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(54) Title
SUBSTITUTED PHENYLACETYLENES, PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS AND PROCESSES FOR THE PREPARATION OF THESE COMPOUNDS AND COMPOSITIONS

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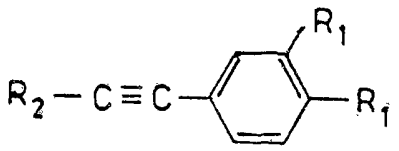
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(57) Claim

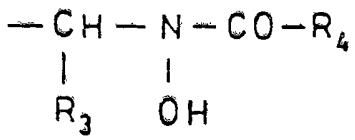
1) Substituted phenylacetylenes of the general formula



I

wherein

one of the symbols R_1 represents a hydrogen atom while the other represents the group of the formula

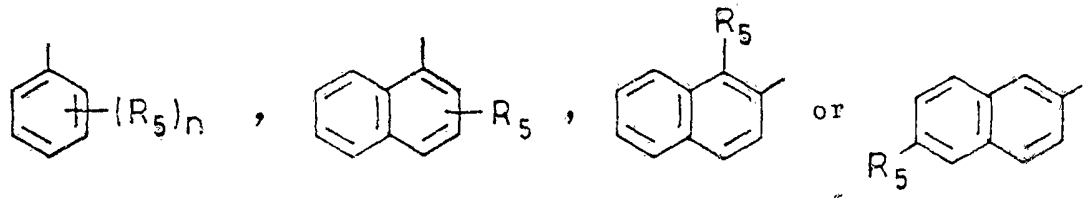


in which R_3 is hydrogen, methyl or ethyl and R_4 represents a methyl or an amino group and

R_2 represents a mono- or binuclear group which is

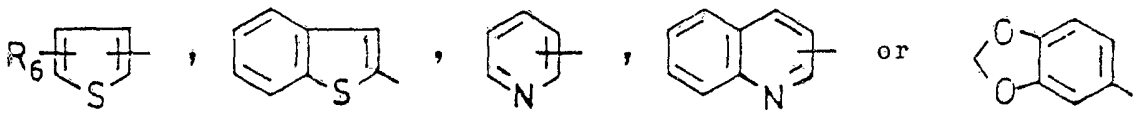
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a) a mono- or binuclear aromatic radical being a member of the group comprising radicals of the formulae



wherein R_5 represents hydrogen, a straight chain or branched alkyl, alkoxy or alkylmercapto group containing 1 to 4 carbon atoms, a benzyloxy group, a fluorine or chlorine atom or a trifluoro methyl group and n represents a number 1, 2 or 3, or

b) a mono- or binuclear heterocyclic radical containing sulfur nitrogen or oxygen and being a member of the group comprising radicals of the formulae



wherein R_6 represents a hydrogen or a chlorine atom or a methyl group

and the stereoisomeres and optically active forms of the substituted phenylacetylenes of formula I.

32. A method for the treatment or prophylaxis of conditions indicating inhibition of 5-lipoxygenase in a mammal requiring said treatment or prophylaxis, which method comprises administering to said mammal an effective amount of at least one compound according to any one of claims 1 to 13 or 29 or 31, or of a composition according to any one of claims 14 to 20.

33. A method for the treatment or prophylaxis of asthma or anaphylactic shock in a mammal requiring said treatment or prophylaxis, which method comprises administering to said mammal an effective amount of at least one compound according to any one of claims 1 to 13, 29 or 31 or of a composition according to any one of claims 14 to 20.

637513

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AUSTRALIA

PATENTS ACT 1990

COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

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Invention Title: Substituted Phenylacetylenes, Pharmaceutical Compositions Containing These Compounds and Processes for the Preparation of These Compounds and Compositions

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

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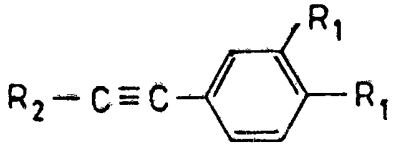
Substituted phenylacetylenes, pharmaceutical compositions containing these compounds and processes for the preparation of these compounds and compositions.

Polyunsaturated higher fatty acids such as arachidonic acid in the metabolism of mammals, including man, serve as substrates for the formation of physiologically important eicosanoids such as prostaglandins and leukotrienes (a group of compounds also known as "Slow Reacting Substance of Anaphylaxis" or "SRS-A"). The pathway to prostaglandins is catalyzed by cyclo-oxygenase (also named "prostaglandin synthetase") whereas the pathway to leukotrienes is catalyzed by 5-lipoxygenase.

The prostaglandins are products of known beneficial functions in mammals while it is known for the leukotrienes or SRS-A, respectively, that they cause allergic reactions, bronchoconstrictions, inflammations, asthma and numerous other harmful effects. Accordingly there is a need for chemically and metabolically stable agents which in the living organism have no effect on the biosynthesis of prostaglandins but inhibit selectively or specifically the activity of 5-lipoxygenase and thus prevent the formation of the undesired leukotrienes.

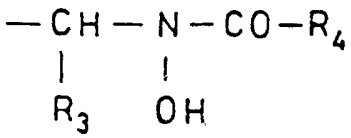
It now has been found that certain substituted phenylacetylenes, which are chemically and (when used as therapeutics) metabolically stable compounds, show a specific inhibiting effect on 5-lipoxygenase and are especially suitable for use as antiasthmatics as well as in treatment of anaphylactic shock.

These new substituted phenylacetylenes correspond to the general formula:



I

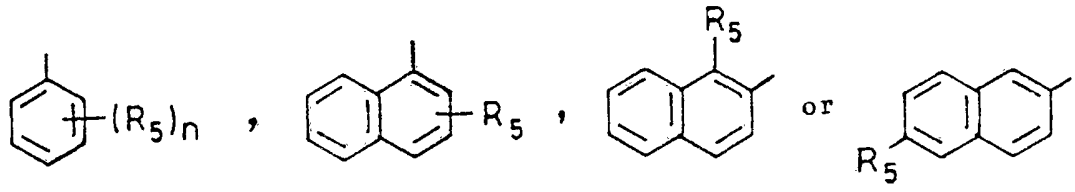
In this formula one of the symbols R_1 represents a hydrogen atom while the other represents the group of the formula



wherein R_3 is hydrogen, methyl or ethyl and R_4 represents methyl or an amino group.

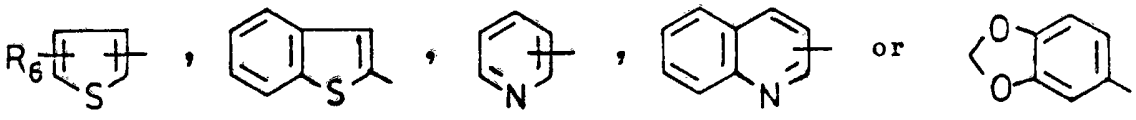
In formula I R_2 represents

a) a mono- or binuclear aromatic radical being a member of the group comprising radicals of the formulae



wherein R_5 represents hydrogen, a straight chain or branched alkyl, alkoxy or alkylmercapto group containing 1 to 4 carbon atoms, a benzyloxy group, a fluorine or chlorine atom or a trifluoro-methyl group and n represents a number 1, 2, or 3, or

b) a mono- or binuclear heterocyclic radical containing sulfur, nitrogen or oxygen and being a member of the group comprising radicals of the formulae

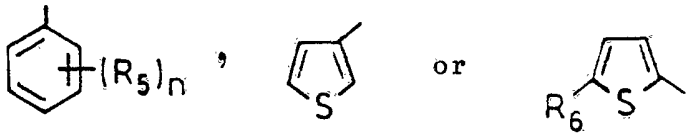


wherein R_6 is a hydrogen or a chlorine atom or a methyl group.

Especially in case that R_3 is methyl or ethyl the carbon atom bearing R_3 becomes an asymmetric center. Such center also results in case R_5 represents a 1-methyl propyl group (i.e. a sec.-butyl

group). It is to be understood that the present invention includes in such cases the enantiomeres as well as the stereoisomers and - especially in case only one asymmetric center is present - the racemates as well as the optically active forms of the compounds of formula I.

In preferred compounds of the invention R_2 represents one of the groups



wherein R_5, R_6 and n have the same meaning as above and R_5 preferably represents methoxy.

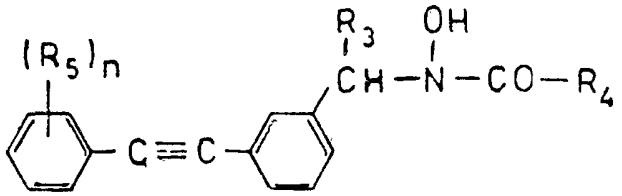
Out of this group of preferred compounds of the formula I such are especially preferred in which R_5 is a methoxy group in 3- and/or 4-position or a fluorine or chlorine atom in 4-position to the acetylene group and wherein n is a number 1 or 2, or such, respectively, in which R_6 is hydrogen.

In case R_2 represents a pyridine or quinoline group this group preferably in its 3-position is attached to the acetylene moiety.

R_3 preferably represents a methyl group.

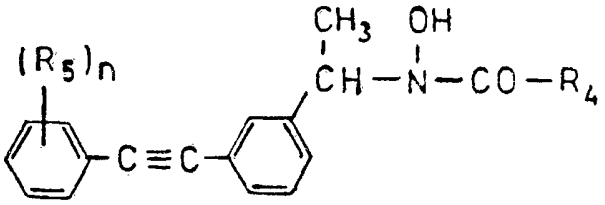
With respect to the position in which the group R_1 being different from hydrogen is attached to the phenyl ring the following applies:

In case R_2 is a mono- or binuclear optionally substituted aromatic radical as defined above as alternative "a", preferably a phenyl radical bearing 1 to 3 substituents R_5, the group R_1 preferably is attached to the phenyl ring in 3-position to the acetylene moiety. Such preferred compounds correspond to the formulae:



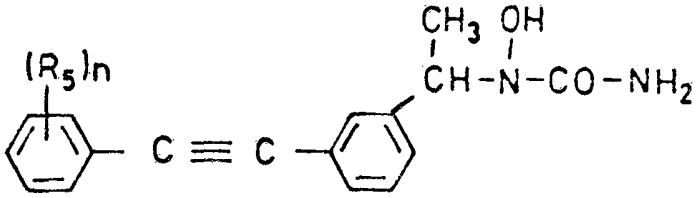
Ia

and especially



Ib

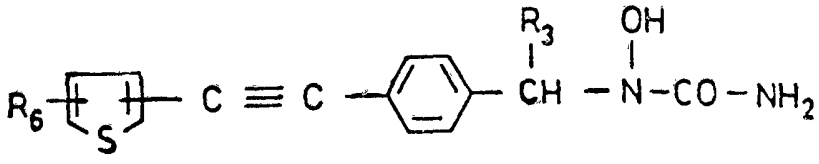
Preferably in these formulae (especially in formula Ib) R_4 represents the amino group:



Ic

In these formulae R_3, R_5 and n have the same meaning as above.

In case, however, R_2 represents a thienyl group (optinally substituted by the radical R_6), the group R_1 preferably is attached to the phenyl ring in 4-position to the acetylene moiety, in which case it furthermore is preferred that R_4 represents an amino group. Such preferred compounds correspond to the formula:



Id

wherein R_3 and R_6 have the same meaning as above.

As stated already hereinabove the compounds of formula I show a specific inhibiting effect on 5-lipoxygenase. This was determined e.g. by in-vitro experiments as follows:

To determine the inhibition of 5-lipoxygenase rat basophilic leukemia cells were cultured in vitro, harvested by centrifugation, washed with 50 mM potassium phosphate buffer of pH 7.4 and then suspended in this buffer at 1.5 x 10^7 cells/ml.

To 1 ml each of this suspension there was added indomethacin (10 µM) and calcium chlorid (2mM) and then the mixture was incubated in presence or absence of a test compound for 3 minutes and thereafter with 20 µM of [^{14}C]-arachidonic acid and 20 µM of the calcium ionophore A 23 187 for 10 minutes. The reaction was stopped by adding 20 µl of glacial acetic acid and then the mixture was extracted with ethyl acetate to isolate the metabolites of arachidonic acid formed by the enzymatic action of 5-lipoxygenase. These were separated by thin layer chromatography using a solvent mixture known to be suitable for leukotriene analysis [c.f. Jakschik et al., Biochem. Biophys. Res. Commun. 102, 624 (1981)]. The distribution of the radioactivity to the different metabolites was measured using a TLC Linear Analyzer. By bringing into relationship the percentages of the amount of the products formed under the action of 5-lipoxygenase (5-HETE, isomers of LTB_4) in the controls (tests performed in absence of test compounds) and in the presence of test compounds of formula I in different concentrations the "IC_{50}-value" (i.e. the concentration of the test compound which causes an 50 %-inhibition of the 5-lipoxygenase) is determined. For standardization these values then were brought into relationship to the IC_{50}-values determined in the same manner for the standard compound nordihydroguaiaretic acid. These standardized "IC_{50}-values (A)" are given in table 1.

The effect of the test compounds on the activity of cyclooxygenase was tested using a suspension of sheep seminal vesicles microsomes in 50 mM potassium phosphate buffer of pH 7.0 which was incubated with the solvent only (as control) or with the test compound and [^{14}C]-arachidonic acid. The "IC_{50}-values (B)" (i.e. the concentration of the test compound which causes an 50 %-inhibition of the cyclooxygenase) were determined by thin layer chromatography and by means of a TLC-Linear-Analyzer.

Thus for instance the following IC_{50} values were determined for the products of the examples listed in table I from which the quotient $\frac{IC_{50}\ (B)}{IC_{50}\ (A)}$ was then calculated.

Table 1

Example	IC_{50} [µM] for inhibition of 5-lipoxygenase (A)	cyclooxygenase (B)	Quotient
1	0,67	> 500	> 746
5a	0,29	440	1517
5b	0,28	> 500	>1786
5c	0,58	> 500	> 862
7	0,65	> 500	> 769
9	0,15	100	667
10b	0,69	> 500	> 725
10c	0,27	> 500	>1852
10d	0,55	500	909
10g	0,32	270	844
10m	0,26	> 500	>1923
10n	0,18	> 500	>2778
11	0,67	> 500	> 746
15	0,41	500	1220
16b	0,29	500	1724
16d	0,37	500	1351
16f	0,41	500	1220

As can be seen from this table the IC_{50}-values for the inhibition of cyclooxygenase often are more than 1000 times higher than the IC_{50}-values for 5-lipoxygenase inhibition. These results show that the test substances of formula I very specifically only inhibit the activity of 5-lipoxygenase.

The bioavailability of the compounds of formula I after oral administration was characterized by means of an ex vivo biochemical

assessment method described by Tateson et al. in Brit. Pharmacol., 94, 528 (1988).

Compounds of formula I were orally administered to male rats (Wistar strain). 1 hour later the rats were bled by heart puncture in letal CO_2-narcosis. The 5-lipoxygenase reaction was triggered by the addition of the calcium-ionophor A23187 to an end concentration of 15 µg/ml to aliquotes of rat whole blood and subsequent incubation for 30 minutes at 37° C in a water bath. At the end of the incubation the samples were centrifuged to collect the cell free plasma. The concentration of the immunoreactive LTB_4 ($iLTB_4$ ng/ml) in each plasma sample was determined by a LTB_4-radioimmunoassay (^3H-LTB_4-RIA, Amersham) by means of a LTB_4-standard curve in diluted rat plasma. For calculation of the percent inhibition of ex vivo $iLTB_4$-formation in whole blood of rats treated with the compounds of formula I rats treated with appropiate vehicle solution were included in all experiments, aliquotes of their blood were run in parallel and were processed in the same way as described. The mean $iLTB_4$-formation per ml plasma of these vehicle treated control rats served as 100 percent value of normal control 5-lipoxygenase activity. The percent inhibition of the ex vivo $iLTB_4$-formation after oral administration of compounds of formula I was calculated as follows: 100 minus 100 times the quotient of the mean $iLTB_4$ concentration per ml plasma of the rats treated with compounds of formula I and the mean $iLTB_4$ concentration per ml plasma of the rats treated with compounds of formula I and the mean $iLTB_4$ concentration per ml plasma of the control rats.

Table 2 shows the resulting percent inhibition of the ex vivo $iLTB_4$-formation after oral administration of 21.5 mg/kg of compounds of formula I:

Table 2

Example	% Inhibition	Example	% Inhibition
2a	76 %	10d	99 %
5a	75 %	10e	81 %
5c	88 %	11	76 %
5e	82 %	12	87 %
7	90 %	15	77 %
8b	99 %	16b	91 %
10b	86 %	16f	97 %

In this assay the product of Example 9 already after oral administration of a dose of 10 mg/kg exerted a 86 % inhibition of the ex vivo $iLTB_4$-formation.

As a test model to evaluate the effects of test compounds in septic shock the endotoxin/galactosamine-induced hepatitis in mice has been used. In this model, the intravenous injection of 0.3 mg/kg endotoxin (lipopolysaccharide from S. abortus equi) in combination with 700 mg/kg galactosamine induces a hepatitis in conscious mice, that is demonstrated 8 hours after the application of endotoxin by an increase of liver specific enzymes (glutamate-pyruvate-transaminase, GPT; sorbitol-dehydrogenase, SDH) in the serum. The intraperitoneal application of 5-lipoxygenase inhibitors 30 minutes before, simultaneously with and 2, 4 and 6 hours after the application of endotoxin inhibitis the hepatitis-induced increase of the serum activities of these enzymes. On administration of compounds of the formula I in doses of 10 mg/kg for each of the five applications the following percentual inhibitions of the increase of the enzymes GPT and SDH were achieved (the increase of enzymatic activities in control animals was set 100 %):

Table 3:

Example	Inhibition of increase of GPT	SDH
1	47	58
4	87	81
9	94	90

The antiasthmatic activity of compounds of formula I was tested in narcotised and ventilated guinea pigs. For the induction of an asthmatic reaction, the animals were passively sensitized by a single intraperitoneal injection of anti-ovalbumin serum. 48 hours afterwards the asthmatic reaction was elicited by intravenous challenge with 0.2 mg/kg ovalbumin. The immediately resulting bronchoconstriction was measured as increase in overflow according to the Konzett-Rössler method for a period of 10 minutes. Effects caused by histamine, serotonin and sympathic counterreaction were eliminated by intravenous pretreatment with 2.15 mg/kg mepyramine, 46.4 µg/kg propranolol, 4.64 mg/kg atropin and 1 mg/kg methysergide, all given 5 minutes before challenge.

After oral application of the product of Example 5a or of the product of Example 9, in doses of 100 mg/kg each, the bronchoconstriction was inhibited by 54 % or by 67 %, respectively.

Due to their favourable effect on the metabolism of polyunsaturated fatty acids, particularly their selective inhibitory action on the 5-lipoxygenase induced production of metabolites of arachidonic acid such as 5-hydroxyperoxyeicosatetraenoic acid (5-HPETE), 5-hydroxyeicosatetraenoic acid (5-HETE) or SRS-A, respectively, the new compounds of formula I exhibit various physiologically valuable actions such as antianaphylactic, antiasthmatic, antiallergic, antiphlogistic, blood pressure lowering and cerebral- and coronary-circulation improving effects, decreasing the risc of leukocyte aggregation and preventing the formation of leukocyte thrombi and other actions. Due to their chemical and metabolical

stability in therapeutical application the compounds of formula I according to the invention are storable and suitable for use as medicaments such as antianaphylactics, antiasthmatics, antiallergics, antiphlogistics, antihypertensive agents, antithrombotic agents, agents for use in treatment or prophylaxis of ischemic myocardial infarction, disorders of coronary and/or cerebral arteries and others.

The compounds of formula I have a low degree of toxicity which is observed only at far higher doses than those to be administered for therapeutic or prophylactic purposes. Accordingly these compounds can be administered to human and animal patients, preferably in form of suitable pharmaceutical compositions.

Further objects of the invention accordingly are medicaments containing one or more of the substituted phenylacetylenes according to the invention. The dosage of the active component to be administered to a patient depends, for instance, on the patients body weight, on the administration route and form, on the indication and on the state of disease in the individual patient to be treated. In consideration of these factors in general an unit dosage form of a medicament according to the present invention contains about 0.01 to 50 mg of the active ingredient whereby compositions for parenteral administration preferably contain about 0.01 to 10 mg and those for oral or rectal administration preferably contain about 0.1 to 50 mg.

The medicaments for parenteral application may be solutions or suspensions but may also be dry formulations suitable for easy reconstitution.

Spray forms are very useful application forms for intranasal or oral applications of the compounds of formula I or for the administration of these substances to the bronchia.

Compositions for oral administration such as tablets, dragees, capsules, granules, drops and syrups are very suitable for prophylactic or therapeutic application of the compounds of formula I

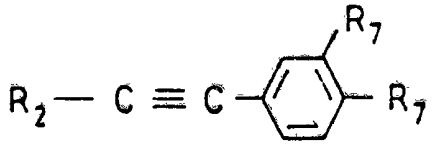
in several cases. Ohter compositions such as suppositories or compositions for percutaneous application of the compounds of formula I, such as plasters or the like containing a solution of the active ingredient and optionally a known membrane penetration enhancer (such as an N-alkyl lactam) are also very convenient in many cases.

The pharmaceutical compositions described above for peroral, rectal, percutaneous or intramuscular administration of the compounds of formula I preferably may be such from which at least a portion of the active ingredient has a delayed release. Thus for a longer period of time, for instance 24 hours, a steady supply of the active ingredient to the patient can be achieved.

All of the pharmaceutical compositions of the invention and their preparation in principle are known per se and as the compounds of formula I are chemically stable products their incorporation into pharmacuetical compositions in the form and dosage desired poses no problems or difficulties for an ordinarily skilled pharmacist. In their production according to the invention conventionally used inorganic or organic adjuvants such as diluents, carriers, binders, lubricants, colors, flavorings etc. are formulated together with the active ingredient of formula I in accordance with accepted standards in a manner known per se. It should be mentioned that the compositions for parenteral use have to be sterile and, if prepared in liquid form, in isotonic condition.

The process for the manufacture of the compounds of formula I according to the invention comprises

i) reacting a compound of the formula

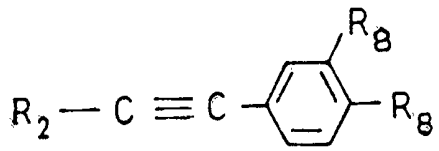


II

wherein R_2 has the same meaning as above and in which one of the symbols R_7 represents a hydrogen atom while the other

represents the group $-COR_3$ in which R_3 is as defined above,

with hydroxylamine or with a salt thereof to form the oxime which then is reducted to a compound of the formula



III

wherein R_2 has the same meaning as above and in which one of the symbols R_8 represents a hydrogen atom while the other represents the group of the formula

$$-CH(R_3)-NH-OH$$

This reaction is performed in a manner known per se for instance in alcoholic or aqueous-alcoholic solution in presence of suitable bases such as e.g. pyridine, potassium carbonate or sodium acetate and the like at temperatures of about 20° to 60° C.

The reduction is performed by means of boron hydrides, preferably sodium cyanoborohydride, in presence of acids such as acetic acid or ethanolic hydrochloric acid at temperatures of e.g. 20° C to 60° C or in alcoholic solution with borane-amine complexes, such as e.g. the borane-pyridine complex, or with the borane-tetrahydrofuran complex each time in presence of an acid, e.g. 6 n hydrochloric acid at temperatures from about 0° C up to about 20° C (c.f. J.B. Summers et al., J. Med. Chem. 31 1960 (1988) and other publications).

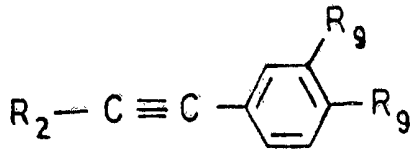
The hydroxylamine derivative of formula III is transformed into the respective compound of formula I by introducing the acyl group of the formula $-COR_4$.

To prepare compounds of formula I in which R_4 represents the amino group (NH_2; N-hydroxy ureas) the compound of formula III is reacted with trimethylsilyl isocyanate in presence of

inert solvents, preferably cyclic ethers such as tetrahydrofuran or 1,4-dioxane, while warming to temperatures between about 20° C and the boiling temperature of the solvent. The thus formed intermediate then is hydrolyzed to split off the trimethylsiyl group, e.g. by treatment with a saturated aqueous solution of ammonium or sodium chloride to obtain the desired compound of formula I in which R_4 is NH_2.

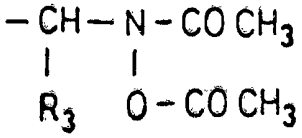
Alternatively such compound of formula I with $R_4 = NH_2$ may also be obtained by reacting a compound of formula III either with sodium or potassium cyanate in an acidic solution or with phosgene or a lower alkyl or benzyl chloroformate in presence of an agent capable of binding acids, such as sodium or potassium carbonate, followed by a treatment with ammonia or e.g. ammonium carbonate.

To prepare compounds of formula I in which R_4 represents the methyl group (acetohydroxamic acids) the compound of formula III, optionally without isolation from the reaction mixture in which it was prepared, is reacted with an acetylating agent, preferably with acetic anhydride or acetyl chloride, in presence of an agent capable of binding acids, such as pyridine or quinoline, whereby a compound of formula



IV

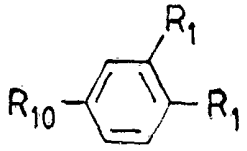
wherein one of the symbols R_9 represents a hydrogen atom whereas the other represents the group of the formula



is formed. On selective hydrolysis in presence of an alcoholic solvent such as methanol or ethanol containing a base at temperatures of about 20° C to 60° C the O-acetyl group is split off and the desired compound of formula I in which R_4 is

methyl is obtained. Suitable bases for this hydrolysis are e.g. 0.1 n to 1 n potassium, sodium or lithium hydroxide which optionally may be added in form of aqueous solutions to the alcoholic solution of the compound of formula IV.

ii) The compounds of formula I may furthermore prepared by reacting a compound of the formula



V

wherein R_1 has the same meaning as above and R_{10} represents a bromine or iodine atom

with a compound of the formula

$$R_2 - C \equiv CH \qquad VI$$

wherein R_2 is as defined above

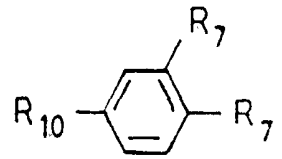
in the presence of a secondary or tertiary amine, which is liquid in the temperature range of about 0° C to 80° C, especially a dialkyl or trialkyl amine containing 2 or 3 carbon atoms in each alkyl group or pyrrolidine or piperidine, and in the presence of catalytic amounts of a complex palladium catalyst, such as bis-(triphenylphosphine)-palladium-(II) chloride or acetate or tetrakis-(triphenylphosphine)palladium and optionally catalytic amounts of copper(I)iodide at about 20° C to 80° C. The term "catalytic amount" means an amount of about 0.01 to 5 percent per mole of the compound of formula VI used.

The starting materials of formulae II or V, respectively, are obtained in a manner known per se.

For instance the compounds of formula II may be obtained in a

high yield by reacting

- a compound of formula VI with a compound of the formula

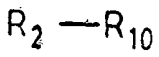


VII

wherein R_7 and R_{10} have the same meanings as above

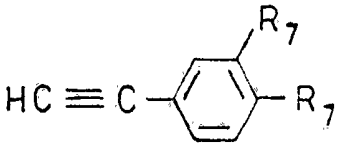
or

- a compound of the formula



VIII

with a compound of the formula



IX

wherein R_2, R_7 and R_{10} have the same meanings as above

under the conditions described above for the reaction of a compound of formula V with a compound of formula VI.

To prepare a starting compound of formula V a compound of formula VII may be reacted with hydroxylamine or a salt thereof followed by reduction of the oxime formed to the corresponding hydroxylamine derivative and finally introducing the group $-COR_4$ in a manner analogous to that described above (in i) for the preparation of a compound of formula I starting with a compound of formula II.

The following non-limitating examples serve further to illustrate the invention, especially the processes for the preparation of the compounds of formula I, the starting materials and the intermediates used in these processes. No importance was attached to obtain maximum yields.

All temperature references are uncorrected.

The ^{1}H-nuclear magnetic spectra were measured at 300 MHz. The chemical shifts are reported in ppm.

The term "ether" as used in the examples means diethyl ether and the term "petroleum ether" indicates that fraction having a boiling range of 50° C to 70° C unless otherwise mentioned.

In column chromatography, silica gel ("Kieselgel 60, 0.040 - 0.063 mm of E. Merck AG, Darmstadt, Germany) was used as the stationary phase unless otherwise indicated.

The reactions in most instances were monitored by thin layer chromatography on plates precoated with silica gel ("HPTLC Fertigplatten, Kieselgel 60 F 254" of E. Merck AG, Germany). In these cases the solvents used are indicated in the examples by "(TLC: ...)".

The ratio of the components of the solvent mixtures used in all of the chromatographic procedures is given in volume/volume.

Example 1

N-[3-(Naphth-2-yl-ethynyl)-benzyl]-acetohydroxamic acid

a) 3-(Naphth-2-yl-ethynyl)-benzaldehyde

To a solution of 15.3 g of naphth-2-yl-acetylene and 16.65 g of 3-bromobenzaldehyde in 120 ml of absolute triethylamine were added at a bath temperature of 50° C while stirring in an atmosphere of dry nitrogen 1.05 g of bis-(triphenylphosphine)-palladium(II) chloride and 0.07 g of copper(I) iodide. Then the mixture was stirred at a bath temperature of 70 - 80° C (TLC: petroleum ether/ether - 5 : 1). When the reaction was finished the mixture was filtered, the residue washed with ethyl acetate and then the filtrates were evaporated in a vacuum. By column chromatography with petroleum ether/ether (4 : 1) the residue is purified to yield 15.1 g (65.5

% of the theoretical yield) of the title compound in the form of crystals melting at 90 - 92° C.

^{1}H-NMR ($CDCl_3$): 7.50 - 7.61 (m, 4H, aromat.); 7.81 - 7.88 (m, 5H, aromat.); 8.08 (s, 2H, aromat.); 10.02 (s, 1H, CHO)

b) 3-(Naphth-2-yl-ethynyl)-benzaldehyde oxime

To a solution of 15 g of the product obtained in Example 1a in 80 ml of methanol was added a solution of 6.08 g of hydroxylamine hydrochloride and of 5.63 g of sodium acetate in 80 ml of water. The mixture was stirred at a bath temperature of 60° C (TLC: petroleum ether/ether - 4 : 1). When the reaction was complete the methanol was evaporated and the aqueous residue extracted twice with ethyl acetate. The extracts were washed with water, then with saturated sodium chloride solution. After drying and evaporating in a vacuum 15.4 g (97.2 % of the theoretical yield) of the title compound were obtained in form of a sand-colored powder (mixture of isomers). E-isomer:

^{1}H-NMR ($CDCl_3$): 7.34 - 7.43 (m, 1H, aromat.); 7.51 - 7,61 (m, 5H, aromat.); 7.78 - 7.86 (m, 4H, aromat.); 8.07 (s, 1H, aromat.); 8.12 (s, 1H, N=CH)

c) N-[3-(Naphth-2-yl-ethynyl)-benzyl]-acetohydroxamic acid

To a solution of 15.3 g of the product obtained in Example 1b in 170 ml of glacial acetic acid were added while stirring at a bath temperature of 50 - 55° C in an atmosphere of dry nitrogen in small portions 4.45 g of sodium cyanoborohydride. After stirring for an additional hour the mixture was allowed to cool and, after adding 13.4 ml of acetic anhydride stirred for further 12 hours. Then the mixture was evaporated in a vacuum, the residue diluted with water and extracted three times with ethyl acetate. The extracts were washed twice each with saturated solutions of sodium hydrogen carbonate and of sodium chloride, and then dried over sodium sulfate. By chromatography with petroleum ether/ether (1 : 1) of the residue obtained on evaporation the O,N-diacetylated intermediate (a compound of the general formula IV) was iso-

lated which then was dissolved in 100 ml of methanol. After adding 100 ml of a 10 % aqueous solution of sodium carbonate the mixture was heated, while stirring, for two hours in a bath at 60° C. The residue obtained on evaporation in a vacuum was recrystallized from ethyl acetate/hexane to yield 11.14 g (62,6 % of the theoretical yield) of the title compound in the form of colorless crystals melting at 144 - 146° C.

^{1}H-NMR (DMSO-d_6): 2.21 (s, 3H, $NCOCH_3$); 4.81 (s, 2H, NCH_2); 7.34 - 7.36 (m, 2H, aromat.); 7.50 - 7.58 (m, 5H, aromat.); 7.81 - 7.84 (m, 3H, aromat.); 8.05 (s, 1H, aromat.)

Example 2

Proceeding as described in Examples 1a - 1c but using the appropriate reactants there were obtained:

a) N-{1-[4-(Phenylethynyl)-phenyl]-ethyl}-acetohydroxamic acid

Melting point: 137 - 138° C

^{1}H-NMR (DMSO-D_6): 1.45, 1.48 (d, 3H, $NCCH_3$); 2.03 (s, 3H, $NCOCH_3$); 5.58 - 5.72 (m, 1H, NCH); 7.32 - 7.58 (m, 9H, aromat.)

b) N-[3-(Naphth-1-yl-ethynyl)-benzyl]-acetohydroxamic acid

Melting point: 98 - 100° C

^{1}H-NMR (DMSO-d_6): 2.08 (s, 3H, $NCOCH_3$); 4.75 (s, 2H, NCH_2); 7.32 - 7.74 (m, 7H, aromat.); 7.83, 7.85 (d, 1H, aromat.); 7.95 - 8.05 (m, 2H, aromat.); 8.35, 8.38 (d, 1H, aromat.)

c) N-{1-[3-(4-Trifluoromethyl-phenylethynyl)-phenyl]-ethyl}-acetohydroxamic acid

Melting point: 97 - 98° C

^{1}H-NMR (DMSO-d_6): 1.47, 1.49 (d, 3H, $NCCH_3$); 2.03 (s, 3H, $NCOCH_3$); 5.58 - 5.69 (m, 1H, NCH); 7.40 - 7.53 (m, 4H, aromat.); 7.78 (s, 4H, aromat.)

d) N-{1-[3-(2,4,6-Trimethyl-phenylethynyl)-phenyl]-ethyl}-acetohydroxamic acid

Melting point: 45 - 47° C

^{1}H-NMR (DMSO-d_6): 1.46, 1.49 (d, 3H, $NCCH_3$); 2.03 (s, 3H, $NCOCH_3$); 2.27 (s, 3H, CH_3); 2.42 (s, 6H, CH_3); 5.57 - 5.68 (m, 1H, NCH); 6.95 (s, 2H, aromat.); 7.32 - 7.45 (m, 4H, aromat.)

Example 3

N-[3-(Phenylethynyl)-benzyl]-acetohydroxamic acid

a) 3-(Phenylethynyl)-benzaldehyde oxime

The procedure was the same as described in Example 1b, except there were used 16.5 g of 3-(phenylethynyl)-benzaldehyde, 8.3 g of hydroxylamine hydrochloride and 8.2 g of sodium acetate to give 16.8 g (94.8 % of the theoretical yield) of the title compound in form of a yellowish powder (mixture of isomers).

b) N-[3-(Phenylethynyl)-benzyl]-acetohydroxamic acid

Following the procedure described in Example 1c 11.95 g of the product obtained in Example 3a were reduced with 5.09 g of sodium cyanoborohydride and the reaction mixture then was treated with 12.8 ml of acetic anhydride. The intermediate thus obtained was reacted as described in Example 1c to yield 9.48 g (66.2 % of the theoretical yield) of colorless crystals of the title compound melting at 91 - 93° C.

^{1}H-NMR (DMSO-d_6): 2.08 (s, 3H, $NCOCH_3$); 4.72 (s, 2H, NCH_2); 7.30 - 7.37 (m, 1H, aromat.); 7.40 - 7.48 (m, 6H, aromat.); 7.54 - 7.58 (m, 2H, aromat.)

c) The product obtained in Example 3b may also be prepared as follows:

i) 3-Bromobenzyl-acetohydroxamic acid

4.0 g of 3-bromobenzaldehyde oxime are reacted following the procedure described in Example 1c with 1.8 g of sodium cyanoborohydride and thereafter with 3.8 ml of acetic anhydride. The intermediate thus obtained is treated with aqueous sodium carbonate solution to yield the title compound (3.32 g = 67.9 % of the theoretical yield) as an almost colorless powder melting at 63 - 64° C.

^{1}H-NMR ($CDCl_3$): 2.18 (s, 3H, $NCOCH_3$); 4.78 (s, 2H, NCH_2); 7.20 - 7.50 (m, 4H, aromat.)

ii) N-[3-(Phenylethynyl)-benzyl]-acetohydroxamic acid

Following the procedure described in Example 1a 2.2 g of the product obtained in Example 3c)i) were reacted with 1.65 ml of phenylacetylene in 30 ml of absolute triethylamine in presence of 0.21 g of bis-(triphenylphosphine)palladium(II) chloride and 0.02 g of copper(I) iodide. The crude product was purified by HPLC with methanol/water (4 : 1), followed by recrystallization from ethyl acetate/n-hexane to yield 0.98 g (41.2 % of the theoretical yield) of the title compound the physical and spectroscopic data of which are identical to those of the product obtained according to Example 3b.

Example 4

N-[3-(4-Methoxy-phenylethynyl)-benzyl]-acetohydroxamic acid

a) 3-(4-Methoxy-phenylethynyl)-benzaldehyde

4-Methoxyphenylacetylene was reacted with 3-bromobenzaldehyde in the manner described in Example 1a to yield the title compound in form of white crystals melting at 52 - 53° C.

^{1}H-NMR ($CDCl_3$): 3.84 (s, 3H, OCH_3); 6.88 - 6.91 (m, 2H, aromat.); 7.44 - 7.53 (m, 3H, aromat.); 7.73 - 7.76 (m, 1H, aromat.); 7.80 - 7.83 (m, 1H, aromat.); 8.00 - 8.02 (m, 1H, aromat.); 10.02 (s, 1H, CHO)

b) 3-(4-Methoxy-phenylethynyl)-benzaldehyde oxime

The procedure was the same as described in Example 1b, except there were used a solution of the product obtained in Example 4a in ethanol and pyridine (instead of sodium acetate as base) and then hydroxylamine hydrochloride was added. The crude product was purified by chromatography with petroleum ether/ethyl acetate (3 : 1) to yield 10.67 g (93.8 % of the theoretical yield) of the title compound. Light yellow crystals melting at 90 - 91° C.

^{1}H-NMR ($CDCl_3$): 3.83 (s, 3H, OCH_3); 6.87 - 6.90 (m, 2H, aromat.); 7.33 - 7.38 (m, 1H; aromat.); 7.45 - 7.55 (m, 4H, aromat.); 7.70, 7.71 (d, 1H, aromat.); 8.12 (s, 1H, N=CH)

c) N-Acetoxy-N-[3-(4-methoxy-phenylethynyl)-benzyl]-acetamide

Following the procedure described in Example 1c 10.23 g of the product obtained in Example 4b were dissolved in 120 ml of glacial acetic acid and reacted with 3.84 g of sodium cyanoborohydride, thereafter with 8.8 ml of acetic anhydride. The crude product was purified by chromatography with ethyl acetate/petroleum ether (1 : 1) to yield 9.98 g (72.2 % of the theoretical yield) of the title compound in form of a colorless oil.

^{1}H-NMR ($CDCl_3$): 2.13 (s, 3H, $NCOCH_3$); 2.20 (s, 3H, $NOCOCH_3$); 3.82 (s, 3H, OCH_3); 4.86 (s, 2H, NCH_2); 6.85 - 6.90 (m, 2H, aromat.); 7.22 - 7.34 (m, 2H, aromat.); 7.42 - 7.49 (m, 4H, aromat.)

d) N-[3-(4-Methoxy-phenylethynyl)-benzyl]-acetohydroxamic acid

To a solution of 1.0 g of the product obtained in Example 4c in

10 ml of methanol 0.205 g of anhydrous potassium carbonate were added while stirring at room temperature. When the reaction was finished (TLC: ethyl acetate/petroleum ether - 1 : 1) the mixture was acidified by adding 5 % hydrochloric acid and diluted with ethyl acetate. The organic layer was separated, washed with water and evaporated in a vacuum. The remaining oil solidified to white crystals on drying over phosphorus pentoxide in an exsiccator. Thus 0.853 g (97.6 % of the theoretical yield) of the title compound melting at 124 - 126° C were obtained.

^{1}H-NMR ($CDCl_3$): 2.17 (s, 3H, $NCOCH_3$); 3.82 (s, 3H, OCH_3); 4.79 (s, 2H, NCH_2); 6.86 - 6.89 (m, 2H, aromat.); 7.24 - 7.55 (m, 6H, aromat.)

Example 5

By using the appropriate reactants and otherwise proceeding as described in Examples 4a - 4d there were obtained:

a) N-{1-[3-(4-Methoxy-phenylethynyl)-phenyl]-ethyl}-acetohydroxyamic acid

Colorless viscous oil

^{1}H-NMR (DMSO-d_6): 1.46, 1.48 (d, 3H, $NCCH_3$); 2.03 (s, 3H, $NCOCH_3$); 3.79 (s, 3H, OCH_3); 5.61 - 5.63 (m, 1H, NCH); 6.95 - 6.99 (m, 2H, aromat.); 7.32 - 7.52 (m, 6H, aromat.)

b) N-{1-[3-(3,4-Dimethoxy-phenylethynyl)-phenyl]-ethyl}-acetohydroxamic acid

Melting point: 107 - 108° C

^{1}H-NMR (DMSO-d_6): 1.45, 1.48 (d, 3H, $NCCH_3$); 2.02 (s, 3H, $NCOCH_3$); 3.79 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 5.53 - 5.69 (m, 1H, NCH); 6.96 - 6.99 (m, 1H, aromat.); 7.10 - 7.14 (m, 2H, aromat.); 7.31 - 7.45 (m, 4H, aromat.)

c) N-{1-[3-(3-Methoxy-phenylethynyl)-phenyl]-ethyl}-acetohydroxamic acid

Colorless viscous oil

^{1}H-NMR ($CDCl_3$): 1.53 - 1.56 (d, 3H, $NCCH_3$); 2.15 (s, 3H, $NCOCH_3$); 3.82 (s, 3H, OCH_3); 4.99 - 5.18 and 5.78 - 5.89 (m, 1H, NCH); 6.88 - 6.92 (m, 1H, aromat.); 7.05 - 7.14 (m, 2H, aromat.); 7.23 - 7.54 (m, 5H, aromat.)

d) N-{1-[4-(3,4-Dimethoxy-phenylethynyl)-phenyl]-ethyl}-acetohydroxamic acid

Melting point: 123 - 124° C

^{1}H-NMR (DMSO-d_6): 1.45, 1.47 (d, 3H, $NCCH_3$); 2.03 (s, 3H, $NCOCH_3$); 3.79 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 5.62 - 5.64 (m, 1H, NCH); 6.95 - 6.98 (m, 1H, aromat.); 7.07 - 7.12 (m, 2H, aromat.); 7.32 - 7.35 (m, 2H, aromat.); 7.45 - 7.48 (m, 2H, aromat.)

e) N-[3-(4-Isopropyl-phenylethynyl)-benzyl]-acetohydroxamic acid

Melting point: 120 - 122° C

^{1}H-NMR (DMSO-d_6): 1.20 - 1.23 (d, 6H, $C(CH_3)_2$); 2.07 (s, 3H, $NCOCH_3$); 2.87 - 2.96 (m, 1H, $CH(C)_2$); 4.70 (s, 2H, NCH_2); 7.26 - 7.48 (m, 8H, aromat.)

f) N-{1-[3-(4-Isopropyl-phenylethynyl)-phenyl]-ethyl}-acetohydroxamic acid acid

Colorless viscous oil

^{1}H-NMR (DMSO-d_6): 1.20, 1.22 (d, 6H, $C(CH_3)_2$); 1.46, 1.48 (d, 3H, $NCCH_3$); 2.02 (s, 3H, $NCOCH_3$); 2.87 - 2.97 (m, 1H, $CH(C)_2$); 5.55 - 5.69 (m, 1H, NCH); 7.27 - 7.49 (m, 8H, aromat.)

g) N-{1-[3-(4-Methoxy-naphth-1-yl-ethynyl)-phenyl]-ethyl}-acetohydroxamic acid

Melting range: 70 - 75° C

^{1}H-NMR (DMSO-d_6): 1.51, 1.53 (d, 3H, $NCCH_3$); 2.07 (s, 3H, $NCOCH_3$); 4.03 (s, 3H, OCH_3); 5.63 - 5.76 (m, 1H, NCH); 7.01, 7.04 (d, 1H, aromat.); 7.38 - 7.45 (m, 2H, aromat.); 7.55 - 7.80 (m, 5H, aromat.); 8.23 - 8.35 (m, 2H, aromat.)

h) N-{1-[4-(4-Methoxy-naphth-1-yl-ethynyl)-phenyl]-ethyl}-aceto-hydroxamic acid

Melting point: 139 - 142° C

^{1}H-NMR (DMSO-d_6): 1.47, 1.49 (d, 3H, $NCCH_3$); 2.03 (s, 3H, $NCOCH_3$); 4.03 (s, 3H, OCH_3); 5.59 - 5.72 (m, 1H, NCH); 7.01, 7.04 (d, 1H, aromat.); 7.37 - 7.40 (m, 2H, aromat.); 7.59 - 7.77 (m, 5H, aromat.); 8.21, 8.24 (d, 1H, aromat.); 8.29, 8.30 (d, 1H, aromat.)

i) N-{1-[3-(2-Methoxy-phenylethynyl)-phenyl]-ethyl}-acetohydroxamic acid

viscous material

^{1}H-NMR (DMSO-d_6): 1.46, 1.48 (d, 3H, $NCCH_3$); 2.03 (s, 3H, $NCOCH_3$); 3.86 (s, 3H, OCH_3); 5.57 - 5.70 (m, 1H, NCH); 6.94 - 6.99 (m, 1H, aromat.); 7.06 - 7.08 (d, 1H, aromat.); 7.35 - 7.49 (m, 6H, aromat.)

k) N-{1-[3-(2-Methoxy-napth-1-yl-ethynyl)-phenyl]-ethyl}-acetohydroxamic acid

Melting point: 138 - 140° C

^{1}H-NMR (DMSO-d_6): 1.49, 1.51 (d, 3H, $NCCH_3$); 2.04 (s, 3H, $NCOCH_3$); 4.02 (s, 3H, OCH_3); 5.65 - 5.67 (m, 1H, NCH); 7.37 - 7.64 (m, 7H, aromat.); 7.91, 7.94 (d, 1H, aromat.); 8.00, 8.03 (d, 1H, aromat.); 8.21, 8.24 (d, 1H, aromat.)

l) N-{1-[3-(3,4,5-Trimethoxy-phenylethynyl)-phenyl]-ethyl}-acetohydroxamic acid

Melting point: 145° C

^{1}H-NMR (DMSO-d_6): 1.46, 1.48 (d, 3H, $NCCH_3$); 2.03 (s, 3H, $NCOCH_3$); 3.70 (s, 3H, OCH_3); 3.82 (s, 6H, OCH_3); 5.58 - 5.63 (m, 1H, NCH); 6.85 (s, 2H, aromat.); 7.35 - 7.47 (m, 4H, aromat.)

m) N-{1-[3-(4-Methylphenylethynyl)-phenyl]-ethyl}-acetohydroxamic acid

viscous material

^{1}H-NMR (DMSO-d_6): 1.45, 1.48 (d, 3H, $NCCH_3$); 2.02 (s, 3H, $NCOCH_3$); 2.34 (s, 3H, CH_3); 5.61 - 5.63 (m, 1H, NCH); 7.22 - 7.25 (m, 2H, aromat.); 7.33 - 7.46 (m, 6H, aromat.)

n) N-[3-(2-Methoxy-phenylethynyl)-benzyl]-acetohydroxamic acid

viscous oil

^{1}H-NMR (DMSO-d_6): 2.19 (s, 3H, $NCOCH_3$); 3.98 (s, 3H, OCH_3); 4.83 (s, 2H, NCH_2); 7.08 - 7.13 (t, 1H, aromat.); 7.20, 7.23 (d, 1H, aromat.); 7.41 - 7.63 (m, 6H, aromat.)

o) N-[3-(4-Chlorophenylethynyl)-benzyl]-acetohydroxamic acid

Melting point: 149° C

^{1}H-NMR (DMSO-d_6): 2.06 (s, 3H, $NCOCH_3$); 4.70 (s, 2H, NCH_2); 7.31 - 7.60 (m, 8H, aromat.)

Example 6

N-Hydroxy-N-[3-(naphth-2-yl-ethynyl)-benzyl]-urea

2.07 g of the product obtained in Example 1b were dissolved in 20 ml of glacial acetic acid and reduced to the corresponding hydroxylamine by reacting with 0.60 g of sodiumcyanoborohydride in the manner described in Example 1c. To a solution of this reduction product in 25 ml of absolute dioxane 2.1 ml of trimethylsilylisocyanate were added and then the mixture was boiled for three hours under reflux. After cooling 50 ml of ethyl acetate were added followed by saturated ammonium chloride solution. The organic layer was separated, washed with saturated ammonium chloride solution and twice with saturated sodium chloride solution, dried over sodium sulfate and evaporated in a vacuum. The oily residue was purified by chromatography with ethyl acetate/petroleum ether (25 : 1) followed by recrystallization of the product from ethyl acetate/n-hexane. Thus 1.45 g (61.0 % of the theoretical yield) of the title compound were obtained in form of colorless crystals melting at 184 - 186° C.

^{1}H-NMR (DMSO-d_6): 4.57 (s, 2H, NCH_2); 6.44 (s, 2H, NH_2); 7.32 - 7.44 (m, 2H, aromat.); 7.48 - 7.65 (m, 5H, aromat.); 7.95 - 7.99 (m, 3H, aromat.); 8.21 (s, 1H, aromat.)

Example 7

N-Hydroxy-N-[3-(naphth-1-yl-ethynyl)-benzyl]-urea

5.43 g of 3-(naphth-1-yl-ethynyl)-benzaldehyde oxime were reduced in the manner described in Example 1c with 1.96 g of sodium cyanoborohydride. To a solution of the hydroxylamine compound thus obtained in 60 ml of absolute tetrahydrofuran 4 ml of trimethylsilylisocyanate were added and then the mixture was stirred for 4 hours at a bath temperature of 50° C. After working up and purifying in the manner described in Example 6 3.78 g (59.7 % of the theoretical yield) of the title compound were obtained which formed colorless crystals melting at 170 - 172° C.

^{1}H-NMR (DMSO-d_6): 4.59 (s, 2H, NCH_2); 6.44 (s, 2H, NH_2); 7.35 - 7.46 (m, 2H, aromat.); 7.55 - 7.73 (m, 5H, aromat.); 7.80 - 7.84 (m, 1H, aromat.); 7.98 - 8.02 (m, 2H, aromat.); 8.35 - 8.39 (m, 1H, aromat.)

Example 8

By using the appropriate reactants and otherwise proceeding as described in Examples 1 and 7 there were obtained:

a) N-Hydroxy-N-{1-[3-(4-methoxy-naphth-1-yl-ethynyl)-phenyl]-ethyl}-urea

Melting point: 162 - 164° C

^{1}H-NMR (DMSO-d_6): 1.45, 1.47 (d, 3H, $NCCH_3$); 4.03 (s, 3H, OCH_3); 5.29 - 5.40 (m, 1H, NCH); 6.37 (s, 2H, NH_2); 7.02, 7.05 (d, 1H, aromat.); 7.38 - 7.40 (m, 2H, aromat.); 7.50 - 7.80 (m, 5H, aromat.); 8.22 - 8.33 (m, 2H, aromat.)

b) N-Hydroxy-N-{1-[3-(4-fluorophenylethynyl)-phenyl]-ethyl}-urea

Melting point: 143 - 144° C

^{1}H-NMR (DMSO-d_6): 1.42, 1.44 (d, 3H, $NCCH_3$); 5.26 - 5.36 (m, 1H, NCH); 7.22 - 7.28 (m, 2H, aromat.); 7.32 - 7.43 (m, 3H, aromat.); 7.51 (s, 1H, aromat.); 7.59 - 7.64 (m, 2H, aromat.)

c) N-Hydroxy-N-{1-[3-(3,4-methylendioxy-phenylethynyl)-phenyl]-ethyl}-urea

Melting point: 153 - 155° C

^{1}H-NMR (DMSO-d_6): 1,42, 1,44 (d, 3H, $NCCH_3$); 5.26 - 5.35 (m, 1H, NCH); 6.08 (s, 2H, OCH_2O); 6.34 (s, 2H, NH_2); 6.93 - 6.96 (m, 1H, aromat.); 7.06 - 7.10 (m, 2H, aromat.); 7.30 - 7.39 (m, 3H, aromat.); 7.48 (s, 1H, aromat.)

d) N-Hydroxy-N-{1-[3-(4-tert-butyl-phenylethynyl)-phenyl]-ethyl}-urea

Melting point: 74 - 76° C

^{1}H-NMR (DMSO-d_6): 1,30 (s, 9H, t.-C_4H_9); 1.43, 1.45 (d, 3H, $NCCH_3$); 5.28 - 5.36 (m, 1H, NCH); 6.35 (s, 2H, NH_2); 7.31 - 7.55 (m, 8H, aromat.)

e) N-Hydroxy-N-{1-[3-(2,4,6-trimethyl-phenylethynyl)-phenyl]-ethyl}-urea

Melting point: 147 - 149° C

^{1}H-NMR (DMSO-d_6): 1.43, 1.45 (d, 3H, $NCCH_3$); 2.26 (s, 3H, CH_3); 2.42 (s, 6H, CH_3); 5.28 - 5.36 (m, 1H, NCH); 6.35 (s, 2H, NH_2); 6.94 (s, 2H, aromat.); 7.31 - 7.42 (m, 3H, aromat.); 7.49 (s, 1H, aromat.)

f) N-Hydroxy-N-[3-(4-fluorophenylethynyl)-benzyl]-urea

Melting point: 166 - 168° C

^{1}H-NMR (DMSO-d_6): 4.55 (s, 2H, NCH_2); 6.42 (s, 2H, NH_2); 7.22 - 7.47 (m, 6H, aromat.); 7.59 - 7.64 (m, 2H, aromat.)

g) N-Hydroxy-N-[3-(4-fluoro-naphth-1-yl-ethynyl)-benzyl]-urea

Melting point: 168 - 170° C

^{1}H-NMR (DMSO-d_6): 4.61 (s, 2H, NCH_2); 6.47 (s, 2H, NH_2); 7.37 - 7.47 (m, 3H, aromat.); 7.58 - 7.63 (m, 2H, aromat.); 7.72 - 7.86 (m, 3H, aromat.); 8.13, 8.16 (d, 1H, aromat.); 8.40, 8.43 (d, 1H, aromat.)

h) N-Hydroxy-N-{1-[3-(3,4-dichlorophenylethynyl)-phenyl]-ethyl}-urea

Melting point: 151 - 152° C

^{1}H-NMR (DMSO-d_6): 1.43, 1.45 (d, 3H, $NCCH_3$), 5.29 - 5.36 (m, 1H, NCH); 6.35 (s, 2H, NH_2); 7.34 - 7.45 (m, 3H, aromat.); 7.52 - 7.56 (m, 2H, aromat.); 7.65, 7.68 (d, 1H, aromat.); 7.83, 7.84 (d, 1H, aromat.)

Example 9

N-Hydroxy-N-{1-[3-(4-methoxy-phenylethynyl)-phenyl]-ethyl}-urea

1.0 g 3-(4-methoxyphenyl-ethynyl)-acetophenone oxime (obtained in a manner analogous to that described in Examples 4a and 4b) dissolved in 10 ml of glacial acetic acid was reduced using 0.355 g of sodium cyanoborohydride in the manner described in Example 1c. The hydroxylamine compound thus obtained was dissolved in 10 ml of absolute tetrahydrofuran and then 0.82 ml of trimethylsilylisocyanate were added dropwise. When the reaction was completed the mixture was diluted with ethyl acetate, mixed with a saturated solution of ammonium chloride, the organic layer was separated and washed with water. The crude product obtained after evaporation was stirred with ethyl acetate and filtered to give white crystals of the title compound melting at 141 - 142° C. Yield: 0.851 g (72.8 % of the theoretical).

^{1}H-NMR (DMSO-d_6): 1.41, 1.43 (d, 3H, $NCCH_3$); 3.79 (s, 3H, OCH_3); 5.27 - 5.34 (m, 1H, NCH); 6.34 (s, 2H, NH_2); 6.95 - 6.98 (m, 2H, aromat.); 7.29 - 7.37 (m, 2H, aromat.); 7.38 - 7.39 (m, 2H, aromat.); 7.47 - 7.50 (m, 2H, aromat.)

Example 10

The procedure was the same as in Example 9 except there were used the appropriate reactants to give:

a) N-Hydroxy-N-{1-[4-(3,4-dimethoxy-phenylethynyl)-phenyl]-ethyl}--urea

Melting point: 167° C

^{1}H-NMR (DMSO-d_6): 1.40, 1.42 (d, 3H, $NCCH_3$); 3.79 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 5.28 - 5.32 (m, 1H, NCH); 6.33 (s, 2H, NH_2); 6.96 - 6.99 (m, 1H, aromat.); 7.07 - 7.12 (m, 2H, aromat.); 7.34 - 7.37 (m, 2H, aromat.); 7.37 - 7.46 (m, 2H, aromat.)

b) N-Hydroxy-N-{1-[3-(3,4-dimethoxy-phenylethynyl)-phenyl]-ethyl}--urea

Melting point: 144 - 146° C

^{1}H-NMR (DMSO-d_6): 1.41, 1.44 (d, 3H, $NCCH_3$); 3.79 (s, 3H, OCH_3); 3.80 (s, 3H, OCH_3); 5.27 - 5.32 (m, 1H, NCH); 6.33 (s, 2H, NH_2); 6.96 - 6.98 (m, 1H, aromat.); 7.10 - 7.14 (m, 2H, aromat.); 7.32 - 7.36 (m, 3H, aromat.); 7.48 (s, 1H, aromat.)

c) N-Hydroxy-N-{1-[3-(3-methoxy-phenylethynyl)-phenyl]-ethyl}-urea

Melting point: 128 - 130° C

^{1}H-NMR (DMSO-d_6): 1.42, 1.44 (d, 3H, $NCCH_3$); 3.79 (s, 3H, OCH_3); 5.30 - 5.34 (m, 1H, NCH); 6.34 (s, 2H, NH_2); 6.96 - 7.10 (m, 1H, aromat.); 7.11 - 7.13 (m, 2H, aromat.); 7.30 - 7.42 (m, 4H, aromat.); 7.51 (s, 1H, aromat.)

d) N-Hydroxy-N-{1-[3-(4-chloro-phenylethynyl)-phenyl]-ethyl}-urea

Melting point: 148 - 149° C

^{1}H-NMR ($CDCl_3$): 1.42, 1.43 (d, 3H, $NCCH_3$); 5.28 - 5.34 (m, 1H, NCH); 6.34 (s, 2H, NH_2); 7.32 - 7.59 (m, 8H, aromat.)

e) N-Hydroxy-N-[3-(4-isopropyl-phenylethynyl)-benzyl]-urea

Melting point: 148 - 149° C

^{1}H-NMR (DMSO-d_6): 1.20, 1.24 (d, 6H, $C(CH_3)_2$); 2.87 - 2.96 (m, 1H, $CH(C)_2$), 4.55 (s, 2H, NCH_2); 6.39 (s, 2H, NH_2); 7.27 - 7.48 (m, 8H, aromat.)

f) N-Hydroxy-N-{1-[3-(6-methoxy-naphth-2-yl-ethynyl)-phenyl]-ethyl}-urea

Melting point: 150 - 152° C

^{1}H-NMR (DMSO-d_6): 1.43, 1.45 (d, 3H, $NCCH_3$); 3.89 (s, 3H, OCH_3); 5.29 - 5.36 (m, 1H, NCH); 6.35 (s, 2H, NH_2); 7.19 - 7.23 (m, 1H, aromat.); 7.35 - 7.57 (m, 6H, aromat.); 7.82 - 7.87 (m, 2H, aromat.); 8.10 - 8.17 (m, 1H, aromat.)

g) N-Hydroxy-N-{1-[3-(2-methoxy-phenylethynyl)-phenyl]-ethyl}-urea

viscous material

^{1}H-NMR (DMSO-d_6): 1.42, 1.44 (d, 3H, $NCCH_3$); 3.86 (s, 3H, OCH_3); 5.27 - 5.34 (m, 1H, NCH); 6.34 (s, 2H, NH_2); 6.94 - 6.99 (m, 1H, aromat.); 7.06 - 7.09 (m, 1H, aromat.); 7.30 - 7.41 (m, 4H, aromat.); 7.46 - 7.49 (m, 2H, aromat.)

h) N-Hydroxy-N-{1-[4-(4-methoxy-naphth-1-yl-ethynyl)-phenyl]-ethyl}-urea

Melting point: 153 - 154° C

^{1}H-NMR (DMSO-d_6): 1.43, 1.45 (d, 3H, $NCCH_3$); 4.02 (s, 3H, OCH_3); 5.31 - 5.38 (m, 1H, NCH); 6.35 (s, 2H, NH_2); 7.01, 7.04 (d, 1H, aromat.); 7.40 - 7.43 (m, 2H, aromat.); 7.57 - 7.77 (m, 5H, aromat.); 8.21, 8.24 (d, 1H, aromat.); 8.29, 8.32 (d, 1H, aromat.)

i) N-Hydroxy-N-{1-[3-(4-methyl-phenylethynyl)-phenyl]-ethyl}-urea

Melting point: 142 - 143° C

^{1}H-NMR (DMSO-d_6): 1.42, 1.44 (d, 3H, $NCCH_3$); 2.35 (s, 3H, CH_3); 5.26 - 5.35 (m, 1H, NCH); 6.35 (s, 2H, NH_2); 7.22, 7.25 (d, 2H, aromat.); 7.31 - 7.50 (m, 6H, aromat.)

k) N-Hydroxy-N-{1-[3-(2-methoxy-naphth-1-yl-ethynyl)-phenyl]-ethyl}-urea

viscous material

^{1}H-NMR (DMSO-d_6): 1.44, 1.46 (d, 3H, $NCCH_3$); 4.02 (s, 3H, OCH_3); 5.30 - 5.37 (m, 1H, NCH); 6.38 (s, 2H, NH_2); 7.38 - 7.65 (m, 7H, aromat.); 7.92, 7.95 (d, 1H, aromat.); 8.00, 8.03 (d, 1H, aromat.); 8.21, 8.23 (d, 1H, aromat.)

l) N-Hydroxy-N-[3-(2-methoxyphenylethynyl)-benzyl]-urea

Melting point: 122 - 123.5° C

^{1}H-NMR (DMSO-d_6): 3.86 (s, 3H, OCH_3); 4.54 (s, 2H, CH_2); 6.40 (s, 2H, NH_2); 6.94 - 6.99 (t, 1H, aromat.); 7.06, 7.09 (d, 1H, aromat.); 7.29 - 7.49 (m, 6H, aromat.)

m) N-Hydroxy-N-[3-(4-chlorophenylethynyl)-benzyl]-urea

Melting point: 165 - 166° C

^{1}H-NMR (DMSO-d_6): 4.54 (s, 2H, NCH_2); 6.41 (s, 2H, NH_2); 7.35 - 7.59 (m, 8H, aromat.)

n) N-Hydroxy-N-[3-(4-methoxyphenylethynyl)-benzyl]-urea

Melting point: 170° C

^{1}H-NMR (DMSO-d_6): 3.79 (s, 3H, OCH_3); 4.54 (s, 2H, NCH_2); 6.40 (s, 2H, NH_2); 6.95 - 6.99 (m, 2H, aromat.); 7.28 - 7.50 (m, 6H; aromat.)

o) N-Hydroxy-N-{1-[3-(3,4,5-trimethoxyphenylethynyl)-phenyl]-ethyl}-urea

Melting point: 166.5° C

^{1}H-NMR (DMSO-d_6): 1.42, 1.44 (d, 3H, $NCCH_3$); 3.70 (s, 3H; OCH_3); 3.82 (s, 6H, OCH_3); 5.28 - 5.30 (m, 1H, NCH); 6.33 (s, 2H, NH_2); 6.86 (s, 2H, aromat.); 7.31 - 7.41 (m, 3H, aromat.); 7.51 (s, 1H, aromat.)

p) N-Hydroxy-N-{1-[3-(phenylethynyl)-phenyl]-ethyl}-urea

Melting point: 136 - 137° C

^{1}H-NMR (DMSO-d_6): 1.42, 144 (d, 3H, $NCCH_3$); 5.28 - 5.35 (m, 1H, NCH); 6.34 (s, 2H; NH_2); 7.32 - 7.57 (m, 9H, aromat.)

q) N-Hydroxy-N-[4-(2,6-dichlorophenylethynyl)-benzyl]-urea

Melting point: 157° C

^{1}H-NMR (DMSO-d_6): 4.57 (s, 2H, NCH_2); 6.41 (s, 2H, NH_2); 7.36 - 7.45 (m, 3H, aromat.); 7.53 - 7.60 (m, 4H, aromat.)

Example 11

N-Hydroxy-N-{1-[3-(4-trifluoromethyl-phenylethynyl)-phenyl]-ethyl}-urea

a) 3-Ethynyl-acetophenone

Following the procedure described in Example 1a 12.53 g of 3-bromoacetophenone were reacted with 11 ml of trimethylsilylacetylene

in presence of 0.62 g of bis-(triphenylphosphine)-palladium(II) chloride and 0.05 g of copper(I) iodide at a temperature of 40° to 50° C. The 3-(trimethylsilylethynyl)-acetophenone was isolated by column chromatography with petroleum ether/ether (3: 1) and then dissolved in 100 ml of methanol to which solution, while chilling with ice-water, then were added 65 ml of 1n sodium hydroxide solution. After stirring for one hour 250 ml of a saturated solution of ammonium chloride were added and the mixture was extracted three times with 150 ml of ether each time. The extracts were washed twice with a saturated solution of sodium chloride, dried over sodium sulfate and then evaporated. Thus 8.60 g (96.2 % of the theoretical yield) of the title compound in form of a slightly yellowish solid melting at 53 - 54° C were obtained.

^{1}H-NMR ($CDCl_3$): 2.61 (s, 3H, $COCH_3$); 3.14 (s, 1H ≡CH); 7.42 - 7.47 (m, 1H, aromat.); 7.66 - 7.70 (m, 1H, aromat.); 7.92 - 7.96 (m, 1H, aromat.); 8.07 - 8.08 (m, 1H, aromat.)

b) 3-(4-Trifluoromethyl-phenylethynyl)-acetophenone

In the manner described in Example 1a 8.60 g of the product obtained in Example 11a were reacted with 9.8 ml of 4-bromo-(trifluoromethyl-benzene) in presence of 0.63 g of bis(triphenylphosphine)-palladium(II) chloride and of 0.03 g of copper(I)iodide. By chromatography with petroleum ether/ether (2 : 1) 14.81 g (86.2 % of the theoretical yield) of the title compound were obtained in the form of colorless crystals melting at 72 - 73° C.

^{1}H-NMR ($CDCl_3$): 2.64 (s, 3H, $COCH_3$); 7.46 - 7.52 (m, 1H, aromat.); 7.61 - 7.67 (m, 4H, aromat.); 7.72 - 7.75 (m, 1H, aromat.); 7.94 - 7.98 (m, 1H, aromat.); 8.13 - 8.14 (m, 1H, aromat.)

c) 3-(4-Trifluoromethyl-phenylethynyl)-acetophenone oxime

By reacting in the manner described in Example 1b 12.1 g of the product obtained in Example 11b with 4.90 g of hydroxylamine hydrochloride and 4.55 g of sodium acetate 12.32 g (96.5 % of the

theoretical yield) of the title compound melting at 117 - 119° C were obtained.

^{1}H-NMR (DMSO-d_6): 2.19 (s, 3H, N=CCH_3); 7.45 - 7.50 (m, 1H, aromat.); 7.58 - 7.62 (m, 1H, aromat.); 7.73 - 7.85 (m, 6H, aromat.)

d) N-Hydroxy-N-{1-[3-(4-trifluoromethyl-phenylethynyl)-phenyl]-ethyl}-urea

In the manner described in Example 7 3.52 g of the product obtained in Example 11c were reduced with 1.20 g of sodium cyanoborohydride to the corresponding hydroxylamine which then was reacted with 3.2 ml of trimethylsilylisocyanate. There were obtained 2.74 g (67.8 % of the theoretical yield) of the title compound in the form of white crystals melting at 151 - 152° C.

^{1}H-NMR (DMSO-d_6): 1.42, 1.44 (d, 3H, NCCH_3); 5.27 - 5.37 (m, 1H, NCH); 7.38 - 7.56 (m, 4H, aromat.); 7.78 (s, 4H, aromat.)

Example 12

N-{1-[3-(4-Chloro-phenylethynyl)-phenyl]-ethyl}-acetohydroxamic acid

a) N-Acetoxy-N-{1-[3-(4-chloro-phenylethynyl)-phenyl]-ethyl}-acetamide

1.0 g of 3-(4-chloro-phenylethynyl)-acetophenone oxime were dissolved in 20 ml of hot ethanol, then chilled to 0° C. Then were added dropwise 0.82 ml of borane-pyridine complex and ten minutes later slowly 1.24 ml of 6n hydrochloric acid. After stirring for two hours at 0° C an additional amount of 3 ml of hydrochloric acid was slowly added. During the next two hours the temperature was allowed to warm to 15° C and then the solution was stirred for additonal two hours at 3° C. Sodium carbonate was added thereafter in small portions until the mixture showed p_H 8. After adding ether the organic layer was separated, washed three times with saturated sodium chloride solution, dried over sodium sulfate

and evaporated in a vacuum to yield a slighly brownish oil. This was dissolved in 10 ml of anhydrous tetrahydrofuran and, while chilling in ice-water, 1.51 ml of pyridine followed by 1.32 ml of acetylchloride were added. (TLC: petroleum ether/ethyl acetate - 1 : 1). When the reaction was finished ethyl acetate and a saturated solution of sodium hydrogen carbonate were added, the organic layer was separated, washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated in a vacuum. The viscous oily residue was purified by chromatography with petroleum ether/ethyl acetate (1 : 1) to yield 1.039 g (83.5 % of the theoretical yield) of the title compound as a colorless oil.

^{1}H-NMR ($CDCl_3$): 1.53, 1.56 (d, 3H, $NCCH_3$); 2.13 (s, 3H, $NOCOCH_3$); 2.16 (s, 3H, $NCOCH_3$); 5.70 - 5.85 (m, 1H, NCH); 7.15 - 7.54 (m, 8H, aromat.)

b) N-{1-[3-(4-Chloro-phenylethynyl)-phenyl]-ethyl}-acetohydroxamic acid

The procedure was the same as described in Example 4d except there were used 1.031 g of the product obtained in Example 12a, 0.20 g of anhydrous potassium carbonate and 11 ml of methanol. On chromatography of the raw product with petroleum ether/ethyl acetate (1: 1) 0.786 g (89.2 % of the theoretical yield) of the title compound were obtained in form of white crystals melting at 129° C.

^{1}H-NMR (DMSO-d_6): 1.46, 1.48 (d, 3H, $NCCH_3$); 2.02 (s, 3H, $NCOCH_3$); 5.53 - 5.68 (m, 1H, NCH); 7.27 - 7.56 (m, 6H, aromat.); 7.57 - 7.59 (m, 2H, aromat.)

Example 13

Following the procedure described in Example 12 there were obtained from the appropriate reactants:

a) N-{1-[4-(4-Isopropyl-phenylethynyl)-phenyl]-ethyl}-acetohydroxamic acid

Colorless crystals melting at 142 - 143° C

^{1}H-NMR (DMSO-d_6): 1.20, 1.22 (d, 6H, $C(CH_3)_2$); 1.45, 1.47 (d, 3H, $NCCH_3$); 2.02 (s, 3H, $NCOCH_3$); 2.87 - 2.96 (m, 1H, $CH(C)_2$); 5.57 - 5.71 (m, 1H, NCH); 7.20 - 7.36 (m, 4H, aromat.); 7.44 - 7.50 (m, 4H, aromat.)

b) N-[4-(2,6-Dichlorophenylethynyl)-benzyl]-acetohydroxamic acid

Melting point: 139 - 139.5° C

^{1}H-NMR (DMSO-d_6): 2.06 (s, 3H, $NCOCH_3$); 4.73 (s, 2H, NCH_2); 7.34 - 7.45 (m, 3H, aromat.); 7.55 - 7.60 (m, 4H, aromat.)

Example 14

N-{1-[4-(Thien-2-yl-ethynyl)-phenyl]-ethyl}-acetohydroxamic acid

a) 4-(Thien-2-yl-ethynyl)-acetophene

Following the procedure described in Example 1a 4-bromoacetophenone and 2-thienylacetylene in triethylamine were reacted in presence of bis-(triphenylphosphine)-palladium(II) chloride and of copper(I) iodide to yield (after purification by chromatography with n-hexane/ethyl acetate - 9 : 1) the title compound in form of a yellowish oil.

^{1}H-NMR ($CDCl_3$): 2.61 (s, 3H, $COCH_3$); 7.05 (dd, 1H, aromat.); 7.34 (m, 2H, aromat.); 7.59 (m, 2H, aromat.); 7.93 (m, 2H, aromat.)

b) 4-(Thien-2-yl-ethynyl)-acetophenone oxime

4.03 g of hydroxylamine hydrochloride, 6.57 g of the product obtained in Example 14a and 3.07 g of sodium carbonate were reacted in 150 ml of a mixture of ethanol and water (2 : 1) at room temperature. The raw product was recrystallized from ethyl acetate to yield 4.62 g (66.0 % of the theoretical yield) of the colorless title compound. Melting point 187 - 188° C.

^{1}H-NMR ($CDCl_3$): 2.25 (s, 3H, N=CCH_3); 7.03 (dd, 1H, aromat.); 7.31 (m, 2H, aromat.); 7.48 (m, 2H, aromat.); 7.66 (m, 2H, aromat.)

c) N-{1-[4-(Thien-2-yl-ethynyl)-phenyl]-ethyl}-hydroxylamine

i) To a solution of 0.24 g of the product of Example 14b in 5 ml of glacial acetic acid at room temperature were added 0.252 g of sodium cyanoborohydride and after stirring for 30 minutes additional 0.126 g of sodium cyanoborohydride followed by stirring for further 30 minutes. The reaction mixture was used as starting material in Example 14d.

ii) To a solution of 0.24 g of the product obtained in Example 14b and of 0.125 g of sodium cyanoborohydride in 5 ml of ethanol were added three drops of a saturated ethanolic solution of methyl orange. To this mixture, while stirring at room temperature, were slowly added 1.05 ml of a 10 % solution of hydrogen chloride in ethanol until the pink colour maintained for 30 seconds. The reaction mixture was poured into 30 ml of saturated sodium chloride solution and then extracted three times with 15 ml of ethyl acetate each time. The extracts were washed with 10 ml of saturated sodium hydrogen carbonate solution, dried over magnesium sulfate and evaporated in a vacuum. The raw product was purified by chromatography with n-hexane/isopropanol (9 : 1) to yield 0.088 g (36 % of the theoretical yield) of the title compound in form of a yellowish oil.

iii) To a solution of 0.24 g of the product obtained in Example 14b were added at 0° C in an atmosphere of nitrogen 0.2 ml of borane-pyridine complex. After stirring for 15 minutes 1.6 ml of a 20 % solution of hydrogen chloride in ethanol were added. The mixture was stirred for one hour at room temperature and then poured into 30 ml of saturated sodium chloride solution. By adding potassium carbonate the p_H was adjusted to 9. The mixture was extracted three times with 10 ml of ethyl acetate each time, the organic extracts were dried over magne-

sium sulfate and evaporated in a vacuum. Thus 0.25 g (practically quantitative yield) of the product were obtained as a yellowish oil.

d) N-Acetoxy-N-{1-[4-(thien-2-yl-ethynyl)-phenyl]-ethyl}-acetamide

i) To the reaction mixture obtained in Example 14c)i) were added 0.5 ml of acetic anhydride and after stirring for 16 hours this mixture was poured in small portions to a solution of 7.0 g of sodium hydrogen carbonate in 100 ml of water. When the formation of carbon dioxide came to an end the mixture was extracted three times with 30 ml of ethyl acetate each time. The extracts were dried over magnesium sulfate, evaporated in a vacuum and the residue was purified by chromatography with n-hexane/ethyl acetate (4 : 1). Thus 0.16 g (49 % of the theoretical yield calculated on the amount of starting material used in Example 14c)i) of a yellowish oil were obtained.

^{1}H-NMR ($CDCl_3$): 1.46 (d, 3H, $NCCH_3$); 1.98 (s, 3H, $NCOCH_3$); 2.18 (s, 3H, $OCOCH_3$); 5.67 (m, 1H, NCH); 7.13 (dd, 1H, aromat.); 7.41 (m, 3H, aromat.); 7.52 (d, 2H, aromat.); 7.65 (m, 1H, aromat.)

ii) To a solution of 0.25 g of the product obtained in Example 14c)iii) in 5 ml of toluene were added 1 ml of acetic anhydride and 0.2 ml of pyridine. The mixture was boiled under reflux for 2 hours, cooled to room temperature and then poured into a mixture of 25 ml of saturated sodium chloride solution and 2 ml of 1n hydrochloric acid. The organic layer was separated, the aqueous layer was extracted twice with 15 ml of ethyl acetate each time. The combined organic extracts were washed with 5 ml of saturated sodium chloride solution, dried over magnesium sulfate and evaporated in a vacuum. The remaining oil was chromatographed with n-hexane/isopropanol (9 : 1) to yield 0.20 g (61 % of the theoretical yield) of a yellowish oil.

e) N-{1-[4-(Thien-2-yl-ethynyl)-phenyl]-ethyl}-acetohydroxamic acid

At room temperature to a solution of 0.145 g of the product obtained in Example 14d were added 0.57 ml of a 1-molar solution of lithium hydroxide in methanol and after stirring for 30 minutes the mixture was poured to 4 ml of saturated sodium chloride solution and 1 ml of saturated sodium hydrogen carbonate solution. The mixture was extracted three times with 2 ml of ethyl acetate each time, the organic extracts were washed with 1 ml of saturated sodium chloride solution, dried over magnesium sulfate and evaporated in a vacuum. The crude product was recrystallized from n-hexane/ethyl acetate to yield 0.065 g (52 % of the theoretical yield) of the title compound as a colorless solid.

Melting point: 128 - 129° C

^{1}H-NMR (DMSO-d_6): 1.46 (d, 3H, $NCCH_3$); 2.03 (s, 3H, $NCOCH_3$);
5.63 (m, 1H, NCH); 7.11 (dd, 1H, aromat.);
7.37 (m, 3H, aromat.); 7.49 (d, 2H, aromat.);
7.64 (m, 1H, aromat.)

Example 15

N-Hydroxy-N-{1-[4-(thien-2-yl-ethynyl)-phenyl]-ethyl}-urea

1.37 g of the hydroxylamine derivative prepared in Example 14c), dissolved in 25 ml of tetrahydrofuran, were reacted with 1 ml of trimethylsilylisocyanate in a manner as described in Example 7. The reaction mixture was worked up as usual and the crude product was recrystallized from n-hexane/ethylacetate. 0.662 g (46.0 % of the theoretical yield) of the title compound were obtained in form of a colorless solid melting at 154 - 155° C.

^{1}H-NMR (DMSO-d_6): 1.53 (d, 3H, $NCCH_3$); 5.48 (q, 1H, NCH);
5.59 (s, 2H, NH_2); 7.02 (dd, 1H, aromat.);
7.29 (m, 2H, aromat.); 7.44 (m, 4H, aromat.)

Example 16

By using the appropriate reactants and otherwise proceeding as described in Examples 14 and 15 there were obtained:

a) N-{1-[4-(Thien-3-yl-ethynyl)-phenyl]-ethyl}-acetohydroxamic acid

Melting point: 130 - 131° C

^{1}H-NMR (DMSO-d_6): 1.51 (d, 3H, $NCCH_3$); 2.09 (s, 3H, $NCOCH_3$);
5.69 (m, 1H, NCH); 7.33 (dd, 1H, aromat.);
7.41 (m, 2H, aromat.); 7.56 (m, 2H, aromat.);
7.70 (dd, 1H, aromat.); 7.95 (dd, 1H, aromat.)

b) N-Hydroxy-N-{1-[4-(thien-3-yl-ethynyl)-phenyl]-ethyl}-urea

Melting point: 156 - 157° C

^{1}H-NMR (DMSO-d_6): 1.42 (d, 3H, $NCCH_3$); 5.32 (q, 1H, NCH);
6.33 (s, 2H, NH_2); 7.24 (dd, 1H, aromat.);
7.37 (d, 2H, aromat.); 7.45 (d, 2H, aromat.);
7.62 (dd, 1H, aromat.); 7.84 (dd, 1H, aromat.)

c) N-[4-(Thien-2-yl-ethynyl)-benzyl]-acetohydroxamic acid

Melting point: 113 - 114° C

^{1}H-NMR (DMSO-d_6): 2.06 (s, 3H, $NCOCH_3$); 4.71 (s, 2H, NCH_2);
7.12 (dd, 1H, aromat.); 7.31 (d, 2H, aromat.);
7.40 (dd, 1H, aromat.); 7.51 (d, 2H, aromat.);
7.64 (dd, 1H, aromat.)

d) N-Hydroxy-N-[4-(thien-2-yl-ethynyl)-benzyl]-urea

Melting point: 177° C

^{1}H-NMR (DMSO-d_6): 4.57 (s, 2H, NCH_2); 6.44 (s, 2H, NH_2);
7.11 (m, 1H, aromat.); 7.34 (d, 2H, aromat.);
7.40 (d, 1H, aromat.); 7.49 (d, 2H, aromat.);
7.63 (d, 1H, aromat.)

e) N-[4-(Thien-3-yl-ethynyl)-benzyl]-acetohydroxamic acid

Melting point: 147 - 152° C

^{1}H-NMR (DMSO-d_6): 2.06 (s, 3H, $NCOCH_3$); 4.71 (s, 2H, NCH_2);
7.25 (d, 1H, aromat.); 7.30 (d, 2H, aromat.);
7.49 (d, 2H, aromat.); 7.63 (m, 1H, aromat.);
7.86 (d, 1H, aromat.)

f) N-Hydroxy-N-[4-(thien-3-yl-ethynyl)-benzyl]-urea

Melting point: 187 - 188° C (decomp.)

^{1}H-NMR (DMSO-d_6): 4.56 (s, 2H, NCH_2); 6.41 (s, 2H, NH_2);
7.25 (d, 1H, aromat.); 7.33 (d, 2H, aromat.);
7.47 (d, 2H, aromat.); 7.62 (m, 1H, aromat.);
7.85 (m, 1H, aromat.)

g) N-Hydroxy-N-{1-[4-(5-chloro-thien-2-yl-ethynyl)-phenyl]-ethyl}-urea

Melting point: 151 - 152° C

^{1}H-NMR (DMSO-d_6): 1.42 (d, 3H, $NCCH_3$); 5.34 (q, 1H, NCH);
6.36 (s, 2H, NH_2); 7.13 (d, 1H, aromat.);
7.28 (d, 1H, aromat.); 7.39 (d, 2H, aromat.);
7.47 (d, 2H, aromat.)

h) N-{1-[4-(5-Chloro-thien-2-yl-ethynyl)-phenyl]-ethyl}-acetohydroxamic acid

Melting point: 130 - 131° C

^{1}H-NMR (DMSO-d_6): 1.47 (d, 3H, $NCCH_3$); 2.04 (s, 3H, $NCOCH_3$);
5.64 (m, 1H, NCH); 7.13 (d, 1H, aromat.);
7.28 (d, 1H, aromat.); 7.37 (d, 2H, aromat.);
7.50 (d, 2H, aromat.)

i) N-Hydroxy-N-{1-[4-(benzothien-2-yl-ethynyl)-phenyl]-ethyl}-urea

Melting point: 164 - 165° C

^{1}H-NMR (DMSO-d_6): 1.44 (d, 3H, $NCCH_3$); 5.35 (m, 1H, NCH); 6.37 (s, 2H, NH_2); 7.35 - 7.96 (m, 9H, aromat.)

k) N-{1-[4-(Benzothien-2-yl-ethynyl)-phenyl]-ethyl}-acetohydroxamic acid

Melting point: 172 - 173° C

^{1}H-NMR (DMSO-d_6): 1.49 (d, 3H, $NCCH_3$); 2.06 (s, 3H, $NCOCH_3$); 5.67 (m, 1H, NCH); 7.39 - 7.45 (m, 4H, aromat.); 7.56 (d, 2H, aromat.); 7.74 (s, 1H, aromat.); 7.86 (m, 1H, aromat.); 7.95 (m, 1H, aromat.)

Example 17

The procedure was the same as described in Example 12 there were used, however, as starting materials the respective (pyridine-3-yl-ethynyl)-acetophenone or -benzaldehyde oximes to prepare:

a) N-{1-[4-(Pyridin-3-yl-ethynyl)-phenyl]-ethyl}-acetohydroxamic acid

Melting point: 121° C

^{1}H-NMR (DMSO-d_6): 1.45, 1.48 (d, 3H, $NCCH_3$); 2.03 (s, 3H, $NCOCH_3$); 5.63 - 5.65 (m, 1H, NCH); 7.37 - 7.56 (m, 5H, aromat.); 7.94 - 7.99 (m, 1H, aromat.); 8.57 - 8.59 (m, 1H, aromat.); 8.73, 8.74 (d, 1H, aromat.)

b) N-[4-(Pyridin-3-yl-ethynyl)-benzyl]-acetohydroxamic acid

Melting point: 125.5° C

^{1}H-NMR (DMSO-d_6): 2.06 (s, 3H, $NCOCH_3$); 4.72 (s, 2H, NCH_2); 7.31 - 7.34 (m, 2H, aromat.); 7.45 - 7.47 (m, 1H, aromat.); 7.54 - 7.57 (m, 2H, aromat.); 7.95 - 7.97 (m, 1H, aromat.); 8.57 - 8.59 (m, 1H, aromat.); 8.74, 8.75 (d, 1H, aromat.)

c) N-[3-(Pyridin-3-yl-ethynyl)-benzyl]-acetohydroxamic acid

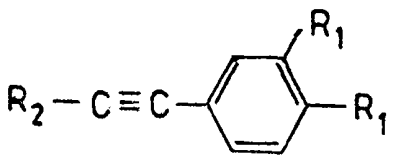
Melting point: 114.5 - 115.5° C

^{1}H-NMR (DMSO-d_6): 2.07 (s, 3H, $NCOCH_3$); 4.71 (s, 2H, NCH_2); 7.33 - 7.51 (m, 5H, aromat.); 7.97 - 7.99 (m, 1H, aromat.); 8.58 - 8.60 (m, 1H, aromat.); 8.76, 8.77 (d, 1H, aromat.)

~~What we claim is:~~

The claims defining the Invention are as follows:

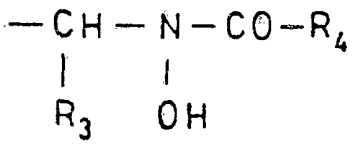
1) Substituted phenylacetylenes of the general formula



I

wherein

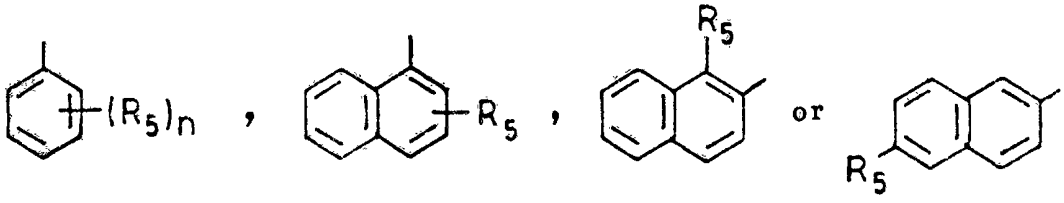
one of the symbols R_1 represents a hydrogen atom while the other represents the group of the formula



in which R_3 is hydrogen, methyl or ethyl and R_4 represents a methyl or an amino group and

R_2 represents a mono- or binuclear group which is

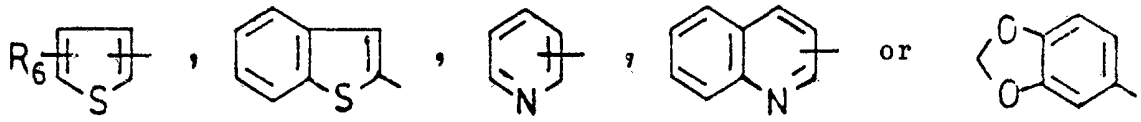
a) a mono- or binuclear aromatic radical being a member of the group comprising radicals of the formulae



wherein R_5 represents hydrogen, a straight chain or branched alkyl, alkoxy or alkylmercapto group containing 1 to 4 carbon atoms, a benzyloxy group, a fluorine or chlorine atom or a trifluoro methyl group and n represents a number 1, 2 or 3, or

b) a mono- or binuclear heterocyclic radical containing sulfur nitrogen or oxygen and being a member of the group comprising

radicals of the formulae

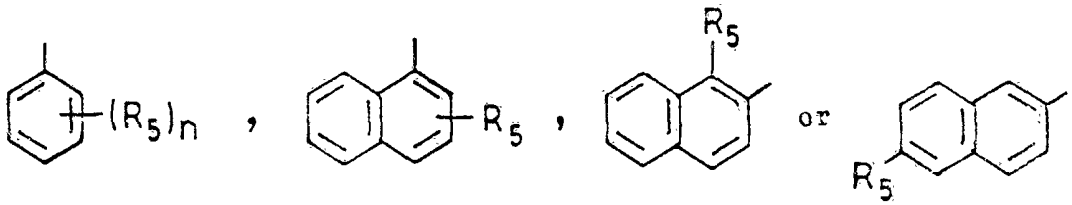


wherein R_6 represents a hydrogen or a chlorine atom or a methyl group

and the stereoisomeres and optically active forms of the substituted phenylacetylenes of formula I.

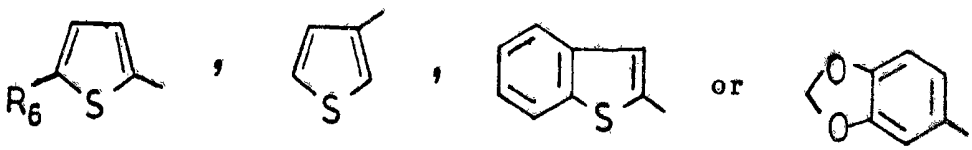
2) Substituted phenylacetylenes of the general formula given in claim I wherein R_1 and R_4 have the same meaning as defined in claim 1, R_3 represents a hydrogen atom or a methyl group and R_2 represents a mono- or binuclear which is

a) a mono- or binuclear aromatic radical being a member of the group comprising radicals of the formulae



wherein R_5 represents hydrogen, a methoxy group, straight or branched alkyl containing 1 to 4 carbon atoms, a fluorine or a chlorine atom or a trifluoro methyl group and n represents a number 1, 2 or 3, or

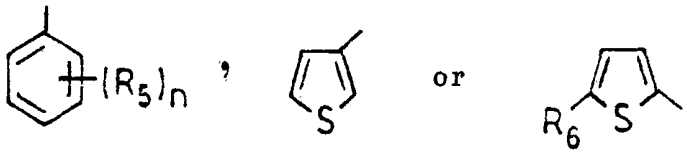
b) a mono- or binuclear heterocyclic radical containing sulfur or oxygen and being a member of the group comprising radicals of the formulae



wherein R_6 represents a hydrogen or a chlorine atom or a methyl group

and the stereoisomeres and optically active forms of these substituted phenylacetylenes of formula I.

3) Substituted phenylacetylenes according to claim 2 of the general formula I given in claim 1, wherein R_2 represents one of the groups



in which R_5, R_6 and n have the meanings defined in claim 2.

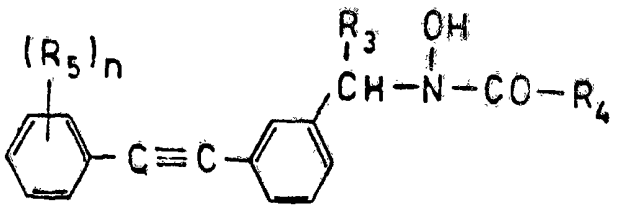
4) Substituted phenylacetylenes according to claim 1 wherein in formula I R_2 represents the quinolyl-3 group or preferably the pyridyl-3 group.

5) Substituted phenylacetylenes according to claim 3 wherein R_5 represents a methoxy group in 3- and/or 4-position to the acetylene group and n represents one of the numbers 1 or 2.

6) Substituted phenylacetylenes according to claim 3 wherein R_5 represents a fluorine or a chlorine atom in 4-position to the acetylene group.

7) Substituted phenylacetylenes according to claims 2 and 3 wherein R_6 represents a hydrogen atom.

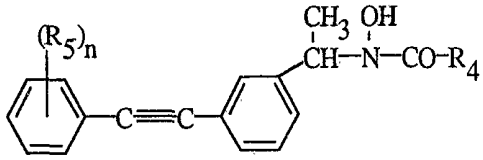
8) Substituted phenylacetylenes according to claims 2, 3, 5 and 6 corresponding to the formula



Ia

wherein R_3 to R_5 and n have the same meanings as above.

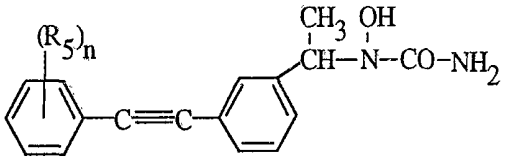
9. Substituted phenylacetylenes according to claims 2, 3, 5 and 6 corresponding to the formula



Ib

wherein R_4 represents a methyl or an amino group and R_5 represents a methoxy group in 3- and/or 4-position to the acetylenic group (in which case n is a number 1 or 2) or a fluorine or chlorine atom in 4-position to the acetylenic group (n being 1 in this case).

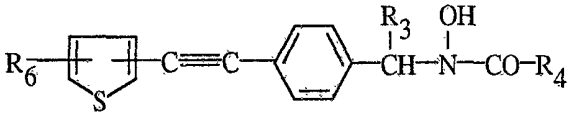
10. Substituted phenylacetylenes according to claim 9 corresponding to the formula



Ic

wherein R_5 and n have the same meanings as defined in claim 9.

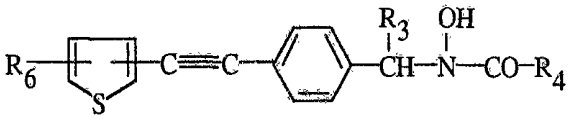
11. Substituted phenylacetylenes according to any one of claims 1 to 3 corresponding to the formula



Id

wherein R_3 is H, methyl or ethyl
R_4 is methyl or NH_2 and
R_6 is H, Cl or methyl

12. Substituted phenylacetylenes according to claims 2, 3 and 11 corresponding to the formula

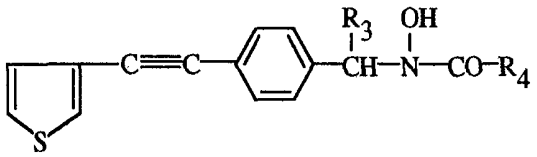


Ie

wherein R_3 is H or methyl
R_4 is methyl or NH_2 and
R_6 is H, Cl or methyl

13. Substituted phenylacetylenes according to claim 2 or claim 3 corresponding to the formula

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If

wherein R_3 is H or methyl and

R_4 is methyl or NH_2.

14. A pharmaceutical composition for parenteral, oral, intranasal, rectal or percutaneous application comprising a prophylactically or therapeutically effective amount of at least one of the substituted phenylacetylenes defined by any one of claims 1 to 13 as active ingredient together with a pharmaceutically acceptable carrier, diluent, excipient, color, flavour, lubricant, organic adjuvant and/or inorganic adjuvant.

15. A pharmaceutical composition according to claim 14 wherein the prophylactically or therapeutically effective amount of said substituted phenylacetylene is from about 0.01 to 50 mg per individual dose.

16. A pharmaceutical composition according to claim 14 or claim 15, suitable for parenteral administration and containing per individual dose from about 0.01 to 10 mg of said substituted phenylacetylene.

17. A pharmaceutical composition according to claim 14 or claim 15, suitable for oral administration and containing per individual dose from about 0.1 to 50 mg of said substituted phenylacetylene.

18. A pharmaceutical composition according to claim 17 for oral administration in the form of tablets, coated tablets or capsules, including those from which the active ingredients have a delayed release.

19. A pharmaceutical composition according to claim 14, suitable for intranasal or oral application or for administration of the active ingredient to the bronchia in spray form containing said substituted phenylacetylene dissolved in a pharmaceutically acceptable liquid carrier.

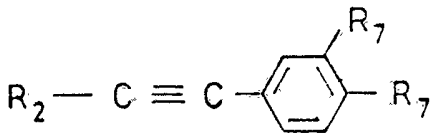
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20) A pharmaceutical composition according to claim 14, suitable for percutaneous application comprising a reservoir attachable to the skin of the patient and containing said substituted phenylacetylene dissolved in a liquid carrier, preferably a carrier consisting of or containing a membran penetration enhancing agent.

21) A process for the preparation of the pharmaceutical compositions according to claims 14 to 20 in which at least one of the substituted phenylacetylenes defined by claims 1 to 13 is formulated together with diluents, carriers or solvents, respectively, and optionally with binders, lubricants, tablet disintegrating materials and other auxiliary products and preparing from the mixture thus obtained the desired dosage forms in a manner known per se.

22) Process for the preparation of the substituted phenylacetylenes defined by claim 1 to 13 of the general formula given in claim 1 comprising

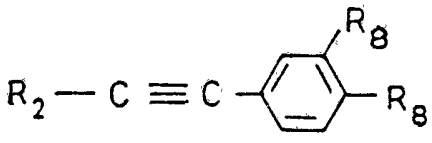
(i) reacting a compound of the formula



II

wherein R_2 has the same meaning as above and in which one of the symbols R_7 represents a hydrogen atom while the other represents the group $-COR_3$ in which R_3 is as defined above

with hydroxylamine or a salt thereof in presence of bases to form the oxime which then by treatment with boron hydrides or with borane-amine complexes in presence of acids is reduced to a compound of the formula



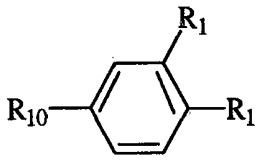
III

wherein one of the symbols R_8 represents a hydrogen atom while the other represents the group of the formula

$$-CH(R_3)-NH-OH$$

and introducing the group -COR_4, wherein R_4 represents a methyl or an amino group or

(ii) reacting a compound of the formula



V

wherein R_1 has the same meaning as above and R_{10} represents a bromine or iodine atom

with a compound of the formula

$$R_2—C\equiv CH \qquad VI$$

wherein R_2 is as defined above

in presence of a secondary or tertiary amine which is liquid in the temperature range of about 0°C to 80°C, especially a dialkyl or trialkyl amine containing 2 or 3 carbon atoms in each alkyl group, pyrrolidine or piperidine, and in the presence of about 0.01 to 5 percent per mole of the compound of formula VI used of a complex palladium catalyst, and optionally in presence of catalytic amounts of copper(I) iodide at about 20°C to 80°C.

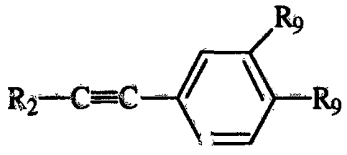
23. Process as claimed in claim 22 wherein said palladium catalyst is bis-(triphenyl-phosphine)-palladium(II) chloride or acetate or tetrakis-(triphenylphosphine)-palladium.

24. Process for the production of substituted phenylacetylenes of the general formula given in claim 1, in which R4 represents an amino group, according to claim 22, process variant (i), comprising reacting a compound of formula III

(a) with trimethylsilyl isocyanate at temperatures between about 20°C and 100°C followed by splitting off the trimethylsilyl group, or

(b) with potassium or sodium cyanate in an acidic solution or with phosgene or a (lower) alkyl or benzyl chloroformate in presence of an agent capable of binding acids followed by a treatment with ammonia or ammonia carbonate.

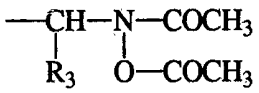
25. Process for the preparation of substituted phenylacetylenes of the general formula I given in claim 1, in which R_4 represents a methyl group, according to claim 22 or claim 23, process variant (i), comprising reacting a compound of formula III with an acetylating agent to form a compound of the formula



IV

wherein one of the symbols R_9 represents a hydrogen atom while the other represents the group

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and splitting off the O-acetyl group by a selective hydrolysis in basic solution.

26. Process according to claim 22 or claim 23, process variant (i), characterized in that the oxime of the compound of formula II is prepared at temperatures of about 20°C to 60°C.

27. Process according to claim 22 or claim 23, process variant (i), characterized in that the oxime of the compound of formula II is reduced with sodium cyanoborohydride in presence of acids at temperatures of about 20°C to 60°C to form the hydroxylamine compound of formula III.

28. Process according to claim 22 or claim 23, process variant (i), characterized in that the oxime of the compound of formula II is reduced with borane-amine complexes in presence of acids at temperatures of about 0°C to 20°C to form the hydroxylamine compound of formula III.

29. A substituted phenylacetylene-acetohydroxamic acid derivative or a substituted phenylacetylene urea derivative substantially as hereinbefore described with reference to any one of the Examples.

30. A process for the preparation of a phenylacetylene-acetohydroxamic acid derivative or a substituted phenylacetylene urea derivative substantially as hereinbefore described with reference to any one of the Examples.

31. A phenylacetylene-acetohydroxamic acid derivative or a substituted phenylacetylene urea derivative prepared by the process of any one of claims 22 to 28 or 30.

32. A method for the treatment or prophylaxis of conditions indicating inhibition of 5-lipoxygenase in a mammal requiring said treatment or prophylaxis, which method comprises administering to said mammal an effective amount of at least one compound according to any one of claims 1 to 13 or 29 or 31, or of a composition according to any one of claims 14 to 20.

33. A method for the treatment or prophylaxis of asthma or anaphylactic shock in a mammal requiring said treatment or prophylaxis, which method comprises administering to said mammal an effective amount of at least one compound according to any one of claims 1 to 13, 29 or 31 or of a composition according to any one of claims 14 to 20.

9 March, 1993

Grunenthal GmbH

Patent Attorneys for the Applicant

SPRUSON AND FERGUSON