

PATENT SPECIFICATION

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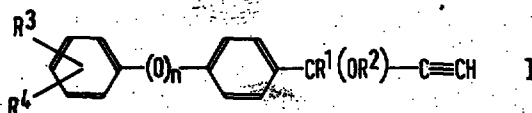
C2C 202 220 226 227 22Y 231 240 242 26X 292 29Y 30Y 311 313
 314 31Y 338 360 362 363 364 366 368 36Y 37X 38Y 491
 504 505 506 50Y 623 624 628 652 658 65X 662 668 697
 699 778 790 79Y BT BZ WM WP

(54) ALKYNE DERIVATIVES AND PROCESS FOR
 THEIR PREPARATION

(71) We, MERCK PATENT GESELLSCHAFT MIT BESCHRANKTER HAFTUNG, a German body corporate, of 61 Darmstadt, Frankfurter Strasse 250, Germany, 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:—

This invention is concerned with certain novel alkyne derivatives, with processes for their preparation, and with compositions containing them.

We have found that alkyne derivatives of formula I:



wherein R¹ is H, alkyl with up to 4 C atoms or phenyl, R² is H, aliphatic acyl with up to 6 C atoms or aroyl with up to 11 C atoms, R³ and R⁴ are each H, F, Cl or Br, and is 0 or 1, provided that when R¹ is H or methyl, R² is H, R³ is H and n is 0, R³ is F, Cl or Br, and their physiologically acceptable metal salts, have valuable pharmacological properties and are well tolerated. These compounds have anti-inflammatory activity as can be demonstrated, for example, on rats by the Newbould adjuvant-arthritis method (*Brit. J. Pharmacol.*, 21, (1963), pages 127—136). These compounds also have analgesic and anti-pyretic activity which can be demonstrated by methods customary for this purpose. Cholesterol level-reducing activity (which can be demonstrated by the method of Levine et al., *Automation in Analytical Chemistry*, Technicon Symposium 1967, Mediad, New York, pages 25—28), triglyceride level-reducing activity (which can be demonstrated by the method of Noble and Campbell, *Clin. Chem.*, 16 (1970), pages 166—170 and thrombocyte aggregation inhibiting activity are also found.

The compounds of formula I and their physiologically acceptable metal salts can, therefore, be used as medicaments in human and veterinary medicine. They can also be used as intermediates in the preparation of further medicaments.

These compounds are novel and constitute one aspect of the present invention.

For the sake of simplicity, the terminal phenyl radical which is substituted by R³ and R⁴ is designated "A" in the following description.

In the compounds of the invention, the R¹ radical is preferably methyl and the R² radical is preferably H. The R³ and R⁴ radicals may be the same or different. Preferably one of these radicals is H and the other is H, F or Cl. Compounds in which R³ and R⁴ are both F are also preferred. The R¹ radical can also be H, ethyl, propyl, isopropyl, butyl, isobutyl, sec.-butyl or tert.-butyl. The R² radical can also be aliphatic acyl with up to 6 C atoms, preferably acetyl, propionyl, butyryl or pivaloyl, and also formyl, isobutyryl, pentanoyl, 2-methylbutyryl or hexanoyl. When R² has the meaning of aroyl with up to 11 C atoms, it is preferably benzoyl but can also be, for example, o-, m- or p-methylbenzoyl, o-, m- or p-fluorobenzoyl, o-, m-, or p-chlorobenzoyl, naphthyl-1-carbonyl or naphthyl-2-carbonyl.

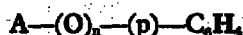
The A radical in the compounds I is thus preferably an unsubstituted or mono-substituted phenyl radical or a phenyl radical which is substituted by 2 fluorine atoms. A single substituent is preferably in the *p*-position, but can also be in the *o*-position or the *m*-position. In the case of disubstitution, the substituents R³ and R⁴ are preferably in the 2,4-positions. However, they can also be in the 2,3-, 2,5-, 2,6-, 3,4- or 3,5-positions.

In detail, the A radical is preferably phenyl, *o*-, *m*- or, in particular, *p*-fluorophenyl, *o*-, *m*- or, in particular, *p*-chlorophenyl, or 2,4-difluorophenyl as well as *o*-, *m*- or *p*-bromophenyl, 2,3-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,5-, 2,6-, 3,4-, 3,5- or, in particular, 2,4-dichlorophenyl, chloro-fluorophenyl, such as 2-chloro-3-, 4-, 5- or 6-fluorophenyl, 3-chloro-2-, 4- or 5-fluorophenyl, 4-chloro-2- or 3-fluorophenyl or 5-chloro-2-fluorophenyl, dibromophenyl, such as 2,4-dibromophenyl, bromo-fluorophenyl, such as 2-bromo-4-fluorophenyl or 4-bromo-2-fluorophenyl, or bromo-chloro-phenyl, such as 2-bromo-4-chlorophenyl or 4-bromo-2-chlorophenyl.

If the parameter n is 1, the group



is preferably 4-(4-chlorophenoxy)-phenyl. Otherwise, the parameter n is preferably 0; accordingly, the group



is then a 4-biphenyl radical which is substituted or unsubstituted on the terminal phenyl group.

Preferred compounds according to the invention are those in which at least one of the radicals or parameters R¹, R², R³, R⁴ or n has one of the preferred meanings mentioned above.

Some preferred groups of compounds can be expressed by the following partial formulae Ia to If, which correspond to formula I and wherein the radicals and parameters which are not designated in more detail have the meanings indicated for formula I, but wherein,

in Ia, A is phenyl, fluorophenyl or difluorophenyl,

in Ib, A is phenyl, *o*- or *p*-fluorophenyl or 2,4-difluorophenyl,

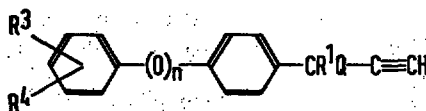
in Ic, A is *o*- or *p*-fluorophenyl, *p*-chlorophenyl or 2,4-difluorophenyl, R¹ is methyl, R² is H, and n is 0,

in Id, A is phenyl, *o*- or *p*-fluorophenyl, *p*-chlorophenyl or 2,4-difluorophenyl, R¹ is methyl, R² is aliphatic acyl with 2-5 C atoms or benzoyl, and n is 0,

in Ie, A is phenyl, *o*- or *p*-fluorophenyl, *p*-chlorophenyl or 2,4-difluorophenyl, R¹ is methyl, R² is H and, n is 1; and

in If, A is phenyl, *o*- or *p*-fluorophenyl, *p*-chlorophenyl or 2,4-difluorophenyl, R¹ is methyl, R² is aliphatic acyl with 2-5 C atoms or benzoyl, and n is 1.

The present invention also comprises a process for the preparation of an alkyne derivative of formula I or a physiologically acceptable metal salt thereof, which comprises treating a compound of formula II:



wherein Q is a functionally modified hydroxyl group and R¹, R³, R⁴ and n have the above-stated meanings, with a solvolysing agent.

When a compound of formula I in which R²=H is obtained, it may, if desired, be treated with an acylating agent. A compound of formula I obtained may, if desired, be treated with a base to form a physiologically acceptable metal salt thereof or a compound of formula I may be liberated from a salt thereof.

The preparation of the compounds of formula I is carried out according to known methods such as are described in the literature (for example in the standard works, such as Houben-Weyl, *Methoden der Organischen Chemie* (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart, and *Organic Reactions*, John Wiley & Sons, Inc., New York) and, in particular, under the reaction conditions which are known and suitable for the reactions in question. Known variants of such processes which are not mentioned in more detail here, can also be used.

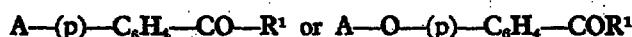
Some of the starting materials for the preparation of the compounds of formula I

are known. Where they are new, they can be prepared by known processes. If desired, the starting materials can be formed *in situ* so that they are not isolated from the reaction mixture in which they are formed, but are immediately reacted further to give the compounds of formula I.

The compounds of formula I are prepared by solvolysis, particularly hydrolysis, of compounds of formula II. In the latter, the Q radical is a functionally modified hydroxyl group which can, for example, be present as a metal alcoholate group or an acyl group.

The Q radical is preferably a metal alcoholate group OM, in which M is one equivalent of a metal atom, for example, an alkali metal or alkaline earth metal atom, preferably Li, Na, K, Rb or Cs, or one of the groups MgHal, CaHal, SrHal or BaHal (Hal=Cl, Br or I). M can also be one equivalent of a heavy metal atom, a metal of sub-groups 1 and 2 of the periodic table (for example, copper, zinc, cadmium or mercury).

Compounds of formula II (Q=OM) are preferably prepared *in situ*. They can be obtained, in particular, by reacting a carbonyl compound of the formula



(wherein A and R¹ have the above stated meanings) with a metal acetylide.

Thus, for example, the carbonyl compound can be reacted with an alkali metal or an alkaline earth metal acetylide, preferably NaC≡CH or LiC≡CH, and also KC≡CH or Ca(C≡CH)₂, in an inert solvent at a temperature of from 0° to 100°C, preferably at 15° to 50°C. Suitable inert solvents for this purpose are, for example, open-chain dialkyl ethers, such as diethyl ether, diisopropyl ether or diisobutyl ether, cyclic ethers, such as tetrahydrofuran (THF) or dioxan, acylamides, such as formamide or acetamide, dialkylacetylides, such as dimethylformamide (DMF), diethylformamide or dimethylacetamide, alkanal acetals, such as methylal, dimethylsulphoxide (DMSO) and/or diethylsulphoxide. If desired, an inert gas, such as N₂ or Ar, may be present during the reaction.

Instead of the alkali metal acetylides, diamine complexes thereof can be used, for example those with ethylenediamine, preferably the lithium acetylide/ethylenediamine complex. This reaction is carried out using any of the solvents mentioned, for example THF, DMSO and/or dioxan, preferably at room temperature and in the presence of an inert gas, such as N₂.

The reaction of the carbonyl compound with the alkali metal or alkaline earth metal acetylide can also advantageously be carried out using a reactant which, together with acetylene, form the acetylide *in situ* under the indicated reaction conditions. Examples of such reactants are alkali metal and alkaline earth metal amides, hydrides or enolates, alkali metals or alkaline earth metals themselves, or alkali metal organometallic compounds, such as phenyl-sodium, -potassium or -lithium or naphthalene-sodium, -potassium or -lithium. Conversely, the reaction can also be carried out by converting the above-mentioned carbonyl compounds (for example in the form of their enolates) into their alkali metal or alkaline earth metal compounds and reacting the latter further, *in situ*, with acetylene.

If desired, alkaline catalysts, such as alkali metal or alkaline earth metal hydroxides, alcoholates or carbonates, for example NaOH, KOH, NaOCH₃, KOCH₃, Na₂CO₃ or K₂CO₃, can be used in the reaction of compounds of the formula



with acetylene. The reaction is carried out in an inert solvent, for example a hydrocarbon, such as benzene, toluene or xylene (if desired, with the addition of 0.5–5% by weight of oleic acid), or with an active solvent, such as a cyclic ether (for example THF or dioxan), a dialkylamide (for example DMF), an ether, such as diethyl ether, diisopropyl ether or di-tert-butyl ether, pyridine and/or short-chain alcohols, such as methanol or ethanol, under the above-mentioned reaction conditions. It is preferred to use potassium hydroxide in ether in the presence of a little ethanol; the reaction is preferably carried out at 20° to 50°C with an excess of KOH for relatively long reaction times (for example 6–24 hours) and under a slight excess pressure of acetylene (for example 2–15 atmospheres, preferably about 8 atmospheres).

The reaction of a compound of the formula



with an alkali metal or alkaline earth metal acetylide (for example, sodium or lithium acetylide and also calcium or potassium acetylide) can also be carried out in liquid ammonia, if desired with the addition of one of the above-mentioned inert solvents. In this case, the reaction mixture is preferably kept saturated with acetylene. Temperatures of from -77° to -33°C are suitable and the mixture is allowed to react for from 30 minutes to 48 hours, preferably from 1 to 14 hours. It may be desirable to operate under pressure (for example 1 to 50 atmospheres); the reaction temperature can then be higher, for example from -30° to $+30^{\circ}\text{C}$.

According to a further embodiment, the compound II ($\text{Q}=\text{OM}$; M =one equivalent of a heavy metal atom, such as Ag, Cu or Hg) can also be obtained *in situ* by ethynylation of the compound



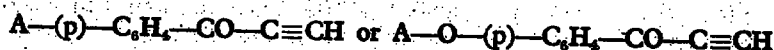
in the presence of a catalyst, preferably in aqueous solution, under an excess pressure of acetylene and at an elevated temperature (50° — 150°C). Catalysts which can be used for this purpose are the acetylides of metals of sub-groups 1 and 2 of the periodic table, for example copper or mercury acetylide, and also addition compounds thereof with acetylene. These catalysts can be carried by or mixed with supports, such as finely divided SiO_2 . The acetylene used can be diluted with an inert gas, such as, for example, N_2 , for example in a ratio of 2:1. The reaction is usually complete in from 20 minutes to 36 hours, preferably in from $\frac{1}{2}$ to 6 hours.

The compounds of formula II ($\text{Q}=\text{OM}$) can also be prepared from a carbonyl compound of the formula

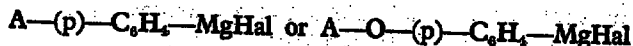


and ethynyl-magnesium halide under the conventional conditions for a Grignard synthesis, preferably in an inert solvent, such as ethers (for example diethyl ether, diisopropyl ether, diethylene glycol diethyl ether or diethylene glycol dibutyl ether), cyclic ethers (for example THF or dioxan) and/or carbon tetrachloride, at a temperature of from 0° to 70°C , more preferably from 0° to 30°C . Instead of the ethynyl-magnesium halide, other metal acetylides of the formula $\text{M}-\text{C}\equiv\text{CH}$ can be used, for example ethynyl-zinc halide or ethynyl-cadmium halide or silver acetylide, under the same or similar reaction conditions.

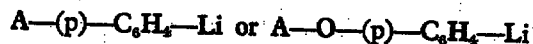
Compounds of formula II can also be prepared by a Grignard synthesis by reacting a carbonyl compound of the formula



with an alkyl-magnesium halide or by reacting a compound of the formula $\text{R}^1-\text{CO}-\text{C}\equiv\text{CH}$ with a biphenyl-magnesium halide or a phenoxyphenyl-magnesium halide of the formula

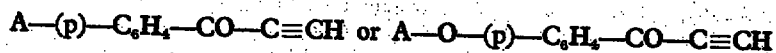


($\text{Hal}=\text{Cl}$, Br or I) under the above-mentioned reaction conditions. In place of the organometallic magnesium compounds mentioned, the corresponding lithium derivatives of the formula R^1Li or

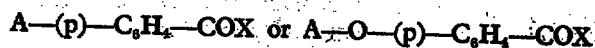


can also be used for this reaction. The reaction is carried out under the same reaction conditions.

The carbonyl compounds of the formula



can be prepared, for example, by reacting a carboxylic acid halide of the formula



($\text{X}=\text{Cl}$ or Br) with silver acetylide or an alkali metal acetylide in, for example, carbon tetrachloride. The carbonyl compound $\text{R}^1-\text{CO}-\text{C}\equiv\text{CH}$ can be prepared analogously by a corresponding conversion of a carboxylic acid halide of the formula R^1COX .

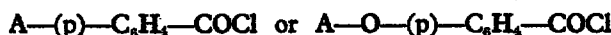
Finally, the carbonyl compound of the formula



can be obtained by Fridel-Crafts acylation of a compound of the formula



with an acid chloride of the formula R^1COCl or (if R^1 =phenyl) also by reaction of benzene with an acid chloride of the formula



in the presence of $AlCl_3$.

The metal acetylides of the formula $M-C\equiv CH$ can be obtained by known methods by reacting acetylene with an alkali metal, such as Li, Na or K, with an alkali metal hydride, such as LiH, NaH or KH, or with an alkali metal amide, such as $LiNH_2$, $NaNH_2$ or KNH_2 , in an anhydrous solvent, such as dioxan, DMSO, THF and/or liquid ammonia.

In compounds of formula II, the Q radical can also be present in the form of an acyloxy group, for example an alkanoyloxy group in which the alkanoyl radical preferably contains up to 7 C atoms (for example, acetyl or oenanthoyl), the benzoyloxy group, an alkylsulphonyloxy group or arylsulphonyloxy group (wherein the alkyl radical preferably contains 1 to 6 C atoms and the aryl radical preferably contains 6 to 10 C atoms), an alkoxy group (wherein the alkyl group preferably contains up to 6 C atoms), an aryloxy group (wherein the aryl group preferably contains 6 to 10 C atoms) or an aralkyloxy group (wherein the aralkyl group preferably has 7 to 11 C atoms). The Q radical can also be Cl, Br or I (a hydrogen halide acid ester group).

The compounds II in which the Q radical is an alkanoyloxy, benzoyloxy, alkylsulphonyloxy or arylsulphonyloxy group can be obtained by reacting a compound II ($Q=Cl$ or Br) with an alkali metal salt of the appropriate acid. Furthermore, compounds II in which Q is an ether group can be obtained by reacting the halogen compound II with the appropriate alkali metal alcoholate and, in addition, compounds II ($Q=I$) can be obtained by reacting the compound II ($Q=Cl$ or Br) with potassium iodide in acetone.

The solvolysis of the compounds II can be carried out in an acidic, neutral or alkaline medium at a temperature of from -20° to $300^\circ C$. Preferred acidic catalysts are HCl, H_2SO_4 or acetic acid as well as salts having an acid reaction, such as ammonium chloride, and suitable basic catalysts are sodium hydroxide, potassium hydroxide or calcium hydroxide, sodium carbonate or potassium carbonate. Suitable solvents are, for example, water, alcohols, such as methanol or ethanol, ethers, such as THF or dioxan, amides, such as DMF, nitriles, such as acetonitriles, and/or sulphones, such as tetramethylenesulphone, and, in particular, mixtures which contain water.

The metal alcoholates of formula II ($Q=OM$), which are preferred as starting materials, are preferably not isolated, but are hydrolysed *in situ* after their formation with dilute acids, for example sulphuric acid or hydrochloric acid, or with aqueous ammonium chloride solution, preferably at a temperature of from 0° to $30^\circ C$.

If desired, a resulting alcohol of formula I ($R^2=H$) can be esterified with an organic carboxylic acid (for example an alkanic acid with up to 6 C atoms or an arylcarboxylic acid with up to 11 C atoms) or with a reactive derivative thereof (for example a halide or anhydride, such as acetyl chloride, *p*-chlorobenzoic acid chloride, acetyl bromide or acetic anhydride). The esterification is preferably carried out in the presence of an acidic or basic catalyst, for example an inorganic or organic acid, such as HCl, HBr, HI, H_2SO_4 , H_3PO_4 , trifluoroacetic acid, benzenesulphonic acid or *p*-toluenesulphonic acid, or an acidic ion exchanger or a base, for example an alkali metal hydroxide, such as NaOH or KOH, an alkali metal carbonate, such as sodium carbonate or potassium carbonate, or an organic base, such as pyridine, if desired in the presence of an inert solvent, such as benzene, toluene or xylene, at a temperature of from 0° to $140^\circ C$, more preferably from 20° to $100^\circ C$. The esterification is preferably carried out with the appropriate acid chloride or acid anhydride in pyridine at room temperature. The alcohol I ($R^2=H$) can also be esterified with a ketene. Formates I ($R^2=CHO$) are preferably obtained from the alcohol I ($R^2=H$) by heating with excess formic acid.

The compounds of formula I can be converted by reaction with a base into one

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of their physiologically acceptable metal salts. Suitable salts are, in particular, the sodium, potassium, calcium, magnesium, copper-I and copper-II salts.

Conversely, compounds of formula I can be liberated from their metal salts by treatment with an acid or water.

The compounds of formula I contain a centre of asymmetry and are usually obtained in racemic form. The racemates can be resolved into their optical antipodes using known mechanical or chemical methods, such as are indicated in the literature.

The compounds of formula I and their physiologically acceptable metal salts can be used in human or veterinary medicine in admixture with solid, liquid and/or semi-liquid inert, physiologically acceptable carriers or excipients. Suitable carriers are organic or inorganic substances which are suitable for enteral or parenteral administration or topical application and which do not react with the new compounds, for example water, vegetable oils, benzyl alcohol, polyethylene glycols, gelatine, lactose, starch, magnesium stearate, talc, white petroleum jelly and cholesterol. Compositions in the form of tablets, dragees, capsules, syrups, elixirs or suppositories are suitable for enteral administration. Compositions in the form of solutions, preferably oily or aqueous solutions, or suspensions, emulsions or implants are suitable for parenteral administration and those in the form of ointments, creams or powders, for topical application. The new compounds can also be lyophilised and the resulting lyophilisates can be used to prepare injection formulations. The composition may be sterilised and/or contain adjuvants, such as lubricants, preservatives, stabilisers and/or wetting agents, emulsifiers, salts for regulating the osmotic pressure, buffer substances, dye-stuffs, flavourings and/or aroma substances. They may, if desired, also contain one or more further active compounds, for example vitamins.

In general, the compounds according to the invention are administered analogously to known commercially available anti-inflammatory agents. The daily dose is preferably from 0.1 to 10 mg/kg of body weight. However, the specific dose for each particular patient depends on very diverse factors, for example on the efficacy of the particular compound employed, on the age, body weight, general state of health, sex, and diet of the patient, on the time, and on the route of administration, the rate of excretion, the combination of medicinal substances and on the severity of the particular illness to which the therapy applies. Oral administration is preferred.

When the composition containing a compound according to the invention is in dosage unit form, each dosage unit preferably contains from 5 to 500, more preferably 10 to 250, mg of the active compound.

Each of the compounds of formula I mentioned in the examples which follow is particularly suitable for the preparation of pharmaceutical compositions.

In order that the invention may be more fully understood, the following examples, in which all temperatures are in °C, are given by way of illustration. In these examples, "customary working up" or "working up in the customary manner" means: water is added to the reaction mixture if necessary, the mixture is extracted with an organic solvent, such as benzene, chloroform or dichloromethane, the organic phase is separated off, dried over sodium sulphate, filtered and evaporated and the product is purified by chromatography and/or crystallisation.

Example 1

A mixture of 0.84 g of sodium hydride and 18 ml of dry DMSO is heated to 70–75° for 30 minutes under nitrogen. After cooling and adding 10 ml of dry THF and a small amount of triphenylmethane (as an indicator), acetylene is passed in until the red colour disappears. A solution of 7.4 g of 4'-fluoro-4-acetylbiphenyl (which can be prepared from 4-fluorobiphenyl and acetyl chloride in the presence of $AlCl_3$) in 20 ml of THF and 7 ml of DMSO is then added, whilst passing nitrogen through the mixture. The resulting reaction mixture, which contains sodium 3-(4'-fluoro-biphenyl-4)-but-1-yn-3-olate, is hydrolysed with an aqueous ammonium chloride solution and worked up in the customary manner. This gives 3-(4'-fluorobiphenyl-4)-3-hydroxybut-1-yne; m.p. 80–82°.

Examples 2 to 45

Analogously to Example 1, the compounds which follow can be obtained from the corresponding acetylbiphenyl or acetyl-4-phenoxyphenyl derivatives and sodium acetylide:

2. 3-(2'-Fluoro-biphenyl-4)-3-hydroxybut-1-yne, m.p. 86–88°.
3. 3-(3'-Fluoro-biphenyl-4)-3-hydroxybut-1-yne.
4. 3-(2'-Chloro-biphenyl-4)-3-hydroxybut-1-yne.

5. 3-(3'-Chloro-biphenyl-4)-3-hydroxybut-1-yne.
6. 3-(4'-Chloro-biphenyl-4)-3-hydroxybut-1-yne, m.p. 106—107°
7. 3-(2'-Bromo-biphenyl-4)-3-hydroxybut-1-yne.
8. 3-(3'-Bromo-biphenyl-4)-3-hydroxybut-1-yne.
- 5 9. 3-(4'-Bromo-biphenyl-4)-3-hydroxybut-1-yne, m.p. 114—116°.
10. 3-(2',3'-Difluoro-biphenyl-4)-3-hydroxybut-1-yne.
11. 3-(2',4'-Difluoro-biphenyl-4)-3-hydroxybut-1-yne, m.p. 64—66°.
12. 3-(2',5'-Difluoro-biphenyl-4)-3-hydroxybut-1-yne.
13. 3-(2',6'-Difluoro-biphenyl-4)-3-hydroxybut-1-yne.
- 10 14. 3-(3',4'-Difluoro-biphenyl-4)-3-hydroxybut-1-yne.
15. 3-(3',5'-Difluoro-biphenyl-4)-3-hydroxybut-1-yne.
16. 3-(2',3'-Dichloro-biphenyl-4)-3-hydroxybut-1-yne.
17. 3-(2',4'-Dichloro-biphenyl-4)-3-hydroxybut-1-yne.
18. 3-(2',5'-Dichloro-biphenyl-4)-3-hydroxybut-1-yne.
- 15 19. 3-(2',6'-Dichloro-biphenyl-4)-3-hydroxybut-1-yne.
20. 3-(3',4'-Dichloro-biphenyl-4)-3-hydroxybut-1-yne.
21. 3-(3',5'-Dichloro-biphenyl-4)-3-hydroxybut-1-yne.
22. 3-(2',4'-Dibromo-biphenyl-4)-3-hydroxybut-1-yne.
23. 3-(4-Phenoxyphenyl)-3-hydroxybut-1-yne.
- 20 24. 3-[4-(2-Fluorophenoxy)-phenyl]-3-hydroxybut-1-yne.
25. 3-[4-(3-Fluorophenoxy)-phenyl]-3-hydroxybut-1-yne.
26. 3-[4-(4-Fluorophenoxy)-phenyl]-3-hydroxybut-1-yne, m.p. 54—56°.
27. 3-[4-(2-Chlorophenoxy)-phenyl]-3-hydroxybut-1-yne.
28. 3-[4-(3-Chlorophenoxy)-phenyl]-3-hydroxybut-1-yne.
- 25 29. 3-[4-(4-Chlorophenoxy)-phenyl]-3-hydroxybut-1-yne, m.p. 55—57°
30. 3-[4-(2-Bromophenoxy)-phenyl]-3-hydroxybut-1-yne.
31. 3-[4-(3-Bromophenoxy)-phenyl]-3-hydroxybut-1-yne.
32. 3-[4-(4-Bromophenoxy)-phenyl]-3-hydroxybut-1-yne.
33. 3-[4-(2,3-Difluorophenoxy)-phenyl]-3-hydroxybut-1-yne.
- 30 34. 3-[4-(2,4-Difluorophenoxy)-phenyl]-3-hydroxybut-1-yne.
35. 3-[4-(2,5-Difluorophenoxy)-phenyl]-3-hydroxybut-1-yne.
36. 3-[4-(2,6-Difluorophenoxy)-phenyl]-3-hydroxybut-1-yne.
37. 3-[4-(3,4-Difluorophenoxy)-phenyl]-3-hydroxybut-1-yne.
38. 3-[4-(3,5-Difluorophenoxy)-phenyl]-3-hydroxybut-1-yne.
- 35 39. 3-[4-(2,3-Dichlorophenoxy)-phenyl]-3-hydroxybut-1-yne.
40. 3-[4-(2,4-Dichlorophenoxy)-phenyl]-3-hydroxybut-1-yne.
41. 3-[4-(2,5-Dichlorophenoxy)-phenyl]-3-hydroxybut-1-yne.
42. 3-[4-(2,6-Dichlorophenoxy)-phenyl]-3-hydroxybut-1-yne.
43. 3-[4-(3,4-Dichlorophenoxy)-phenyl]-3-hydroxybut-1-yne.
- 40 44. 3-[4-(3,5-Dichlorophenoxy)-phenyl]-3-hydroxybut-1-yne.
45. 3-[4-(2,4-Dibromophenoxy)-phenyl]-3-hydroxybut-1-yne.

Example 46

- Analogously to Example 1, 3-(4'-fluorobiphenyl-4)-3-hydroxypent-1-yne of m.p. 69—71° is obtained by reacting 8 g of 4'-fluoro-4-propionylbiphenyl (which can be prepared from 4-fluorobiphenyl and propionyl chloride in the presence of $AlCl_3$) with sodium acetylide and subsequently hydrolysing the reaction product.

Examples 47 to 114

- Analogously to Example 46, the alkyne compounds which follow can be obtained from the corresponding 1-formyl-, 1-propionyl-, 1-butyryl-, 1-pentanoyl- or 1-benzoyl-biphenyl- or -(4-phenoxy)-phenyl derivatives and sodium acetylide:

47. 3-(2'-Fluoro-biphenyl-4)-3-hydroxypropyne.
48. 3-(4'-Fluoro-biphenyl-4)-3-hydroxypropyne.
49. 3-(2'-Chloro-biphenyl-4)-3-hydroxypropyne.
50. 3-(4'-Chloro-biphenyl-4)-3-hydroxypropyne.
- 55 51. 3-(4'-Bromo-biphenyl-4)-3-hydroxypropyne.
52. 3-(2',4'-Difluoro-biphenyl-4)-3-hydroxypropyne.
53. 3-(4-Phenoxyphenyl)-3-hydroxypropyne.
54. 3-[4-(2-Fluorophenoxy)-phenyl]-3-hydroxypropyne.
55. 3-[4-(4-Fluorophenoxy)-phenyl]-3-hydroxypropyne.
- 60 56. 3-[4-(2-Chlorophenoxy)-phenyl]-3-hydroxypropyne.
57. 3-[4-(4-Chlorophenoxy)-phenyl]-3-hydroxypropyne.
58. 3-[4-(4-Bromophenoxy)-phenyl]-3-hydroxypropyne.

59. 3-[4-(2,4-Difluorophenoxy)-phenyl]-3-hydroxypropyne.
60. 3-(Biphenyl-4)-3-hydroxypent-1-yne.
61. 3-(2'-Fluoro-biphenyl-4)-3-hydroxypent-1-yne.
62. 3-(2'-Chloro-biphenyl-4)-3-hydroxypent-1-yne.
63. 3-(4'-Chloro-biphenyl-4)-3-hydroxypent-1-yne.
64. 3-(4'-Bromo-biphenyl-4)-3-hydroxypent-1-yne.
65. 3-(2',4'-Difluoro-biphenyl-4)-3-hydroxypent-1-yne.
66. 3-(4-Phenoxyphenyl)-3-hydroxypent-1-yne.
67. 3-[4-(2-Fluorophenoxy)-phenyl]-3-hydroxypent-1-yne.
68. 3-[4-(4-Fluorophenoxy)-phenyl]-3-hydroxypent-1-yne.
69. 3-[4-(2-Chlorophenoxy)-phenyl]-3-hydroxypent-1-yne.
70. 3-[4-(4-Chlorophenoxy)-phenyl]-3-hydroxypent-1-yne.
71. 3-[4-(4-Bromophenoxy)-phenyl]-3-hydroxypent-1-yne.
72. 3-[4-(2,4-Difluorophenoxy)-phenyl]-3-hydroxypent-1-yne.
73. 3-(Biphenyl-4)-3-hydroxy-hex-1-yne.
74. 3-(2'-Fluoro-biphenyl-4)-3-hydroxy-hex-1-yne.
75. 3-(4'-Fluoro-biphenyl-4)-3-hydroxy-hex-1-yne.
76. 3-(2'-Chloro-biphenyl-4)-3-hydroxy-hex-1-yne.
77. 3-(4'-Chloro-biphenyl-4)-3-hydroxy-hex-1-yne.
78. 3-(4'-Bromo-biphenyl-4)-3-hydroxy-hex-1-yne.
79. 3-(2',4'-Difluoro-biphenyl-4)-3-hydroxy-hex-1-yne.
80. 3-(4-Phenoxyphenyl)-3-hydroxy-hex-1-yne.
81. 3-[4-(2-Fluorophenoxy)-phenyl]-3-hydroxy-hex-1-yne.
82. 3-[4-(4-Fluorophenoxy)-phenyl]-3-hydroxy-hex-1-yne.
83. 3-[4-(2-Chlorophenoxy)-phenyl]-3-hydroxy-hex-1-yne.
84. 3-[4-(4-Chlorophenoxy)-phenyl]-3-hydroxy-hex-1-yne.
85. 3-[4-(4-Bromophenoxy)-phenyl]-3-hydroxy-hex-1-yne.
86. 3-[4-(2,4-Difluorophenoxy)-phenyl]-3-hydroxy-hex-1-yne.
87. 3-(Biphenyl-4)-3-hydroxy-hept-1-yne.
88. 3-(2'-Fluoro-biphenyl-4)-3-hydroxy-hept-1-yne.
89. 3-(4'-Fluoro-biphenyl-4)-3-hydroxy-hept-1-yne, m.p. 61—63°.
90. 3-(2'-Chloro-biphenyl-4)-3-hydroxy-hept-1-yne.
91. 3-(4'-Chloro-biphenyl-4)-3-hydroxy-hept-1-yne.
92. 3-(4'-Bromo-biphenyl-4)-3-hydroxy-hept-1-yne.
93. 3-(2',4'-Difluoro-biphenyl-4)-3-hydroxy-hept-1-yne.
94. 3-(4-Phenoxyphenyl)-3-hydroxy-hept-1-yne.
95. 3-[4-(2-Fluorophenoxy)-phenyl]-3-hydroxy-hept-1-yne.
96. 3-[4-(4-Fluorophenoxy)-phenyl]-3-hydroxy-hept-1-yne.
97. 3-[4-(2-Chlorophenoxy)-phenyl]-3-hydroxy-hept-1-yne.
98. 3-[4-(4-Chlorophenoxy)-phenyl]-3-hydroxy-hept-1-yne.
99. 3-[4-(4-Bromophenoxy)-phenyl]-3-hydroxy-hept-1-yne.
100. 3-[4-(2,4-Difluorophenoxy)-phenyl]-3-hydroxy-hept-1-yne.
101. 3-(Biphenyl-4)-3-phenyl-3-hydroxypropyne.
102. 3-(2'-Fluoro-biphenyl-4)-3-phenyl-3-hydroxypropyne.
103. 3-(4'-Fluoro-biphenyl-4)-3-phenyl-3-hydroxypropyne, m.p. 95—97°.
104. 3-(2'-Chloro-biphenyl-4)-3-phenyl-3-hydroxypropyne.
105. 3-(4'-Chloro-biphenyl-4)-3-phenyl-3-hydroxypropyne.
106. 3-(4'-Bromo-biphenyl-4)-3-phenyl-3-hydroxypropyne.
107. 3-(2',4'-Difluoro-biphenyl-4)-3-phenyl-3-hydroxypropyne.
108. 3-(4-Phenoxyphenyl)-3-phenyl-3-hydroxypropyne.
109. 3-[4-(2-Fluorophenoxy)-phenyl]-3-phenyl-3-hydroxypropyne.
110. 3-[4-(4-Fluorophenoxy)-phenyl]-3-phenyl-3-hydroxypropyne.
111. 3-[4-(2-Chlorophenoxy)-phenyl]-3-phenyl-3-hydroxypropyne.
112. 3-[4-(4-Chlorophenoxy)-phenyl]-3-phenyl-3-hydroxypropyne.
113. 3-[4-(4-Bromophenoxy)-phenyl]-3-phenyl-3-hydroxypropyne.
114. 3-[4-(2,4-Difluorophenoxy)-phenyl]-3-phenyl-3-hydroxypropyne.

Example 115

214 g of 4'-fluoro-4-acetylbiphenyl are added dropwise, in the course of 3 hours, to a solution of sodium acetylide, prepared from 25 g of sodium, in 600 ml of liquid ammonia. The mixture is stirred for 150 minutes at -35°, 65 g of ammonium chloride are then added to the solution, which contains sodium 3-(4'-fluoro-biphenyl-4)-but-1-yn-3-olate and the ammonia is evaporated off in the course of about 12 hours. After customary working up, this gives 3-(4'-fluorobiphenyl-4)-3-hydroxybut-1-yne; m.p. 80—82°.

(17)

Example 116

8.34 g of lithium are introduced at -70° , in the course of three hours, into 900 ml of liquid ammonia saturated with acetylene. When the blue colour has disappeared 214 g of 4'-fluoro-4-acetylbiphenyl in 200 ml of ether are added in the course of one hour and, at the same time, acetylene is passed into the mixture. Subsequently, the ammonia is allowed to evaporate from the solution, which contains lithium 3-(4'-fluoro-biphenyl-4)-but-1-yn-3-olate, at $+25^{\circ}$ and, at the same time, ether is added in such an amount, that the volume of the mixture remains approximately constant. After the ammonia has been removed, no further acetylene is passed in and the mixture is left to stand for 12 hours at 20° . The reaction product is then hydrolysed with 150 ml of water and the ether layer is worked up in the customary manner. This gives 3-(4'-fluorobiphenyl-4)-3-hydroxybut-1-yne; m.p. $80-82^{\circ}$.

Example 117

A solution of 2.47 g of 4'-chloro-4-acetyldiphenyl ether (which can be prepared from 4-chlorodiphenyl ether and acetyl chloride in the presence of AlCl_3) in 6 ml of THF and 2 ml of DMSO is added dropwise to a suspension of 1.38 g of the lithium acetylide/ethylenediamine complex in a mixture of 3 ml of absolute THF and 4 ml of absolute DMSO, whilst passing acetylene through the mixture. The mixture is stirred for one hour whilst nitrogen is passed through, an aqueous solution of ammonium chloride is added to the solution which contains lithium 3-[4-(4-chlorophenoxy)-phenyl]-but-1-yn-3-olate and the mixture is poured into water and worked up in the customary manner. This gives 3-[4-(4-chlorophenoxy)-phenyl]-3-hydroxybut-1-yne, m.p. $55-57^{\circ}$.

Example 118

An acetylene-magnesium bromide solution is prepared from 8 g of magnesium, 52.5 g of bromobenzene and acetylene and, whilst stirring and cooling, 71 g of 4'-fluoro-4-acetyl-biphenyl in 200 ml of ether are added. The solution is left to stand for 3 days at 20° and ice water is then added in order to hydrolyse the 3-(4'-fluoro-biphenyl-4)-but-1-ynyl-3-oxy-magnesium bromide. The mixture is then acidified with dilute sulphuric acid and extracted with ether. After drying over sodium sulphate and removing the solvent this gives 3-(4'-fluoro-biphenyl-4)-3-hydroxybut-1-yne; m.p. $80-82^{\circ}$.

Example 119

A solution of 22.4 g of (4'-fluorobiphenyl-4)-ethynyl ketone (which can be prepared from 3-(4'-fluoro-biphenyl-4)-3-hydroxy-prop-1-yne by oxidation with chromium trioxide/sulphuric acid in water/acetone) in 100 ml of absolute diethyl ether is added dropwise to a Grignard solution, cooled to 0° , which has previously been prepared from 5.3 g of magnesium and 31.2 g of methyl iodide in 200 ml of diethyl ether. The temperature is allowed to rise to 20° , whilst stirring, and the solution containing 3-(4'-fluoro-biphenyl-4)-but-1-yn-3-yloxy-magnesium iodide is hydrolysed with an aqueous solution of ammonium chloride in the customary manner. This gives 3-(4'-fluoro-biphenyl-4)-3-hydroxybut-1-yne; m.p. $80-82^{\circ}$.

Example 120

A solution of 6.8 g of acetylacetylene in 50 ml of diethyl ether is added, at 0° , to a solution of 70 g of 4'-fluoro-biphenyl-4-magnesium iodide (which can be prepared by nitrating 4-fluorobiphenyl, reducing the resulting 4'-fluoro-4-nitro-biphenyl to the amine, converting the latter to 4'-fluoro-4-iodo-biphenyl by a Sandmeyer reaction and subsequently reacting this with magnesium) in 400 ml of diethyl ether. The temperature of the solution is allowed to rise to 20° , whilst stirring, and the solution is stirred for a further 2 hours at 20° . An aqueous solution of ammonium chloride is then added in order to hydrolyse the 3-(4'-fluoro-biphenyl-4)-but-1-yn-3-yloxy-magnesium bromide and the product is worked up in the customary manner. This gives 3-(4'-fluoro-biphenyl-4)-3-hydroxybut-1-yne; m.p. $80-82^{\circ}$.

Example 121

A solution of 6.8 g of acetylacetylene in 50 ml of diethyl ether is added, at 0° , to a solution of 35 g of 4-lithium-4'-fluorobiphenyl (which can be prepared by brominating 4-fluorobiphenyl and subsequently reacting the product with lithium) in 200 ml of diethyl ether. After warming to 20° , the solution is boiled for 2 hours, and an aqueous solution of ammonium chloride is added in order to hydrolyse the lithium 3-(4'-fluoro-biphenyl-4)-but-1-yn-3-olate. The product is then worked up in the customary manner. This gives 3-(4'-fluoro-biphenyl-4)-3-hydroxybut-1-yne; m.p. $80-82^{\circ}$.

Example 122

A mixture of 5 g of 3-(4'-fluorobiphenyl-4)-3-hydroxybut-1-yne, 25 ml of acetic anhydride and 25 ml of pyridine is heated to 60° for 20 hours. The reaction mixture is then poured into water and worked up in the customary manner. This gives 3-(4'-fluoro-biphenyl-4)-3-acetoxy-but-1-yne; m.p. 103—104°.

Examples 123 to 195

Analogously to Example 122, the compounds of the formula I which follow can be obtained by acylating the corresponding 3-biphenyl- and 3-(4-phenoxy-phenyl)-3-hydroxy-prop-1-yne (and -but-1-yne, -pent-1-yne, -hex-1-yne and -hept-1-yne) derivatives:

123. 3-(Biphenyl-4)-3-acetoxybut-1-yne.
124. 3-(2'-Fluoro-biphenyl-4)-3-acetoxybut-1-yne, m.p. 66—68°.
125. 3-(3'-Fluoro-biphenyl-4)-3-acetoxybut-1-yne.
126. 3-(4'-Chloro-biphenyl-4)-3-acetoxybut-1-yne.
127. 3-(4'-Bromo-biphenyl-4)-3-acetoxybut-1-yne, m.p. 121—123°.
128. 3-(2',4'-Difluoro-biphenyl-4)-3-acetoxybut-1-yne, m.p. 99—101°.
129. 3-(3',4'-Difluoro-biphenyl-4)-3-acetoxybut-1-yne.
130. 3-(3',5'-Difluoro-biphenyl-4)-3-acetoxybut-1-yne.
131. 3-(2',4'-Dichloro-biphenyl-4)-3-acetoxybut-1-yne.
132. 3-(2',4'-Dibromo-biphenyl-4)-3-acetoxybut-1-yne.
133. 3-(4-Phenoxyphenyl)-3-acetoxybut-1-yne.
134. 3-[4-(2-Fluorophenoxy)-phenyl]-3-acetoxybut-1-yne.
135. 3-[4-(3-Fluorophenoxy)-phenyl]-3-acetoxybut-1-yne.
136. 3-[4-(4-Fluorophenoxy)-phenyl]-3-acetoxybut-1-yne.
137. 3-[4-(4-Chlorophenoxy)-phenyl]-3-acetoxybut-1-yne.
138. 3-[4-(4-Bromophenoxy)-phenyl]-3-acetoxybut-1-yne.
139. 3-[4-(2,4-Difluorophenoxy)-phenyl]-3-acetoxybut-1-yne.
140. 3-[4-(2,4-Dichlorophenoxy)-phenyl]-3-acetoxybut-1-yne.
141. 3-[4-(2,4-Dibromophenoxy)-phenyl]-3-acetoxybut-1-yne.
142. 3-(Biphenyl-4)-3-acetoxypropyne.
143. 3-(4'-Fluoro-biphenyl-4)-3-acetoxypropyne.
144. 3-(2',4'-Difluoro-biphenyl-4)-3-acetoxypropyne.
145. 3-(4-Phenoxyphenyl)-3-acetoxypropyne.
146. 3-[4-(4-Fluorophenoxy)-phenyl]-3-acetoxypropyne.
147. 3-[4-(2,4-Difluorophenoxy)-phenyl]-3-acetoxypropyne.
148. 3-(Biphenyl-4)-3-acetoxypent-1-yne.
149. 3-(4'-Fluoro-biphenyl-4)-3-acetoxypent-1-yne.
150. 3-(2',4'-Difluoro-biphenyl-4)-3-acetoxypent-1-yne.
151. 3-(4-Phenoxyphenyl)-3-acetoxypent-1-yne.
152. 3-[4-(4-Fluorophenoxy)-phenyl]-3-acetoxypent-1-yne.
153. 3-[4-(2,4-Difluorophenoxy)-phenyl]-3-acetoxypent-1-yne.
154. 3-(Biphenyl-4)-3-acetoxy-hex-1-yne.
155. 3-(4'-Fluoro-biphenyl-4)-3-acetoxy-hex-1-yne.
156. 3-(2',4'-Difluoro-biphenyl-4)-3-acetoxy-hex-1-yne.
157. 3-(4-Phenoxyphenyl)-3-acetoxy-hex-1-yne.
158. 3-[4-(4-Fluorophenoxy)-phenyl]-3-acetoxy-hex-1-yne.
159. 3-[4-(2,4-Difluorophenoxy)-phenyl]-3-acetoxy-hex-1-yne.
160. 3-(Biphenyl-4)-3-acetoxy-hept-1-yne.
161. 3-(4'-Fluoro-biphenyl-4)-3-acetoxy-hept-1-yne.
162. 3-(2',4'-Difluoro-biphenyl-4)-3-acetoxy-hept-1-yne.
163. 3-(4-Phenoxyphenyl)-3-acetoxy-hept-1-yne.
164. 3-[4-(4-Fluorophenoxy)-phenyl]-3-acetoxy-hept-1-yne.
165. 3-[4-(2,4-Difluorophenoxy)-phenyl]-3-acetoxy-hept-1-yne.
166. 3-(Biphenyl-4)-3-phenyl-3-acetoxypropyne.
167. 3-(4'-Fluoro-biphenyl-4)-3-phenyl-3-acetoxypropyne.
168. 3-(2',4'-Difluoro-biphenyl-4)-3-phenyl-3-acetoxypropyne.
169. 3-(4-Phenoxyphenyl)-3-phenyl-3-acetoxypropyne.
170. 3-[4-(4-Fluorophenoxy)-phenyl]-3-phenyl-3-acetoxypropyne.
171. 3-[4-(2,4-Difluorophenoxy)-phenyl]-3-phenyl-3-acetoxypropyne.
172. 3-(4'-Fluorobiphenyl-4)-3-formyloxy-but-1-yne.
173. 3-(4'-Fluorobiphenyl-4)-3-propionyloxy-but-1-yne.
174. 3-(4'-Fluorobiphenyl-4)-3-butyryloxy-but-1-yne.
175. 3-(Biphenyl-4)-3-pivaloyloxy-but-1-yne.

176. 3-(4'-Fluorobiphenyl-4)-3-pivaloyloxy-propyne.
 177. 3-(4'-Fluorobiphenyl-4)-3-pivaloyloxy-but-1-yne.
 178. 3-(4'-Fluorobiphenyl-4)-3-pivaloyloxy-pent-1-yne.
 179. 3-(4'-Fluorobiphenyl-4)-3-pivaloyloxy-hex-1-yne.
 180. 3-(4'-Fluorobiphenyl-4)-3-pivaloyloxy-hept-1-yne.
 181. 3-(4'-Fluorobiphenyl-4)-3-phenyl-3-pivaloyloxy-propyne.
 182. 3-(4'-Fluorobiphenyl-4)-3-hexanoyloxy-but-1-yne.
 183. 3-(4'-Fluorobiphenyl-4)-3-benzoyloxy-but-1-yne.
 184. 3-[4-(4-Fluorophenoxy)-phenyl]-3-formyloxy-but-1-yne.
 185. 3-[4-(4-Fluorophenoxy)-phenyl]-3-propionyloxy-but-1-yne.
 186. 3-[4-(4-Fluorophenoxy)-phenyl]-3-butyryloxy-but-1-yne.
 187. 3-(4-Phenoxyphenyl)-3-pivaloyloxy-butyne.
 188. 3-[4-(4-Fluorophenoxy)-phenyl]-3-pivaloyloxy-propyne.
 189. 3-[4-(4-Fluorophenoxy)-phenyl]-3-pivaloyloxy-but-1-yne.
 190. 3-[4-(4-Fluorophenoxy)-phenyl]-3-pivaloyloxy-pent-1-yne.
 191. 3-[4-(4-Fluorophenoxy)-phenyl]-3-pivaloyloxy-hex-1-yne.
 192. 3-[4-(4-Fluorophenoxy)-phenyl]-3-pivaloyloxy-hept-1-yne.
 193. 3-[4-(4-Fluorophenoxy)-phenyl]-3-phenyl-3-pivaloyloxy-propyne.
 194. 3-[4-(4-Fluorophenoxy)-phenyl]-3-hexanoyloxy-but-1-yne.
 195. 3-[4-(4-Fluorophenoxy)-phenyl]-3-benzoyloxy-but-1-yne.

Example 196

A mixture of 1 g of 3-(4'-fluorobiphenyl-4)-3-hydroxybutyne in 20 ml of ethanol-containing water is shaken vigorously with an excess of an ammoniacal solution of copper-I chloride and the precipitate is filtered off. This gives the copper-I salt of 3-(4'-fluorobiphenyl-4)-3-hydroxybutyne as an amorphous powder.

The following examples of pharmaceutical compositions which contain an active compound of formula I are given by way of illustration:

Example A:

Tablets

A mixture consisting of 1 kg of 3-(4'-fluoro-biphenyl-4)-3-hydroxybut-1-yne, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed in conventional manner to form tablets, each containing 100 mg of the active compound.

Example B:

Dragées

Tablets are pressed analogously to Example A and are then coated in conventional manner with a coating consisting of sugar, maize starch, talce and tragacanth.

Example C:

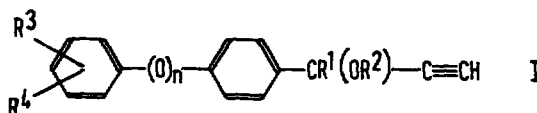
Capsules

5 kg of 3-(4'-fluoro-biphenyl-4)-3-hydroxybut-1-yne are filled into hard gelatine capsules in conventional manner to form capsules, each containing 250 mg of the active compound.

Tablets, dragées and capsules containing one or more of the other active compounds of formula I or their physiologically acceptable salts can be obtained analogously.

WHAT WE CLAIM IS:—

1. Alkyne derivatives of formula I:



wherein R¹ is H, alkyl with up to 4 C atoms or phenyl, R² is H, aliphatic acyl with up to 6 C atoms or aroyl with up to 11 C atoms, R³ and R⁴ are each H, F, Cl or Br, and n is 0 or 1, provided that when R¹ is H or methyl, R² is H, R⁴ is H and n is 0, R³ is F, Cl or Br, and their physiologically acceptable metal salts.

2. 3-(4'-Fluorobiphenyl-4)-3-hydroxy-propyne.
 3. 3-(2'-Fluorobiphenyl-4)-3-hydroxy-but-1-yne.
 4. 3-(4'-Fluorobiphenyl-4)-3-hydroxy-but-1-yne.



176. 3-(4'-Fluorobiphenyl-4)-3-pivaloyloxy-propyne.
 177. 3-(4'-Fluorobiphenyl-4)-3-pivaloyloxy-but-1-yne.
 178. 3-(4'-Fluorobiphenyl-4)-3-pivaloyloxy-pent-1-yne.
 179. 3-(4'-Fluorobiphenyl-4)-3-pivaloyloxy-hex-1-yne.
 180. 3-(4'-Fluorobiphenyl-4)-3-pivaloyloxy-hept-1-yne.
 181. 3-(4'-Fluorobiphenyl-4)-3-phenyl-3-pivaloyloxy-propyne.
 182. 3-(4'-Fluorobiphenyl-4)-3-hexanoyloxy-but-1-yne.
 183. 3-(4'-Fluorobiphenyl-4)-3-benzoyloxy-but-1-yne.
 184. 3-[4-(4-Fluorophenoxy)-phenyl]-3-formyloxy-but-1-yne.
 185. 3-[4-(4-Fluorophenoxy)-phenyl]-3-propionyloxy-but-1-yne.
 186. 3-[4-(4-Fluorophenoxy)-phenyl]-3-butyryloxy-but-1-yne.
 187. 3-(4-Phenoxyphenyl)-3-pivaloyloxy-butyne.
 188. 3-[4-(4-Fluorophenoxy)-phenyl]-3-pivaloyloxy-propyne.
 189. 3-[4-(4-Fluorophenoxy)-phenyl]-3-pivaloyloxy-but-1-yne.
 190. 3-[4-(4-Fluorophenoxy)-phenyl]-3-pivaloyloxy-pent-1-yne.
 191. 3-[4-(4-Fluorophenoxy)-phenyl]-3-pivaloyloxy-hex-1-yne.
 192. 3-[4-(4-Fluorophenoxy)-phenyl]-3-pivaloyloxy-hept-1-yne.
 193. 3-[4-(4-Fluorophenoxy)-phenyl]-3-phenyl-3-pivaloyloxy-propyne.
 194. 3-[4-(4-Fluorophenoxy)-phenyl]-3-hexanoyloxy-but-1-yne.
 195. 3-[4-(4-Fluorophenoxy)-phenyl]-3-benzoyloxy-but-1-yne.

Example 196

A mixture of 1 g of 3-(4'-fluorobiphenyl-4)-3-hydroxybutyne in 20 ml of ethanol-containing water is shaken vigorously with an excess of an ammoniacal solution of copper-I chloride and the precipitate is filtered off. This gives the copper-I salt of 3-(4'-fluorobiphenyl-4)-3-hydroxybutyne as an amorphous powder.

The following examples of pharmaceutical compositions which contain an active compound of formula I are given by way of illustration:

Example A:

Tablets

A mixture consisting of 1 kg of 3-(4'-fluoro-biphenyl-4)-3-hydroxybut-1-yne, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed in conventional manner to form tablets, each containing 100 mg of the active compound.

Example B:

Dragées

Tablets are pressed analogously to Example A and are then coated in conventional manner with a coating consisting of sugar, maize starch, talce and tragacanth.

Example C:

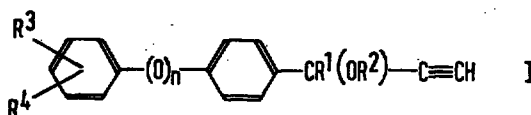
Capsules

5 kg of 3-(4'-fluoro-biphenyl-4)-3-hydroxybut-1-yne are filled into hard gelatine capsules in conventional manner to form capsules, each containing 250 mg of the active compound.

Tablets, dragées and capsules containing one or more of the other active compounds of formula I or their physiologically acceptable salts can be obtained analogously.

WHAT WE CLAIM IS:—

1. Alkyne derivatives of formula I:



wherein R¹ is H, alkyl with up to 4 C atoms or phenyl, R² is H, aliphatic acyl with up to 6 C atoms or aroyl with up to 11 C atoms, R³ and R⁴ are each H, F, Cl or Br, and n is 0 or 1, provided that when R¹ is H or methyl, R² is H, R⁴ is H and n is 0, R³ is F, Cl or Br, and their physiologically acceptable metal salts.

2. 3-(4'-Fluorobiphenyl-4)-3-hydroxy-propyne.

3. 3-(2'-Fluorobiphenyl-4)-3-hydroxy-but-1-yne.

4. 3-(4'-Fluorobiphenyl-4)-3-hydroxy-but-1-yne.

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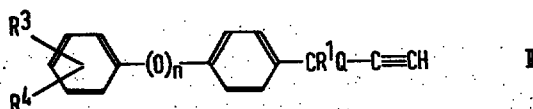
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5. 3-(2',4'-Difluorobiphenyl-4)-3-hydroxy-but-1-yne.
6. 3-(4'-Chlorobiphenyl-4)-3-hydroxy-but-1-yne.
7. 3-(4'-Bromobiphenyl-4)-3-hydroxy-but-1-yne.
8. 3-[4-(4-Fluorophenoxy)-phenyl]-3-hydroxy-but-1-yne.
9. 3-[4-(4-Chlorophenoxy)-phenyl]-3-hydroxy-but-1-yne.
10. 3-(4'-Fluorobiphenyl-4)-3-hydroxy-pent-1-yne.
11. 3-(4'-Fluorobiphenyl-4)-3-hydroxy-hept-1-yne.
12. 3-[4-(4-Fluorophenoxy)-phenyl]-3-hydroxy-hept-1-yne.
13. 3-(2'-Fluorobiphenyl-4)-3-acetoxy-but-1-yne.
14. 3-(4'-Fluorobiphenyl-4)-3-acetoxy-but-1-yne.
15. 3-(4'-Fluorobiphenyl-4)-3-benzoyloxy-but-1-yne.
16. 3-(2',4'-Difluorobiphenyl-4)-3-acetoxy-but-1-yne.
17. 3-(4'-Chlorobiphenyl-4)-3-acetoxy-but-1-yne.
18. 3-(4'-Bromobiphenyl-4)-3-acetoxy-but-1-yne.
19. 3-[4-(4-Fluorophenoxy)-phenyl]-3-acetoxy-but-1-yne.
20. 3-[4-(4-Chlorophenoxy)-phenyl]-3-acetoxy-but-1-yne.
21. 3-(4'-Fluorobiphenyl-4)-3-acetoxy-hept-1-yne.

22. A process for the preparation of an alkyne derivative of formula I specified in claim 1, or a physiologically acceptable metal salt thereof, which comprises treating a compound of formula II:



wherein Q is a functionally modified hydroxyl group and R¹, R³, R⁴ and n have the meanings specified in claim 1 with a solvolysing agent.

23. A process according to claim 22, in which, when a compound of formula I in which R²=H is obtained, it is treated with an acylating agent.

24. A process according to claim 22 or 23, in which the compound of formula I obtained is treated with a base to form a physiologically acceptable metal salt thereof or, when a salt of a compound of formula I is obtained, it is treated with an acid or water to liberate the compound of formula I therefrom.

25. A process for the preparation of a compound of formula I specified in claim 1, substantially as herein described in any of Examples 1 to 196.

26. A pharmaceutical composition which comprises at least one compound according to any of claims 1 to 21 and an inert, physiologically acceptable carrier.

27. A pharmaceutical composition substantially as herein described in any of Examples A to C.

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