extract is washed successively with water, a saturated aqueous sodium bicarbonate solution and again with water, dried over sodium sulphate and evaporated under reduced pressure. There is obtained 2,4,6-triisopropylbenzyl chloride which boils at 70° C/0.05 Torr after rectification.

69.6 g of 2,4,6-triisopropylbenzyl chloride are dissolved in 1000 ml of xylene. The solution is treated with 79.5 g of triphenylphosphine. The mixture is stirred for 18 hours at 125° C and then cooled. The 2,4,6-triisopropylbenzyl-triphenylphosphonium chloride that has already precipitated at 80° C melts at 237°—238° C after trituration and washing with benzene.

The 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester employed as the reaction component can be prepared as described in Example 4.

Example 6.

In a manner analogous to that described in Example 4, 9-(pentamethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester (oil) is manufactured from pentamethyl-benzyl-triphenylphosphonium chloride by reaction with 7-formyl-3-methylocta-2,4,6-trien-1-oic acid butyl ester. From this product, there is manufactured 9-(pentamethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid of melting point 228°—229° C.

The pentamethyl-benzyl-triphenylphosphonium chloride employed as the starting material can be prepared, for example, as follows:

184.5 g of pentamethylbenzene, 193 ml of glacial acetic acid, 355 ml of concentrated hydrochloric acid and 44 g of formaldehyde (35%) are heated to 65° C. The mixture is stirred at this temperature first for 3 hours and then, after a further addition of 18.1 g of formaldehyde (35%), for a further 3 hours. The mixture is cooled to room temperature and thoroughly extracted for 12 hours with benzene. The benzene extract is washed successively with water, dilute sodium hydroxide and water, dried over sodium sulphate and evaporated under reduced pressure. There is obtained pentamethylbenzyl chloride which melts at 80°—81° C after recrystallisation from hexane.

101.6 g of pentamethylbenzyl chloride, 149 g of triphenylphosphine and 250 ml of toluene are stirred for 5 hours at 100° C. The pentamethyl-benzyl-triphenylphosphonium chloride that precipitates with cooling melts at 258°—259° C after trituration and washing with low-boiling petroleum ether.

Example 7.

16 g of 3-chloro-2,4,6-trimethylbenzyl-triphenylphosphonium chloride and 10 g of 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester are heated to boiling with stirring after the addition of 40 g of 1,2-butylene oxide. The 1,2-butylene oxide is slowly distilled off. The mixture is stirred for 30 minutes at 80°—82° C, cooled and thoroughly extracted with hexane. The hexane extract is shaken out five times with 50 ml of methanol/water (70:30) each time, dried over sodium sulphate and evaporated under reduced pressure. There is obtained 9-(3-chloro-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester which can be converted into the free acid as follows:

5 g of 9-(3-chloro-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-

oic acid butyl ester are heated to boiling under nitrogen gassing in 50 ml of a 5% ethanolic potassium hydroxide solution. The solution which becomes clear with boiling is cooled after 30 minutes, introduced into water and made acidic by the addition of acetic acid. The precipitated 9-(3-chloro-2,4,6-trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid melts at 208°—209° C after recrystallisation from benzene.

The 3 - chloro - 2,4,6 - trimethyl - benzyl-triphenylphosphonium chloride employed as the starting material can be prepared, for example, as follows:

119 g of chloromesitylene, 11.9 g of paraformaldehyde and 5.95 g of anhydrous zinc chloride are heated to 60° C and gassed with hydrogen chloride with stirring firstly for 8 hours and then, after the addition of a further 11.9 g of paraformaldehyde, for a further 8 hours. The mixture is then poured onto ice and thoroughly extracted with ether. The ether extract is washed successively with water, a saturated aqueous sodium bicarbonate solution and again with water, dried over sodium sulphate and evaporated. There is obtained 3 - chloro - 2,4,6 - trimethyl - benzyl chloride which boils at 138° C/17 Torr after rectification.

71.25 g of 3-chloro-2,4,6-trimethyl-benzyl chloride, 92 g of triphenylphosphine and 375 ml of absolute toluene are heated at 100° C for 12 hours. The 3-chloro-2,4,6-trimethyl-benzyl-triphenylphosphonium chloride which precipitates with cooling melts at 233°—235° C.

Example 8.

In a manner analogous to that described in Example 7, 9 - (3 - nitro - 2,4,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid butyl ester (oil) is manufactured from 3-nitro-2,4,6-trimethyl-benzyl-triphenylphosphonium chloride by reaction with 7 - formyl - 3 - methyl - hepta - 2,4,6-trien-1-oic acid butyl ester. From this product, there is manufactured 9-(3-nitro-2,4,6-trimethyl - phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid of melting point 205°—206° C.

The 3 - nitro - 2,4,6 - trimethyl - benzyl-triphenylphosphonium chloride employed as the starting material can be prepared, for example, as follows:

10 g of nitromesitylene, 2 g of paraformaldehyde and 1 g of anhydrous zinc chloride are heated to 60° C and gassed with hydrogen chloride for 16 hours with stirring. The mixture is then poured onto ice and thoroughly extracted with ether. The ether extract is washed successively with water, a saturated, aqueous sodium bicarbonate solution and again with water, dried over sodium sulphate and evaporated. There is obtained 3-nitro-2,4,6-

trimethyl-benzyl chloride as an oil; $n_D^{22} = 1.5373$.

11.6 g of 3-nitro-2,4,6-trimethyl-benzyl chloride, 14 g of triphenylphosphine and 100 ml of absolute benzene are heated to boiling under reflux conditions for 24 hours. The 3 - nitro - 2,4,6 - trimethyl - benzyl - triphenylphosphonium chloride that precipitates with cooling melts at 252°—253° C.

Example 9.

In a manner analogous to that described in Example 7, 9 - (4 - methoxy - 2,3,5,6-tetramethyl - phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid butyl ester (oil) is manufactured from 4-methoxy-2,3,5,6-tetramethyl - benzyl - triphenylphosphonium chloride by reaction with 7-formyl-3-methylocta - 2,4,6 - trien - 1 - oic acid butyl ester. From this product, there is manufactured 9-(4 - methoxy - 2,3,5,6 - tetramethyl - phenyl) - 3,7 - dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid of melting point 230°—233° C.

The 4 - methoxy - 2,3,5,6 - tetramethyl-benzyl-triphenylphosphonium chloride employed as the starting material can be prepared, for example, as follows:

15 g of 2,3,5,6-tetramethylphenol are dissolved in 55.3 ml of methanol and, after the addition of 7.25 g of potassium hydroxide in 5.5 ml of water, treated dropwise at 0°—5° C with 18.8 g of methyl iodide. The mixture is stirred for 2 hours at room temperature, for 12 hours at 60° C, cooled, diluted with 150 ml of water and extracted with 100 ml of ether. The ether extract is washed successively with 3-N sodium hydroxide and water, dried over sodium sulphate and evaporated under reduced pressure. There is obtained 2,3,5,6-tetramethylanisole which melts at 53°—55° C after purification by adsorption on silica gel using methylene chloride as the eluent.

43 g of 2,3,5,6-tetramethylanisole in 110 ml of anhydrous acetic acid are introduced into 203 ml of 37% hydrochloric acid and treated dropwise with 21.6 g of 37% formaldehyde. The mixture is heated at 70° C for 3 hours with stirring and, after a further addition of 8.3 g of 37% formaldehyde, stirred for a further 3 hours at 70° C. The mixture is subsequently cooled to room temperature and extracted with 500 ml of benzene. The benzene extract is separated. The aqueous phase is shaken out with benzene. The combined benzene extracts are washed successively with water, a saturated, aqueous sodium carbonate solution and again with water, dried and evaporated under reduced pressure. There is obtained 4-methoxy-2,3,5,6-tetramethyl-benzyl chloride which melts at 104°—105° C after recrystallisation from ethyl acetate/hexane (1:3).

28 g of 4-methoxy-2,3,5,6-tetramethyl-benzyl chloride, 34.7 g of triphenylphosphine

and 153 ml of toluene are heated at 100° C for 12 hours. The 4-methoxy-2,3,5,6-tetramethyl-benzyl-triphenylphosphonium chloride that precipitates with cooling melts at 251°—252° C.

Example 10.

In a manner analogous to that described in Example 7, 9-(2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester is manufactured from 2,4,6-trimethyl-benzyl-triphenylphosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester. From this product, there is manufactured 9-(2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid of melting point 214°—215° C.

The 2,4,6-trimethyl-benzyl-triphenylphosphonium chloride employed as the starting material can be prepared in a manner analogous to that described in Example 7 by haloformylation of mesitylene to give 2,4,6-trimethyl-benzyl chloride (boiling point 112° C/12 Torr) and reaction of the latter compound with triphenylphosphine.

Example 11.

In a manner analogous to that described in Example 7, 9-(2,3,4,6-tetramethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester is manufactured from 2,3,4,6-tetramethyl-benzyl-triphenylphosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester. From this product, there is manufactured 9-(2,3,4,6-tetramethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid of melting point 201°—202° C.

The 2,3,4,6-tetramethyl-benzyl-triphenylphosphonium chloride employed as the starting material can be prepared in a manner analogous to that described in Example 7 by haloformylation of 1,2,3,5-tetramethyl-benzene to give 2,3,4,6-tetramethyl-benzyl chloride ($n_D^{20}=1.5571$) and reaction of the latter compound with triphenylphosphine.

Example 12.

In a manner analogous to that described in Example 7, 9-(4-methoxy-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester is manufactured from 4-methoxy-2,6-dimethyl-benzyl-triphenylphosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester. From this product, there is manufactured 9-(4-methoxy-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid of melting point 207°—208° C.

The 4-methoxy-2,6-dimethyl-benzyl-triphenylphosphonium chloride employed as the starting material can be prepared in a

manner analogous to that described in Example 7 by haloformylation of 3,5-dimethyl-anisole to give 4-methoxy-2,6-dimethyl-benzyl chloride ($n_D^{20}=1.5475$) and reaction of the latter compound with triphenylphosphine.

Example 13.

In a manner analogous to that described in Example 7, 9-(3-methoxy-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester is manufactured from 3-methoxy-2,4,6-trimethyl-benzyl-triphenylphosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester. From this product, there is manufactured 9-(3-methoxy-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid of melting point 196°—198° C.

The 3-methoxy-2,4,6-trimethyl-benzyl-triphenylphosphonium chloride employed as the starting material can be prepared in a manner analogous to that described in Example 7 by haloformylation of 2,4,6-trimethylanisole to give 3-methoxy-2,4,6-trimethyl-benzyl chloride ($n_D^{27}=1.5415$) and reaction of the latter compound with triphenylphosphine. The 3-methoxy-2,4,6-trimethyl-benzyl-triphenylphosphonium chloride melts at 308°—310° C.

Example 14.

In a manner analogous to that described in Example 7, 9-(4-methoxy-3-allyl-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester is manufactured from 4-methoxy-3-allyl-2,6-dimethyl-benzyl-triphenylphosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester. From this product, there is manufactured 9-(4-methoxy-3-allyl-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid of melting point 160°—161° C.

The 4-methoxy-3-allyl-2,6-dimethyl-benzyl-triphenylphosphonium chloride employed as the starting material can be prepared in a manner analogous to that described in Example 7 by haloformylation of 3,5-dimethyl-2-allyl-anisole to give 4-methoxy-3-allyl-2,6-dimethyl-benzyl chloride ($n_D^{20}=1.5690$) and reaction of the latter compound with triphenylphosphine.

Example 15.

In a manner analogous to that described in Example 7, 9-(4-methoxy-3-nitro-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester is manufactured from 4-methoxy-3-nitro-2,6-dimethyl-benzyl-triphenylphosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid ethyl ester. From this product, there is manufactured 9-(4-methoxy-3-nitro-2,6-dimethyl-phenyl)-3,7-dimethyl-

nona-2,4,6,8-tetraen-1-oic acid of melting point 109°—110° C.

The 4-methoxy-3-nitro-2,6-dimethylbenzyl-triphenylphosphonium chloride employed as the starting material can be prepared in a manner analogous to that described in Example 7 by haloformylation of 2-nitro-3,5-dimethyl-anisole to give 4-methoxy-3-nitro-2,6-dimethyl-benzyl chloride (melting point 109°—110° C) and reaction of the latter compound with triphenylphosphine. The 4-methoxy-3-nitro-2,6-dimethylbenzyl-triphenylphosphonium chloride melts at 230°—232° C.

Example 16.

In a manner analogous to that described in Example 7, 9-(4-ethoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester (melting point 96°—97° C) is manufactured from 4-ethoxy-2,3,6-trimethyl-benzyl-triphenylphosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid ethyl ester.

The 4-ethoxy-2,3,6-trimethyl-benzyl-triphenylphosphonium chloride employed as the starting material can be prepared by alkylation of 2,3,5-trimethylphenol to give 2,3,5-trimethyl-phenyl ethyl ether (melting point 93°—95° C), by haloformylation of the ether obtained to give 4-ethoxy-2,3,6-trimethyl-benzyl chloride (melting point 63°—64° C) and by reaction of the latter compound with triphenylphosphine.

Example 17.

In a manner analogous to that described in Example 7, 9-(4-isopropoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester is manufactured from 4-isopropoxy-2,3,6-trimethylbenzyl-triphenylphosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester. From this product, there is manufactured 9-(4-isopropoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid of melting point 176°—177° C.

The 4-isopropoxy-2,3,6-trimethylbenzyl-triphenylphosphonium chloride employed as the starting material can be prepared in a manner analogous to that described in Example 8 by alkylation of 2,3,5-trimethylphenol to give 2,3,5-trimethyl-phenyl isopropyl ether (boiling point 115° C/11 Torr), by haloformylation of the ether obtained to give 4-isopropoxy-2,3,6-trimethyl-benzyl chloride ($n_D^{20} = 1.5433$) and by reaction of the latter compound with triphenylphosphine.

Example 18.

In a manner analogous to that described in Example 7, 9-(3-dimethylamino-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-

2,4,6,8-tetraen-1-oic acid ethyl ester (bright-yellow oil) is manufactured from 3-dimethylamino-2,4,6-trimethyl-benzyl-triphenylphosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid ethyl ester.

The 3-dimethylamino-2,4,6-trimethylbenzyl-triphenylphosphonium chloride employed as the starting material can be prepared in a manner analogous to that described in Example 7 by haloformylation of N,N-dimethylmesidine to give 3-dimethyl-amino-2,4,6-trimethyl-benzyl chloride (boiling point 71° C/11 Torr) and reaction of the latter compound with triphenylphosphine.

Example 19.

1.7 g of 8-diethoxyphosphono-3,7-dimethylocta-2,4,6-trien-1-oic acid ethyl ester are introduced in 8.0 ml of tetrahydrofuran. The solution is cooled to 0° C after the addition of 0.27 g of sodium hydride (50—60%), then stirred for 30 minutes at 0° C and thereafter a solution of 0.96 g of 2,3,6-trimethyl-p-anisaldehyde in 3 ml of tetrahydrofuran is added dropwise during 15 minutes. The mixture is stirred for 7 hours at room temperature, then poured into ice and, after the addition of 2-N hydrochloric acid, extracted with ether. The ether extract is washed neutral with water, dried over sodium sulphate and evaporated under reduced pressure. The residual 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester melts at 104°—105° C.

Instead of the 0.27 g of sodium hydride used in the preceding paragraph there can also be used as the condensation agent an alkali metal alcoholate; for example, sodium ethylate (0.125 g of sodium in 5 ml of ethanol).

The 8-diethoxyphosphono-3,7-dimethylocta-2,4,6-trien-1-oic acid ethyl ester used as the starting material can be prepared, for example, as follows:

3.03 g of 8-bromo-3,7-dimethylocta-2,4,6-trien-1-oic acid ethyl ester are heated slowly to 125° C with 1.66 g of triethylphosphite. The surplus bromo ester is distilled off. The residue is cooled, poured into ice and extracted with ether and an aqueous solution of sodium hydrogen carbonate, dried and evaporated under reduced pressure. The residual 8-diethoxyphosphono-3,7-dimethylocta-2,4,6-trien-1-oic acid ethyl ester is immediately treated with 2,3,6-trimethyl-p-anisaldehyde as described earlier.

Example 20.

A) 2 g of 1-phenylsulphonylmethyl-4-methoxy-2,3,6-trimethyl-benzene are introduced into 10 ml of tetrahydrofuran. The solution is cooled to -78° C and, after the addition of 0.51 g of butyl lithium, treated with a solution of 1.8 g of 8-bromo-3,7-dimethylocta-2,4,6-trien-1-oic acid ethyl ester in 8 ml

of tetrahydrofuran. The mixture is stirred for 2 hours at -78°C , for 2 hours at -40°C and for 16 hours at 0°C to $+5^{\circ}\text{C}$. The mixture is poured into ice and, after the addition of 2-N hydrochloric acid, extracted with ether. The ether extract is washed neutral with water, dried over sodium sulphate and evaporated under reduced pressure. The residual 9-(4-methoxy-2,3,6-trimethyl-phenyl)-9-phenyl-sulphonyl-3,7-dimethyl-nona-2,4,6-trien-1-oic acid ethyl ester (2.8 g) is diluted with 8 ml of absolute ethanol. The solution is treated at 0°C in two portions with 1.2 g of sodium ethylate powder. The mixture is stirred for 30 minutes at 0°C and then for 2 hours at 80°C , then cooled, poured into ice and, after the addition of 2-N hydrochloric acid, extracted with ether. The ether extract is washed neutral with water, dried over sodium sulphate and evaporated under reduced pressure. The residual 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester melts at 105°C .

The 1-phenylsulphonylmethyl-4-methoxy-2,3,6-trimethyl-benzene used as the starting material can be prepared, for example, as follows:

16.8 g of 4-methoxy-2,3,6-trimethyl-benzyl alcohol, 17.4 g of the sodium salt of benzenesulphonic acid, 20.0 ml of isopropanol and 30.0 ml of glacial acetic acid are heated for 16 hours under nitrogen and reflux conditions. The mixture is cooled, treated portionwise with 200 ml of water and neutralised by the addition of sodium hydrogen carbonate. The organic layer is separated, washed several times with an aqueous solution of 5% sodium hydrogen carbonate, dried over sodium sulphate and evaporated under reduced pressure. The residual 1-phenylsulphonylmethyl-4-methoxy-2,3,6-trimethyl-benzene shows the following IR data: 1592, 1580, 1302, 1149, 1118 cm^{-1} .

B) 1.08 g of 4-methoxy-2,3,6-trimethyl-benzyl chloride, 1.67 g of 8-phenylsulphonyl-3,7-dimethyl-octa-2,4,6-trien-1-oic acid ethyl ester and 10 ml of dimethylformamide are cooled to 0°C and treated with 0.374 g of solid sodium ethylate. The mixture is stirred for 30 minutes at room temperature, then poured into ice and, after the addition of 2-N hydrochloric acid, extracted with ether. The ether extract is washed neutral, dried over sodium sulphate and evaporated under reduced pressure. The residual 9-(4-methoxy-2,3,6-trimethyl-phenyl)-8-phenylsulphonyl-3,7-dimethyl-nona-2,4,6-trien-1-oic acid ethyl ester is transformed in the same manner as described in A) hereinbefore, with the formation of benzenesulphonic acid as a byproduct and an additional carbon-carbon double-bond in the main product, into

the desired 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetra-1-oic acid ethyl ester of melting point 104°C — 105°C .

The 8-phenylsulphonyl-3,7-dimethyl-octa-2,4,6-trien-1-oic acid ethyl ester used as the starting material can be prepared, for example, as follows:

8.5 g of 8-bromo-3,7-dimethyl-octa-2,4,6-trien-1-oic acid ethyl ester are dissolved into 95 ml of dimethyl sulphoxide. The solution is treated under nitrogen in the cold with 0.45 g of the sodium salt of benzenesulphonic acid. The mixture is stirred for 1 hour at room temperature, then poured into ice and extracted with ether. The ether extract is washed with water, dried over sodium sulphate and evaporated under reduced pressure. The residual 8-phenyl-sulphonyl-3,7-dimethyl-octa-2,4,6-trien-1-oic acid ethyl ester melts at 114°C — 115°C .

Example 21.

60 g of 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid are dissolved in 1000 ml of acetone. After the addition of 128 g of methyl iodide and 128 g of potassium carbonate, the solution is stirred under nitrogen gassing for 16 hours at 55°C — 60°C and subsequently evaporated under reduced pressure. The residue is dissolved in 1300 ml of petroleum ether (boiling point 80°C — 105°C). The 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid methyl ester that crystallises out at -20°C , melts at 98°C — 99°C .

In a manner analogous to that just described, 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester (melting point 104°C — 105°C) is manufactured from 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid and ethyl iodide; 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid isopropyl ester (oil) is manufactured from 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid and isopropyl iodide; and 9-(4-methoxy-2,3,5,6-tetramethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester (melting point 105°C — 106°C) is manufactured from 9-(4-methoxy-2,3,5,6-tetramethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid and ethyl iodide.

Example 22.

20 g of 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid are dissolved in 200 ml of tetrahydrofuran. After the addition of 5.5 ml of phosphorus trichloride, the solution is stirred for 2 hours at room temperature, cooled to

0° C and treated firstly with 50 ml of pyridine and then dropwise at 0°—5° C with 50 ml of propargyl alcohol. The mixture is stirred for 2 hours at room temperature and then diluted with water. The organic phase is washed successively with water, dilute hydrochloric acid and a 2% aqueous sodium bicarbonate solution, dried over sodium sulphate and evaporated. There is obtained 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid propargyl ester which melts at 94°—95° C after adsorption on aluminium oxide using benzene as the eluent.

In a manner analogous to that just described, 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid allyl ester (melting point 66°—68° C) is manufactured from 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid and allyl alcohol.

Example 23.

28.6 g of 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid are introduced into 300 ml of benzene and treated under nitrogen gassing with 12 g of phosphorus trichloride. The benzene is subsequently distilled off under reduced pressure. There is obtained 9-(4-methoxy-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid chloride which is then dissolved in 1200 ml of ether. The solution is added dropwise at -33° C to 500 ml of liquid ammonia and stirred for 3 hours. The mixture is then diluted with 500 ml of ether and stirred without cooling for a further 12 hours during which the ammonia evaporates. The residue is dissolved in 10 litres of methylene chloride. The solution is washed twice with 3 litres of water, dried over sodium sulphate and evaporated under reduced pressure. There is obtained 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid amide which melts at 207°—209° C after recrystallisation from ethanol.

In a manner analogous to that just described, 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl amide (melting point 179°—180° C) is manufactured from 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid chloride and ethylamine; 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid diethylamide (melting point 105°—106° C) is manufactured from 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid chloride and diethylamine; 9-(4-methoxy-2,3,5,6-tetramethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethylamide (melting point 200°—201° C) is manufactured from

9-(4-methoxy-2,3,5,6-tetramethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid chloride and ethylamine; 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid morpholide is manufactured from 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid chloride and morpholine.

Example 24.

15 g of 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester (50:50 cis/trans mixture) are chromatographed on 1.5 kg of aluminium oxide (activity stage 1) using hexane/ether (80:20) as the eluent. From the front, there is isolated 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2-trans,4-cis,6-trans,8-trans-tetraen-1-oic acid ethyl ester as a light-yellow oil.

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

Example A.

A capsule filling material of the following composition was manufactured:

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester	0.1 g	
Wax mixture	51.4 g	
Vegetable oil	103.0 g	
Trisodium salt of ethylenediamine tetraacetic acid	0.5 g	
Individual weight of a capsule	150 mg	
Active material content of a capsule	10 mg	

Example B.

An ointment of the following composition, which contained 2.0% of active ingredient, was manufactured:

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid	2.0 g	
Cetyl alcohol	2.7 g	
Lanoline	6.0 g	
White Vaseline	15.0 g	
Distilled water q.s. ad	100.0 g	

(The word "Vaseline" is a registered Trade Mark).

Example C.

A water/fat emulsion of the following composition, which contained 0.3% of active ingredient, was manufactured:

- 9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl amide. 0.3 g
 5 Magnesium stearate 2.0 g
 Perhydrosqualene 13.0 g

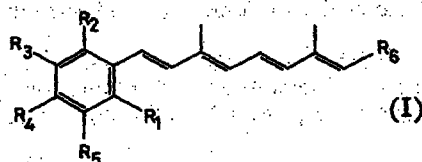
Example D.

- A solution of the following composition, which contained 0.1% of active ingredient, was manufactured:

- 9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl amide. 0.1 g
 15 Propyleneglycol 70.0 g
 Ethanol 96% q.s. ad 100 ml

WHAT WE CLAIM IS:—

1. Compounds of the general formula



- 20 wherein R_1 and R_2 each represent a lower alkyl group, R_3 represents a hydrogen or halogen atom or a lower alkyl, lower alkoxy, lower alkenoxy, nitro, amino, mono(lower alkyl)-amino, di(lower alkyl)amino, lower alkanoyl-amino or N-heterocyclic group, R_4 represents a hydrogen atom or a lower alkyl, lower alkenyl, lower alkoxy, lower alkenoxy, nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, lower alkanoylamino or N-heterocyclic group and R_5 represents a hydrogen or halogen atom or a lower alkyl, lower alkenyl, lower alkoxy, lower alkenoxy, nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, lower alkanoylamino or N-heterocyclic group (provided that at least one of R_3 , R_4 and R_5 represents other than a hydrogen atom and, when R_3 or R_5 represents a halogen atom, R_4 represents other than a lower alkoxy group) and R_6 represents a formyl, hydroxymethyl, alkoxymethyl, alkanoyloxymethyl, carboxyl, alkoxycarbonyl, alkenoxycarbonyl, alkynoxycarbonyl, carbamoyl, mono-(lower alkyl)carbamoyl, di(lower alkyl)-carbamoyl or N-heterocyclic carbonyl group, and salts thereof.

2. Compounds of formula I given in claim 1 in which R_1 and R_2 each represent a lower alkyl group, R_3 , R_4 and R_5 each represent a hydrogen atom or a lower alkyl, lower alkoxy, lower alkenoxy, nitro, amino, lower alkanoyl-amino or N-heterocyclic group (provided that at least one of R_3 , R_4 and R_5 represents other than a hydrogen atom) and R_6 represents a formyl, hydroxymethyl, alkoxymethyl, alkanoyloxymethyl, carboxyl, alkoxycarbonyl, carbamoyl, mono(lower alkyl)carbamoyl, di-

(lower alkyl)carbamoyl or N-heterocyclic carbonyl group, and salts thereof.

3. Compounds of formula I given in claim 1 in which R_1 and R_2 each represent a lower alkyl group, R_3 and R_5 have the significance given in claim 2 or can each individually represent a halogen atom, R_4 has the significance given in claim 2 with the exception of a lower alkoxy group (provided that at least one of R_3 , R_4 and R_5 represents other than a hydrogen atom) and R_6 has the significance given in claim 2, and salts thereof.

4. Compounds of formula I given in claim 1 in which R_1 and R_2 each represent a lower alkyl group, R_3 , R_4 and R_5 have the significance given in claim 2 or R_4 and/or R_5 can represent a lower alkenyl group (provided that at least one of R_3 , R_4 and R_5 represents other than a hydrogen atom) and R_6 has the significance given in claim 2, and salts thereof.

5. 9 - (2,3,6 - Trimethyl - phenyl) - 3,7-dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid.

6. 9 - (2,4,6 - Trimethyl - phenyl) - 3,7-dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid.

7. 9 - (2,4,6 - Triisopropyl - phenyl) - 3,7-dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid.

8. 9 - (2,3,4,6 - Tetramethyl - phenyl) - 3,7 - dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid.

9. 9 - (Pentamethyl - phenyl) - 3,7-dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid.

10. 9 - (4 - Methoxy - 2,6 - dimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid.

11. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid.

12. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid methyl ester.

13. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid ethyl ester.

14. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2 - trans,4-cis,6 - trans,8 - trans - tetraen - 1 - oic acid ethyl ester.

15. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid isopropyl ester.

16. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid butyl ester.

17. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid allyl ester.

18. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid propargyl ester.

19. 1 - Acetoxy - 9 - (4 - methoxy - 2,3,6-

	9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl amide.	0.3 g
5	Magnesium stearate	2.0 g
	Perhydrosqualene	13.0 g

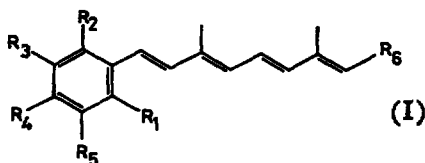
Example D.

A solution of the following composition, which contained 0.1% of active ingredient, was manufactured:

	9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl amide	0.1 g
15	Propyleneglycol	70.0 g
	Ethanol 96% q.s. ad	100 ml

WHAT WE CLAIM IS:—

1. Compounds of the general formula



wherein R_1 and R_2 each represent a lower alkyl group, R_3 represents a hydrogen or halogen atom or a lower alkyl, lower alkoxy, lower alkenoxy, nitro, amino, mono(lower alkyl)-amino, di(lower alkyl)amino, lower alkanoyl-amino or N-heterocyclic group, R_4 represents a hydrogen atom or a lower alkyl, lower alkenyl, lower alkoxy, lower alkenoxy, nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, lower alkanoylamino or N-heterocyclic group and R_5 represents a hydrogen or halogen atom or a lower alkyl, lower alkenyl, lower alkoxy, lower alkenoxy, nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, lower alkanoylamino or N-heterocyclic group (provided that at least one of R_3 , R_4 and R_5 represents other than a hydrogen atom and, when R_3 or R_5 represents a halogen atom, R_4 represents other than a lower alkoxy group) and R_6 represents a formyl, hydroxymethyl, alkoxymethyl, alkanoyloxymethyl, carboxyl, alkoxycarbonyl, alkenoxycarbonyl, alkynoxycarbonyl, carbamoyl, mono-(lower alkyl)carbamoyl, di(lower alkyl)-carbamoyl or N-heterocyclcarbonyl group, and salts thereof.

2. Compounds of formula I given in claim 1 in which R_1 and R_2 each represent a lower alkyl group, R_3 , R_4 and R_5 each represent a hydrogen atom or a lower alkyl, lower alkoxy, lower alkenoxy, nitro, amino, lower alkanoyl-amino or N-heterocyclic group (provided that at least one of R_3 , R_4 and R_5 represents other than a hydrogen atom) and R_6 represents a formyl, hydroxymethyl, alkoxymethyl, alkanoyloxymethyl, carboxyl, alkoxycarbonyl, carbamoyl, mono(lower alkyl)carbamoyl, di-

(lower alkyl)carbamoyl or N-heterocyclcarbonyl group, and salts thereof.

3. Compounds of formula I given in claim 1 in which R_1 and R_2 each represent a lower alkyl group, R_3 and R_5 have the significance given in claim 2 or can each individually represent a halogen atom, R_4 has the significance given in claim 2 with the exception of a lower alkoxy group (provided that at least one of R_3 , R_4 and R_5 represents other than a hydrogen atom) and R_6 has the significance given in claim 2, and salts thereof.

4. Compounds of formula I given in claim 1 in which R_1 and R_2 each represent a lower alkyl group, R_3 , R_4 and R_5 have the significance given in claim 2 or R_4 and/or R_5 can represent a lower alkenyl group (provided that at least one of R_3 , R_4 and R_5 represents other than a hydrogen atom) and R_6 has the significance given in claim 2, and salts thereof.

5. 9 - (2,3,6 - Trimethyl - phenyl) - 3,7-dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid.

6. 9 - (2,4,6 - Trimethyl - phenyl) - 3,7-dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid.

7. 9 - (2,4,6 - Triisopropyl - phenyl) - 3,7-dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid.

8. 9 - (2,3,4,6 - Tetramethyl - phenyl) - 3,7 - dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid.

9. 9 - (Pentamethyl - phenyl) - 3,7-dimethyl - nona - 2,4,6,8 - tetraen - 1 - oic acid.

10. 9 - (4 - Methoxy - 2,6 - dimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid.

11. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid.

12. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid methyl ester.

13. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid ethyl ester.

14. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2 - trans,4-cis,6 - trans,8 - trans - tetraen - 1 - oic acid ethyl ester.

15. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid isopropyl ester.

16. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid butyl ester.

17. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid allyl ester.

18. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid propargyl ester.

19. 1 - Acetoxy - 9 - (4 - methoxy - 2,3,6-

trimethyl - phenyl) - 3,7 - dimethyl - nona-2,4,6,8-tetraene.

20. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid amide.

21. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid ethyl amide.

22. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid diethylamide.

23. 9 - (4 - Methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid morpholide.

24. 9 - (4 - Ethoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid ethyl ester.

25. 9 - (4 - Isopropoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid.

26. 9 - (3 - Methoxy - 2,4,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid.

27. 9 - (4 - Methoxy - 2,3,5,6 - tetramethyl - phenyl) - 3,7 - dimethyl - nona-2,4,6,8-tetraen-1-oic acid.

28. 9 - (4 - Methoxy - 2,3,5,6 - tetramethyl - phenyl) - 3,7 - dimethyl - nona-2,4,6,8-tetraen-1-oic acid ethyl ester.

29. 9 - (4 - Methoxy - 2,3,5,6 - tetramethyl - phenyl) - 3,7 - dimethyl - nona-2,4,6,8-tetraen-1-oic acid ethyl amide.

30. 9 - (4 - Methoxy - 3 - allyl - 2,6-dimethyl - phenyl) - 3,7 - dimethyl - nona-2,4,6,8-tetraen-1-oic acid.

31. 9 - (4 - Methoxy - 3 - nitro - 2,6-dimethyl - phenyl) - 3,7 - dimethyl - nona-2,4,6,8-tetraen-1-oic acid ethyl ester.

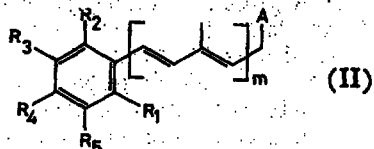
32. 9 - (3 - Nitro - 2,4,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid.

33. 9 - (3 - Dimethylamino - 2,4,6 - trimethyl - phenyl) - 3,7 - dimethyl - nona-2,4,6,8-tetraen-1-oic acid ethyl ester.

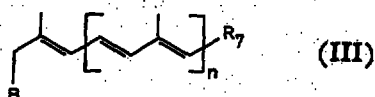
34. 9 - (3 - Chloro - 2,4,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid.

35. 9 - (4 - Allyloxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid.

36. A process for the manufacture of the polyene derivatives claimed in claim 1, which process comprises reacting a compound of the general formula

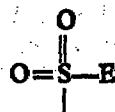


with a compound of the general formula



wherein m stands for zero and n stands for 1 or m stands for 1 and n stands for zero, one of the two symbols A and B represents an oxo group and the other symbol represents a triarylphosphonium group of the formula $-P[X]_3Y^{\oplus}$, in which X represents an aryl group and Y represents the anion of an inorganic or organic acid, or a dialkoxyposphinyl group of the formula $-P[Z]_2$,

in which Z represents an alkoxy group, or one of the two symbols A and B represents a sulphone group of the formula



in which E represents an aryl or aralkenyl group which may be substituted by one or more electron-releasing or weakly electron-withdrawing substituents, and the other symbol represents a halogen atom or an alkanesulphonyloxy or arylsulphonyloxy group, R_1 , R_2 , R_3 , R_4 and R_5 have the significance given in claim 1 and R_6 represents a carboxy, alkoxy-carbonyl, alkenoxycarbonyl, alkynoxycarbonyl, di(lower alkyl) carbamoyl or heterocyclyl-carbonyl group, or, when B represents an oxo group, R_6 can also represent an alkoxy-methyl or alkanoyloxymethyl group, or, when B represents a halogen atom or an alkanesulphonyloxy or arylsulphonyloxy group, R_6 can also represent a formyl, alkoxy-methyl or alkanoyloxymethyl group, or, when B represents a triarylphosphonium group or a dialkoxyposphinyl group or a sulphone group, R_6 can also represent a formyl group, and cleaving off any sulphone group which may be present in the reaction product with the formation of an additional carbon-carbon bond and, if desired, converting an acid or amine obtained into a salt; or transforming a carboxylic acid of formula I into a carboxylic acid ester of formula I or into an amide of formula I; or transforming a carboxylic acid ester of formula I into a carboxylic acid of formula I or into an amide of formula I; or reducing a carboxylic acid of formula I or a carboxylic acid ester of formula I to the corresponding alcohol of formula I and optionally etherifying or esterifying said alcohol; or saponifying an alcohol ester of formula I; or oxidising an alcohol or alcohol ester of formula I to the corresponding carboxylic acid.

37. A process according to claim 36 for the manufacture of the polyene compounds claimed in claim 2, which process comprises reacting a compound of formula II with a compound of formula III, in which formulae m and n have the significance given in claim 39, one of the two symbols A and B represents an oxo group and the other symbols represents

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20 a triarylphosphonium group of the formula
—P[X]₃Y⁺, wherein X represents an aryl
group and Y represents the anion of an in-
organic or organic acid, R₁, R₂, R₃, R₄ and R₅
5 have the significance given in claim 2 and R₆
represents a carboxyl or alkoxycarbonyl group
when B represents an oxo group or a formyl,
carboxyl or alkoxycarbonyl group when B
represents an triarylphosphonium group, and,
10 in optional sequence and if desired, esterifying
or amidating a carboxylic acid obtained, or
hydrolysing or amidating a carboxylic acid
ester obtained, or reducing a carboxylic acid
or carboxylic acid ester obtained to the cor-
15 responding alcohol and optionally etherifying
or esterifying said alcohol, or saponifying an
alcohol ester obtained, or oxidising an alcohol
or alcohol ester obtained to the corresponding
carboxylic acid.

20 38. A process according to claim 37 for the
manufacture of the polyene compounds
claimed in claim 3, which process comprises
reacting an appropriately substituted compound
of formula II with an appropriate compound
25 of formula III and, if desired, subjecting the
product obtained to any of the subsequent
procedures set forth in claim 37.

30 39. A process according to claim 37 for
the manufacture of the polyene compounds
claimed in claim 4, which process comprises
reacting an appropriately substituted com-
pound of formula II with an appropriate
compound of formula III and, if desired, sub-
35 jecting the product obtained to any of the
subsequent procedures set forth in claim 37.

40 40. A process according to any one of
claims 36 to 39 inclusive, wherein a phos-
phonium salt of formula II or III is reacted
with an aldehyde of formula III or II in the
presence of an epoxide, if necessary with the
addition of a solvent.

41. A process according to claim 40, where-
in said epoxide is ethylene oxide which may
be substituted by lower alkyl.

42. A process according to claim 41, where-
in 1,2-butylene oxide is used.

43. A process according to claim 36, where-
in a phosphonate of formula II or III is
reacted with an aldehyde of formula III or
50 II in an inert organic solvent in the presence
of a base.

44. A process according to claim 43, where-
in the reaction is carried out in the presence
of sodium hydride in benzene.

45. A process according to claim 36, where-
in a sulphone of formula II or III is reacted
with a halide of formula III or II in the
presence of a condensation agent and an inert
organic solvent.

46. A process according to claim 45, where-
in said inert organic solvent is dimethyl-
formamide or tetrahydrofuran.

47. A process according to any one of
claims 36 to 42 inclusive, wherein a 4-methoxy-
65 2,3,6 - trimethyl - benzyl - triphenylphos-

phonium halide is reacted with 7-formyl-3-
methyl - octa - 2,4,6 - trien - 1 - oic acid
or with the ethyl ester thereof.

48. A process according to any one of
claims 36 to 42 inclusive, wherein a 5-(4-
methoxy - 2,3,6 - trimethyl - phenyl) - 3-
methyl - penta - 2,4 - dien - 1 - triphenyl-
phosphonium halide is reacted with 3-formyl-
crotonic acid or with the ethyl ester thereof.

49. A process according to any one of claims
36 to 42 inclusive, wherein 4-methoxy-2,3,6-
trimethyl-benzaldehyde is reacted with a 1-
(carboxy or ethoxycarbonyl)-2,6-dimethyl-
hepta - 1,3,5 - trien - 7 - triphenylphos-
phonium halide.

50. A process according to any one of claims
36 to 42 inclusive, wherein 5-(4-methoxy-
2,3,6 - trimethyl - phenyl) - 3 - methyl-
penta-2,4-dien-1-al is reacted with a 3-methyl-
crotonic acid 4-triphenylphosphonium halide
or with the ethyl ester thereof.

51. A process according to claim 36, claim
43 or claim 44, wherein 4-methoxy-2,3,6-
trimethyl - benzyl - diethylphosphonate is
reacted with 7-formyl-3-methyl-octa-2,4,6-
trien-1-oic acid or with the ethyl ester thereof.

52. A process according to claim 36, claim
43 or claim 44, wherein 5-(4-methoxy-2,3,6-
trimethyl - phenyl) - 3 - methyl - penta-
2,4-dien-1-diethylphosphonate is reacted with
3-formyl-crotonic acid or with the ethyl ester
thereof.

53. A process according to claim 36, claim
43 or claim 44, wherein 4-methoxy-2,3,6-
trimethyl-benzaldehyde is reacted with 1-
(carboxy or ethoxycarbonyl) - 2,6 - dimethyl-
hepta-1,3,5-trien-7-diethylphosphonate.

54. A process according to claim 36, claim
43 or claim 44, wherein 5-(4-methoxy-2,3,6-
trimethyl - phenyl) - 3 - methyl - penta-
2,4-dien-1-al is reacted with 3-methyl-crotonic
acid 4-diethylphosphonate or with the ethyl
ester thereof.

55. A process according to claim 36, claim
45 or claim 46, wherein 1-(phenylsulphonyl)-
methyl - 4 - methoxy - 2,3,6 - trimethyl-
benzene is reacted with 8-bromo-3,7-dimethyl-
octa-2,4,6-trien-1-oic acid or with the ethyl
ester thereof.

56. A process according to claim 36, claim
45 or claim 46, wherein 1-phenylsulphonyl-
5 - (4 - methoxy - 2,3,6 - trimethyl - phenyl)-
3-methyl-penta-2,4-diene is reacted with 4-
bromo-3-methyl-crotonic acid.

57. A process according to claim 36, claim
45 or claim 46, wherein 4-methoxy-2,3,6-
trimethyl-benzyl chloride is reacted with 1-
(carboxy or ethoxycarbonyl) - 7 - phenyl-
sulphonyl-2,6-dimethyl-hepta-1,3,5-triene.

58. A process according to claim 36, claim
45 or claim 46, wherein 1-bromo-5-(4-
methoxy - 2,3,6 - trimethyl - phenyl) - 3-
methyl-penta-2,4-diene is reacted with 4-
phenylsulphonyl - 3 - methyl - crotonic acid
or with the ethyl ester thereof.



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59. A process according to any one of claims 36 to 39 inclusive, wherein a carboxylic acid of formula I obtained is converted into an acid halide and the acid halide is reacted with ammonia or with a mono(lower alkyl)amine or a di(lower alkyl)amine.

60. A process according to claim 59, wherein 9 - (4 - methoxy - 2,3,6 - trimethyl-phenyl) - 3,7 - dimethyl - nona - 2,4,6,8-tetraen-1-oic acid is converted into the acid chloride and this acid chloride is reacted with ethyl amine.

61. A process according to any one of claims 36 to 39 inclusive, wherein an alcohol or alcohol ester of formula I obtained is oxidised to the corresponding carboxylic acid with the aid of silver (I) oxide in the presence of an alkali metal hydroxide.

62. A process for the manufacture of the polyene derivatives claimed in claim 1, substantially as hereinbefore described with reference to any one of the foregoing Examples.

63. Polyene derivatives as set forth in claim 1, when manufactured by the process claimed in any one of claims 36 to 62 inclusive.

64. A pharmaceutical preparation containing a polyene derivative as set forth in claim 1 in association with a compatible pharmaceutical carrier.

65. A pharmaceutical preparation according to claim 64, wherein said polyene derivative is 9 - (4 - methoxy - 2,3,6 - trimethyl - phenyl) - 3,7 - dimethyl - nona - 2,4,6,8 - tetraen - 1-oic acid.

66. A pharmaceutical preparation according to claim 64, wherein said polyene derivative is 9 - (4 - methoxy - 2,3,6 - trimethyl - phenyl) - 3,7 - dimethyl - nona - 2,4,6,8 - tetraen - 1-oic acid ethyl ester.

67. A pharmaceutical preparation according to claim 64, wherein said polyene derivative is 9 - (4 - methoxy - 2,3,6 - trimethyl - phenyl) - 3,7 - dimethyl - nona - 2,4,6,8 - tetraen - 1-oic acid ethyl amide.

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