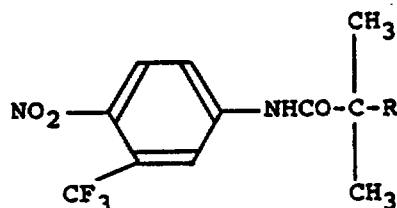


Description

This invention relates to new amide derivatives and more particularly it relates to novel acylanilides which possess antiandrogenic properties.

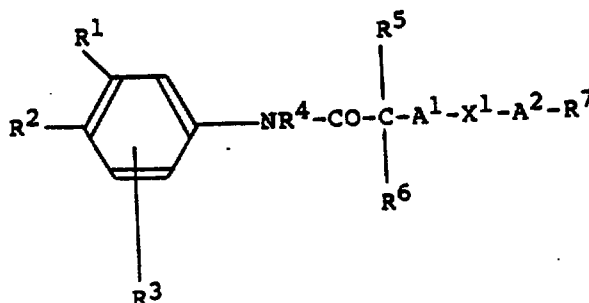
Many acylanilides are known which possess antiandrogenic activity. In particular, the compound of the formula:—



wherein R is hydrogen, which compound is known as FLUTAMIDE, is under development for use as an antiandrogen. It is believed that flutamide is oxidised *in vivo* to the corresponding compound wherein R is hydroxy.

Other acylanilides which possess antiandrogenic activity are known from European Specification Nos. 2309, 2892 and 40932, and from Japanese Specification No. 52—128329.

According to the present invention there is provided an acylanilide of the formula:—



wherein R¹ is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo or hydrogen, or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;

wherein R² is cyano, carbamoyl, nitro, fluoro, chloro, bromo or iodo, or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;

wherein R³ is hydrogen or halogen;

wherein R⁴ is hydrogen or alkyl of up to 4 carbon atoms, or is joined to R⁵ as stated below;

wherein R⁵ is hydroxy or alkoxy or acyloxy each of up to 15 carbon atoms, or is joined to R⁴ to form an oxycarbonyl group such that together with the —N—CO—C— part of the molecule it forms an oxazolidinedione group;

wherein R⁶ is alkyl or halogenoalkyl of up to 4 carbon atoms, or has the formula —A³—R⁸ or —A⁴—X²—A⁵—R⁹;

wherein A¹ and A⁴, which may be the same or different, each is alkylene of up to 6 carbon atoms;

wherein A², A³ and A⁵, which may be the same or different, each is a direct link or alkylene of up to 6 carbon atoms;

wherein X¹ and X², which may be the same or different, each is sulphur, sulphinyl (—SO—) or sulphonyl (—SO₂—);

wherein R⁷ and R⁹, which may be the same or different, each is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbon atoms, or R⁷ or R⁹ is phenyl which bears one, two or three substituents selected from hydrogen, halogen, nitro, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxy carbonyl and N-alkyl carbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or R⁷ or R⁹ is naphthyl; or R⁷ or R⁹ is 5- or 6-membered saturated or unsaturated heterocyclic which contains one, two or three heteroatoms selected from oxygen, nitrogen and sulphur, which heterocyclic may be a single ring or may be fused to a benzo-ring, and which heterocyclic is unsubstituted or bears one or two halogen, cyano or amino, or alkyl, alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl each of up to 4 carbon atoms, or oxy or hydroxy substituents, or which if sufficiently saturated may bear one or two oxo substituents; and wherein R⁸ is phenyl, naphthyl or heterocyclic as defined above for R⁷ or R⁹.

It will be observed that the acylanilide derivative of the invention possesses an asymmetric carbon atom, namely the carbon atom which bears the substituents R^5 and R^6 , and it can therefore exist in racemic and optically-active forms. It is to be understood that this invention encompasses the racemic form of the acylanilide derivative and any optically-active form which possesses antiandrogenic activity, it being a matter of common general knowledge how a racemic compound may be resolved into its optically-active forms and how any antiandrogenic activity present in any of these forms may be determined.

A suitable value for R^1 , R^4 or R^{10} when it is alkyl, or for an alkyl substituent in R^7 , R^8 or R^9 when R^7 , R^8 or R^9 is phenyl or heterocyclic substituted by alkyl is, for example, methyl or ethyl.

A suitable value for R^1 when it is alkoxy, or for an alkoxy substituent in R^7 , R^8 or R^9 when R^7 , R^8 or R^9 is phenyl or heterocyclic substituted by alkoxy is, for example, methoxy or ethoxy.

A suitable value for R^1 or R^2 when it is alkanoyl, or for an alkanoyl substituent in R^7 , R^8 or R^9 when R^7 , R^8 or R^9 is phenyl substituted by alkanoyl is, for example, formyl or acetyl.

A suitable value for R^1 or R^2 when it is alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl, or for such a substituent in R^7 , R^8 or R^9 when R^7 , R^8 or R^9 is phenyl or heterocyclic bearing such a substituent is, for example, methylthio, ethylthio, methylsulphinyl, methylsulphonyl, trifluoromethyl, pentafluoroethyl, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl.

A suitable value for R^3 when it is halogen, or for a halogen substituent in R^7 , R^8 or R^9 when R^7 , R^8 or R^9 is phenyl or heterocyclic substituted by halogen, is fluoro, chloro, bromo or iodo.

R^3 is preferably hydrogen or chloro, especially hydrogen.

R^4 is preferably hydrogen.

A suitable value for an alkoxycarbonyl or *N*-alkylcarbamoyl substituent in R^7 , R^8 or R^9 when R^7 , R^8 or R^9 is phenyl bearing such a substituent is, for example, methoxycarbonyl, ethoxycarbonyl or *N*-methylcarbamoyl.

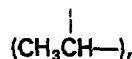
A suitable value for R^5 when it is alkoxy is, for example, methoxy, ethoxy, propyloxy, *n*-butyloxy or decyloxy.

A suitable value for R^5 when it is acyloxy is, for example, alkanoyloxy or aroyloxy each of up to 15 carbon atoms, for example acetoxy, propionyloxy, decanoyloxy, dodecanoyloxy or benzoyloxy.

R^5 is preferably hydroxy.

A suitable value for R^6 when it is alkyl or halogenoalkyl is, for example, methyl, ethyl, *n*-propyl, fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, chloromethyl, dichloromethyl or trichloromethyl. R^6 is preferably methyl or trifluoromethyl, especially methyl.

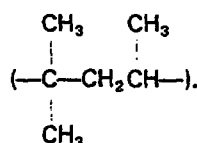
A suitable value for A^1 , A^2 , A^3 , A^4 or A^5 when it is alkylene is, for example, methylene, ethylene, ethylidene



trimethylene, tetramethylene, 1-methyl-ethylene



or 1,1,3-trimethylpropane-1,3-diyl



A suitable value for R^7 or R^9 when it is alkyl, alkenyl, hydroxyalkyl or cycloalkyl is, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, allyl, 2-methylprop-2-enyl, 2-hydroxyethyl, cyclopentyl or cyclohexyl.

A suitable value for R^7 , R^8 or R^9 when it is heterocyclic is, for example, furyl, thienyl, pyrrolyl, pyridyl, imidazolyl, thiazolyl, pyrimidinyl, thiadiazolyl, triazolyl, benzimidazolyl, benzothiazolyl, indolyl, benzothienyl, benzofuryl, quinolyl, isoquinolyl or 1,2-dihydro-2-oxoquinolyl.

A preferred combination of values for R^1 and R^2 is as follows:—

R ¹	R ²
trifluoromethyl	nitro
trifluoromethyl	cyano
chloro	chloro
chloro	nitro
chloro	cyano
cyano	cyano

A preferred acylanilide of the invention has the formula stated above wherein R¹ is cyano, nitro, trifluoromethyl, chloro, methyl or methoxy, R² is cyano, nitro, trifluoromethyl or chloro, R³ and R⁴ are both hydrogen, R⁵ is hydroxy, R⁶ is methyl or trifluoromethyl, A¹ is methylene, ethylene or ethylidene, X¹ is sulphur, sulphonyl or sulphonyl, A² is a direct link or methylene and R⁷ is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbon atoms, or phenyl which is unsubstituted or which bears one fluoro, chloro, cyano, nitro, methoxy or methylthio substituent, or thienyl, imidazolyl, thiazolyl, benzothiazolyl, thiadiazolyl, pyridyl or pyrimidinyl which is unsubstituted or which bears one chloro, bromo or methyl substituent.

A particularly preferred acylanilide of the invention has the formula stated above wherein R¹ is trifluoromethyl, R² is cyano or nitro, R³ and R⁴ are both hydrogen, R⁵ is hydroxy, R⁶ is methyl, A¹ is methylene, X¹ is sulphur, sulphonyl or sulphonyl, A² is a direct link and R⁷ is alkyl of up to 3 carbon atoms, especially ethyl, or is allyl, phenyl, *p*-fluorophenyl, thiazol-2-yl, 4-methylthiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl or 2-pyridyl.

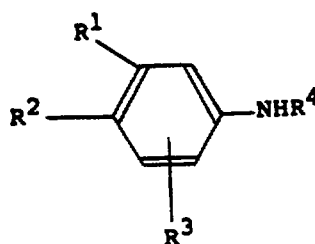
Specific acylanilides of the invention are hereinafter described in the Examples.

Particularly active compounds are:

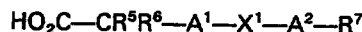
3-chloro-4-cyano-*N*-(3-ethylthio-2-hydroxy-2-methylpropionyl)aniline;
 3-chloro-4-cyano-*N*-(3-ethylsulphonyl-2-hydroxy-2-methylpropionyl)aniline;
 4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-phenylsulphonylpropionyl)aniline;
 4-cyano-3-trifluoromethyl-*N*-(3-ethylsulphonyl-2-hydroxy-2-methylpropionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-3-phenylsulphonyl-2-methylpropionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(3-ethylsulphonyl-2-hydroxy-2-methylpropionyl)aniline;
 3-chloro-4-nitro-*N*-(2-hydroxy-3-phenylthio-2-methylpropionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(thiazol-2-ylthio)propionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(3-allylthio-2-hydroxy-2-methylpropionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(3-*p*-fluorophenylthio-2-hydroxy-2-methylpropionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(pyrid-2-ylthio)propionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)propionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(4-methylthiazol-2-ylthio)propionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(pyrid-2-ylsulphonyl)propionyl)aniline;
 4-nitro-3-trifluoromethyl-*N*-(3-*p*-fluorophenylsulphonyl-2-hydroxy-2-methylpropionyl)aniline;
 4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(thiazol-2-ylthio)propionyl)aniline;
 4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(pyrid-2-ylthio)propionyl)aniline;
 4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-methylthiopropionyl)aniline;
 4-cyano-3-trifluoromethyl-*N*-(3-*p*-fluorophenylthio-2-hydroxy-2-methylpropionyl)aniline; and
 4-cyano-3-trifluoromethyl-*N*-(3-*p*-fluorophenylsulphonyl-2-hydroxy-2-methylpropionyl)aniline;
 and of these the last-mentioned is especially preferred.

The acylanilides of the invention may be manufactured by any chemical process known to be suitable for the manufacture of chemically-analogous compounds.

One preferred process for the manufacture of an acylanilide of the invention comprises the reaction of an amine of the formula:—



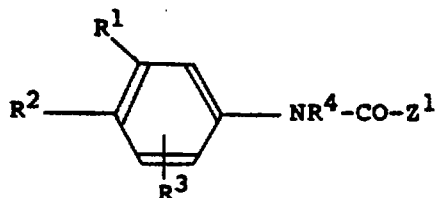
wherein R^1 , R^2 , R^3 and R^4 have the meanings stated above, with an acid of the formula:—



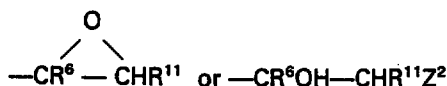
5 wherein R^5 , R^6 , R^7 , X^1 , A^1 and A^2 have the meanings stated above, or with a reactive derivative of said acid.

A suitable reactive derivative of an acid is, for example, an acid anhydride, or an acyl halide, for example an acyl chloride, or a lower alkyl ester of said acid, for example the methyl or ethyl ester. Preferably the reaction is carried out in *N,N*-dimethylacetamide solution using an acyl chloride (prepared from the acid and thionyl chloride) as reactant.

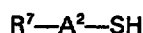
10 A second preferred process for the manufacture of an acylanilide of the invention wherein R^5 is hydroxy and X^1 is sulphur comprises the reaction of an epoxide of the formula:—



wherein R^1 , R^2 , R^3 and R^4 have the meanings stated above and wherein Z^1 has the formula



wherein R^6 has the meaning stated above, wherein Z^2 is a displaceable group and wherein R^{11} is such that $-CHR^{11}-$ is $-A^1-$ as stated above, with a thiol of the formula:—

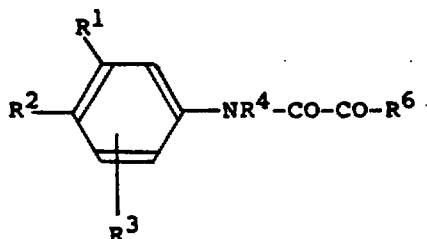


wherein R^7 and A^2 have the meanings stated above.

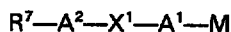
35 A suitable value for Z^2 is, for example, a halogeno or sulphonyloxy group, for example the chloro, bromo, iodo, methanesulphonyloxy or *p*-toluenesulphonyloxy group. The abovementioned reaction is preferably carried out in an inert diluent or solvent, for example tetrahydrofuran, and in the presence of a base, for example sodium hydride.

The epoxide used as starting material may be obtained by the epoxidation, for example with a peracid, of the corresponding unsaturated acylanilide.

40 A third preferred process for the manufacture of an acylanilide of the invention wherein R^5 is hydroxy comprises the reaction of a compound of the formula:—



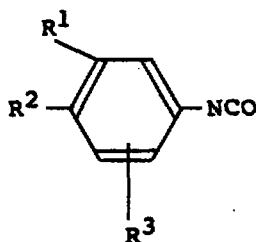
wherein R^1 , R^2 , R^3 , R^4 and R^6 have the meanings stated above, with an organometallic compound of the formula —



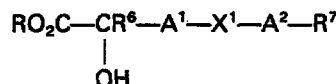
wherein A^1 , A^2 , R^7 and X^1 have the meanings stated above and M is a metal radical, for example the lithium radical.

60 The last-mentioned reaction is preferably carried out in an inert solvent, for example diethyl ether or tetrahydrofuran, at a low temperature, for example at between $-60^\circ C$ and $-100^\circ C$.

An acylanilide of the invention wherein R^4 and R^5 are joined together to form a carbonyloxy group, that is, an oxazolidinedione, may be prepared by the reaction of an isocyanate of the formula:—



10 wherein R¹, R² and R³ have the meanings stated above, with an ester of the formula:—



15 wherein R⁶, R⁷, X¹, A¹ and A² have the meanings stated above, and wherein R is alkyl of up to 6 carbon atoms, for example methyl or ethyl. This reaction is preferably carried out in an organic solvent, for example diethyl ether, at laboratory temperature.

20 An acylanilide of the invention wherein R⁵ is hydroxy may be prepared by the hydrolysis of the corresponding acylanilide wherein R⁵ is acyloxy, and an acylanilide of the invention wherein R⁵ is hydroxy and R⁴ is hydrogen may be prepared by the hydrolysis of the corresponding oxazolidinedione, which may be prepared as described in the preceding paragraph.

An acylanilide of the invention wherein R⁴ is alkyl may be prepared by the alkylation of the corresponding acylanilide wherein R⁴ is hydrogen.

25 An acylanilide of the invention wherein R⁵ is acyloxy may be prepared by the acylation of the corresponding acylanilide wherein R⁵ is hydroxy.

An oxazolidinedione of the invention, wherein R⁴ and R⁵ are joined together to form a carbonyloxy group, may be prepared by the reaction of the corresponding acylanilide wherein R⁴ is hydrogen and R⁵ is hydroxy with phosgene (COCl₂).

30 An acylanilide of the invention wherein X¹ or X² is sulphinyl or sulphonyl or wherein one or more of R¹, R² and a substituent in the phenyl or heterocyclic group R⁷, R⁸ or R⁹ is alkylsulphinyl, perfluoroalkylsulphinyl or phenylsulphinyl, or is alkylsulphonyl, perfluoroalkylsulphonyl or phenylsulphonyl, may be prepared by the oxidation of the corresponding acylanilide wherein X¹ or X² is sulphur or wherein one or more of R¹, R² and a substituent in the phenyl or heterocyclic group R⁷, R⁸ or R⁹ is alkylthio, perfluoroalkylthio or phenylthio, respectively. The oxidising agent and conditions used will determine whether a sulphinyl or a sulphonyl compound is obtained. Thus, oxidation with sodium metaperiodate in methanol solution at or below laboratory temperature will generally convert a thio compound into the corresponding sulphinyl compound; and oxidation with a per-acid, for example *m*-chloroperbenzoic acid, in methylene chloride solution at or above laboratory temperature will generally convert a thio compound into the corresponding sulphonyl compound.

40 A racemic acylanilide of the invention wherein R⁵ is hydroxy may be separated into its optical isomers by forming an ester of the hydroxy group R⁵ with an optically-active acid, for example (–)-camphanic acid, separating the diastereoisomeric esters thus obtained, by fractional crystallisation or, preferably, by flash-chromatography, and then hydrolysing each separate ester to the alcohol. Alternatively, an optically active acylanilide of the invention may be obtained by using any of the processes described above with an optically-active starting material.

45 As stated above, an acylanilide of the invention possesses antiandrogenic properties as demonstrated by its ability to decrease the weight of the seminal vesicles of a mature male rat when administered orally for 4 successive days. An acylanilide of the invention may therefore be used in the treatment of, for example, malignant or benign prostatic disease or of androgen dependent disease conditions, such as acne, hirsutism or seborrhoea, in warm-blooded vertebrates including man. It may also be used to improve ovulation in a domestic animal.

50 A preferred acylanilide of the invention is up to 10 times more active as an antiandrogen than the known, chemically-related antiandrogens flutamide and hydroxyflutamide. At a dose of an acylanilide of the invention which produces antiandrogenic activity in rats no symptoms of toxicity are apparent.

The acylanilide of the invention may be administered to a warm-blooded animal in the form of a pharmaceutical or veterinary composition which comprises the acylanilide in association with a pharmaceutically-acceptable diluent or carrier.

55 The composition may be in a form suitable for oral dosage, as a tablet, capsule, aqueous or oily solution or suspension or emulsion. It may alternatively be in the form of a sterile solution or suspension suitable for parenteral administration, or be in the form of an ointment or lotion for topical administration, or be in the form of a suppository for anal or vaginal administration.

60 The composition may additionally contain one or more drugs selected from anti-oestrogens, for example tamoxifen; aromatase inhibitors, for example testolactone or aminoglutethamide; progestins, for example medroxyprogesterone acetate; inhibitors of gonadotrophin secretion, for example danazol;

LH—RH-analogues, for example buserelin; cytotoxic agents, for example cyclophosphamide; antibiotics, for example penicillin or oxytetracyclin; and anti-inflammatory agents, for example, especially for topical use, fluocinolone acetonide.

The acylanilide of the invention will normally be administered to a warm-blooded animal at a dose of between 0.1 mg. and 125 mg. per kg. bodyweight.

The invention is illustrated but not limited by the following Examples:—

Example 1

Thionyl chloride (0.6 ml.) was added to a stirred solution of 2-hydroxy-2-methyl-3-phenylthiopropionic acid (1.7 g) in *N,N*-dimethylacetamide (40 ml.) which was cooled to $-15^{\circ}\text{C}.$, at such a rate that that temperature was maintained, and the mixture was stirred at that temperature for 15 minutes. 4-Cyano-3-trifluoromethylaniline (1.5 g.) was added, the mixture was stirred at $-15^{\circ}\text{C}.$ for 30 minutes and then at laboratory temperature for 15 hours, and was then poured into water (800 ml.). The mixture was extracted six times with diethyl ether (80 ml. each time) and the combined extracts were washed successively (50 ml. portions each time) twice with aqueous 3*N*-hydrochloric acid, once with saturated aqueous sodium chloride solution, twice with saturated aqueous sodium bicarbonate solution, and again once with saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was purified by chromatography on a silica gel column (Merck 7734) using methylene chloride as eluant. The product was crystallised from a 5:1 v/v mixture of toluene and petroleum ether (b.p. $60-80^{\circ}\text{C}.$) and there was thus obtained 4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-phenylthiopropionyl)aniline, m.p. $81.5-83^{\circ}\text{C}.$

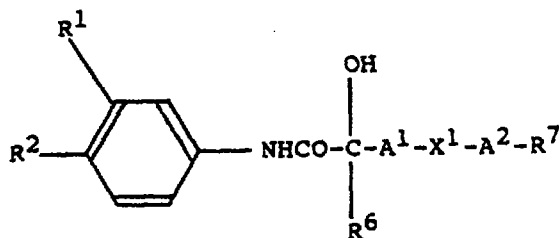
The 2-hydroxy-2-methyl-3-phenylthiopropionic acid used as starting material was obtained as follows:—

Route A

A solution of methyl 2,3-epoxy-2-methyl-propionate (4.06 g.) in tetrahydrofuran (40 ml.) was added during 20 minutes to a stirred suspension of thiophenol (7.7 g.) and sodium hydride (2.9 g. of a 60% dispersion in mineral oil) in tetrahydrofuran (75 ml.) which was maintained under an atmosphere of nitrogen, and the mixture was stirred at laboratory temperature for 15 minutes, then at $60^{\circ}\text{C}.$ for 4 hours, cooled and neutralised by dropwise addition of a solution of concentrated sulphuric acid (0.5 ml.) in ethanol (5 ml.). A solution of potassium hydroxide (10 g.) in a mixture of water (30 ml.) and ethanol (150 ml.) was added and the mixture was heated under reflux for 22 hours. The organic solvents were removed by evaporation under reduced pressure, water (50 ml.) was added and the mixture was washed twice with diethyl ether (25 ml. each time). The aqueous solution was then acidified with concentrated aqueous hydrochloric acid and extracted four times with diethyl ether (100 ml. each time). The combined extracts were washed with saturated aqueous sodium chloride solution (50 ml.), dried over magnesium sulphate and evaporated to dryness, and the residue was crystallised from a 5:1 v/v mixture of petroleum ether (b.p. $60-80^{\circ}\text{C}.$) and toluene. There was thus obtained 2-hydroxy-2-methyl-3-phenylthiopropionic acid, m.p. $95.5-97^{\circ}\text{C}.$

Example 2

The process described in Example 1 was repeated except that the appropriate aniline and the appropriate 2-hydroxy-substituted-alkanoic acid were used as starting materials. There was thus obtained the compounds described in the following table:—



R ¹	R ²	R ⁶	A ¹	X ¹	A ²	R ⁷	m.p. (°C)
CF ₃	NO ₂	CH ₃	CH ₂	S	—	phenyl	105—106
CF ₃	NO ₂	CH ₃	CH ₂	S	—	2-nitrophenyl	52—54
CF ₃	NO ₂	CH ₃	CH ₂	S	—	methyl	109—110
CF ₃	NO ₂	CH ₃	CH ₂	S	—	ethyl	(gum)
CF ₃	NO ₂	CH ₃	CH ₂	S	—	n-propyl	(gum)
CF ₃	NO ₂	CH ₃	CH ₂	S	—	isopropyl	66—68
CF ₃	CN	CH ₃	CH ₂	S	—	ethyl	(gum)
CF ₃	CN	CH ₃	CH ₂	S	—	n-propyl	(gum)
CF ₃	CN	CH ₃	CH ₂	S	—	isopropyl	98—100
CF ₃	CN	CH ₃	CH ₂	S	—	methyl	108.5—109.5
CN	CN	CH ₃	CH ₂	S	—	phenyl	82—83.5
Cl	Cl	CH ₃	CH ₂	S	—	methyl	90.5—91.5
Cl	CN	CH ₃	CH ₂	S	—	phenyl	60—62
Cl	CN	CH ₃	CH ₂	S	—	ethyl	96—98
NO ₂	Cl	CH ₃	CH ₂	S	—	phenyl	77—78
Cl	NO ₂	CH ₃	CH ₂	S	—	phenyl	88—90
Cl	NO ₂	CH ₃	CH ₂	S	—	ethyl	(gum)
Cl	NO ₂	CH ₃	CH ₂	S	—	n-butyl	(gum)
CH ₃ O	CN	CH ₃	CH ₂	S	—	phenyl	(gum)
CH ₃	CN	CH ₃	CH ₂	S	—	phenyl	98—99
CF ₃	NO ₂	CH ₃	CH ₂	S	CH ₂	phenyl	79—80
CF ₃	NO ₂	CH ₃	CH ₂ CH ₂	S	—	phenyl	(gum)
CF ₃	CN	CH ₃	CH ₂ CH ₂	S	—	phenyl	115—116.5
CF ₃	CN	CH ₃	CH ₂	S	CH ₂	phenyl	105—106
Cl	CN	CH ₃	CH ₂	S	CH ₂	phenyl	123—124
CF ₃	NO ₂	CF ₃	CH ₂	S	—	phenyl	139—140
CF ₃	NO ₂	CF ₃	CH ₂	S	—	4-chlorophenyl	147—148
CF ₃	NO ₂	CF ₃	CH ₂	S	—	4-nitrophenyl	145—146
CF ₃	NO ₂	CF ₃	CH ₂	S	—	methyl	82—85
CF ₃	NO ₂	CF ₃	CH ₂	S	—	ethyl	79—81
CF ₃	NO ₂	CF ₃	CH ₂	S	—	n-propyl	67—68

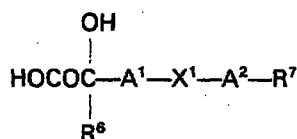
	R ¹	R ²	R ⁶	A ¹	X ¹	A ²	R ⁷	m.p. (°C.)
5	CF ₃	NO ₂	CF ₃	CH ₂	S	—	isopropyl	88—89
	CF ₃	CN	CF ₃	CH ₂	S	—	phenyl	143—144
	CF ₃	CN	CF ₃	CH ₂	S	—	4-chlorophenyl	178—179
10	CF ₃	CN	CF ₃	CH ₂	S	—	methyl	120.5—122
	CF ₃	CN	CF ₃	CH ₂	S	—	ethyl	119—120
15	CF ₃	CN	CF ₃	CH ₂	S	—	n-propyl	88—90
	CF ₃	CN	CF ₃	CH ₂	S	—	isopropyl	107—109
	Cl	Cl	CF ₃	CH ₂	S	—	phenyl	104
20	Cl	Cl	CF ₃	CH ₂	S	—	methyl	84—85
	Cl	Cl	CF ₃	CH ₂	S	—	ethyl	57—59
	Cl	Cl	CF ₃	CH ₂	S	—	n-propyl	60—61
25	Cl	Cl	CF ₃	CH ₂	S	—	isopropyl	57—59
	Cl	CN	CF ₃	CH ₂	S	—	phenyl	152
30	Cl	CN	CF ₃	CH ₂	S	—	methyl	121—122.5
	Cl	CN	CF ₃	CH ₂	S	—	ethyl	95—96
	Cl	CN	CF ₃	CH ₂	S	—	n-propyl	89—90
35	Cl	CN	CF ₃	CH ₂	S	—	isopropyl	87—88
	CF ₃	NO ₂	CF ₃	CH ₂	S	CH ₂	phenyl	120—121
40	CF ₃	CN	CF ₃	CH ₂	S	CH ₂	phenyl	138—139
	Cl	Cl	CF ₃	CH ₂	S	CH ₂	phenyl	145—146

45 All the anilines used as starting materials are known compounds. The 2-hydroxy-substituted-alkanoic acids were obtained either by the process described in the second part of Example 1 (Route A), or by the process exemplified below (Route B). Those acids which are novel and which were characterised by melting point are described in the table below:—

50 *Route B*

1,1,1-Trifluoro-3-phenylthioprop-2-one (13.1 g.) was added dropwise to a cooled stirred solution of potassium cyanide (4.4 g.) in water (16 ml.) at such a rate that the temperature of the mixture was maintained at between 0° and 5°C. A 4:1 v/v mixture of water and concentrated sulphuric acid (17.1 ml.) was added at such a rate as to maintain the above temperature, and the mixture was then stirred at laboratory temperature for 15 hours and then extracted three times with diethyl ether (25 ml. each time). The combined extracts were washed three times with water (25 ml. each time), dried over magnesium sulphate and evaporated to dryness under reduced pressure.

55 A mixture of the cyanhydrin thus obtained (3.0 g.) and concentrated aqueous hydrochloric acid (30 ml.) was heated in a sealed tube at 110°C. for 6 hours, cooled and poured onto ice. The aqueous mixture was extracted four times with diethyl ether (25 ml. each time) and the combined ethereal solutions were extracted twice with saturated aqueous sodium bicarbonate solution (40 ml. each time). The combined extracts were acidified with aqueous hydrochloric acid and then extracted twice with diethyl ether (40 ml. each time). The combined extracts were dried over magnesium sulphate and evaporated to dryness and the residue was stirred with petroleum ether (b.p. 60—80°C.). The mixture was filtered and there was thus obtained as solid residue 2-hydroxy-3-phenylthio-2-trifluoromethylpropionic acid, m.p. 83—84°C.



R ⁶	A ¹	X ¹	A ²	R ⁷	Route	m.p. (°C)
CH ₃	CH ₂	S	—	2-nitrophenyl	B	85—88
CH ₃	CH ₂	S	—	methyl	A	48—52
CH ₃	CH ₂	S	—	isopropyl	A	50—52
CH ₃	CH ₂	S	CH ₂	phenyl	A	62—63
CF ₃	CH ₂	S	—	4-nitrophenyl	B	169—171*
CF ₃	CH ₂	S	—	methyl	B	73—76
CF ₃	CH ₂	S	—	n-propyl	B	37—40
CF ₃	CH ₂	S	—	isopropyl	B	57—59
CF ₃	CH ₂	S	CH ₂	phenyl	B	91—92

*m.p. of dicyclohexylamine salt used for characterisation.

The thio-alkanones used in Route B were prepared by the reaction of the appropriate thiol with the appropriate bromoketone by conventional means (for example as described in Zhur.org.Khim., 1971, 7, 2221). Those which are novel and were characterised are described in the following table:—



A ²	R ⁷	b.p. (°C./mm.Hg.)
—	4-nitrophenyl	84.5—86 (m.p.)
—	methyl	39—47/100
—	n-propyl	72—82/65
—	isopropyl	75—85/87
CH ₂	phenyl	118—122/17

Example 3

A solution of ethanethiol (0.45 ml.) in tetrahydrofuran (5 ml.) was added dropwise to a stirred suspension of sodium hydride (0.28 g. of a 60% dispersion in mineral oil) in tetrahydrofuran (10 ml.) which was maintained at 0—5°C., and the mixture was then stirred at laboratory temperature for 15 minutes. A solution of 3,4-dichloro-*N*-(2,3-epoxy-2-methylpropionyl)aniline (1.5 g.) in tetrahydrofuran (15 ml.) was added dropwise and the mixture was stirred at laboratory temperature for 15 hours. Water (50 ml.) was added, the organic layer was separated and the aqueous layer was extracted twice with diethyl ether (25 ml. each time). The combined organic solutions were dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was purified by flash-chromatography on silica gel (Merck 9385) using a 1:1 v/v mixture of ethyl acetate and petroleum ether (b.p. 60—80°C.) as eluant. The product was crystallised from a 5:1 v/v mixture of toluene and petroleum ether (b.p. 60—80°C.) and there was thus obtained 3,4-dichloro-*N*-(3-ethylthio-2-hydroxy-2-methylpropionyl)aniline, m.p. 81—83°C.

The 3,4-dichloro-*N*-(2,3-epoxy-2-methylpropionyl)aniline used as starting material was obtained as follows:—

A solution of 3,4-dichloroaniline (10 g.) in dimethylacetamide (25 ml.) was added dropwise to a stirred, cooled solution of methacryloyl chloride (10 ml.) in dimethylacetamide (50 ml.) at such a rate that the internal temperature of the mixture did not exceed 0°C., and the mixture was then stirred at laboratory

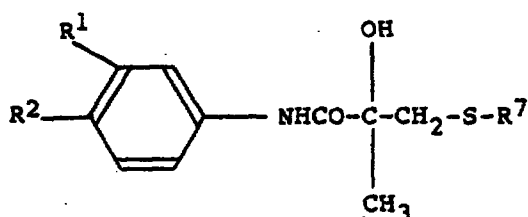
(21)

temperature for 16 hours and then poured into cold water (1 litre). The mixture was extracted 5 times with diethyl ether (100 ml. each time) and the combined extracts were dried and evaporated to dryness. The residue was crystallised from a 1:1 v/v mixture of toluene and petroleum ether (b.p. 60–80°C.) at –50°C., and there was thus obtained 3,4-dichloro-*N*-methacryloylaniline, m.p. 120–122°C.

m-Chloroperbenzoic acid (3.4 g.) was added portionwise to a boiling solution of 3,4-dichloro-*N*-methacryloylaniline (2.2 g.) and 4-methyl-2,6-di-*t*-butylphenol (0.05 g.) in 1,1,1-trichloroethane (75 ml.) and the mixture was heated under reflux for 4 hours, cooled and washed successively (25 ml. portions each time) once with saturated aqueous sodium sulphite solution, twice with saturated aqueous sodium bicarbonate solution and once with saturated sodium chloride solution, dried over magnesium sulphate and evaporated to dryness. The residue was purified by chromatography on a silica gel (Merck 7734) column using a 1:1 v/v mixture of ethyl acetate and petroleum ether (b.p. 60–80°C.) as eluant. The product was crystallised from petroleum ether (b.p. 60–80°C.) and there was thus obtained 3,4-dichloro-*N*-(2,3-epoxy-2-methylpropionyl)aniline, m.p. 90–92°C.

Example 4

The process described in Example 3 was repeated using the appropriate thiol and the appropriate *N*-(2,3-epoxy-2-methylpropionyl)aniline as starting materials, and there were thus obtained the compounds described in the following table:—



R ¹	R ²	R ⁷	m.p. (°C.)
Cl	Cl	thiazol-2-yl	105–107
Cl	Cl	pyrimidin-2-yl	103–105
CF ₃	NO ₂	2-chlorophenyl	98–100
CF ₃	NO ₂	3-chlorophenyl	132–133
CF ₃	NO ₂	4-chlorophenyl	101–103
CF ₃	NO ₂	4-fluorophenyl	112–113
CF ₃	NO ₂	4-cyanophenyl	108–111
CF ₃	NO ₂	4-nitrophenyl	139–141
CF ₃	NO ₂	4-methoxyphenyl	120–121
CF ₃	NO ₂	4-methylthiophenyl	111–112
CF ₃	NO ₂	<i>n</i> -pentyl	(oil)
CF ₃	NO ₂	2-hydroxyethyl	(oil)
CF ₃	NO ₂	allyl	80–81
CF ₃	NO ₂	2-methylallyl	78–79
CF ₃	NO ₂	cyclopentyl	87–88.5
CF ₃	NO ₂	pyrid-2-yl	155–157
CF ₃	NO ₂	pyrid-3-yl	149–150

(22)

R ¹	R ²	R ⁷	m.p. (°C.)
CF ₃	NO ₂	pyrid-4-yl	193—195
CF ₃	NO ₂	6-chloropyrid-2-yl	159—162
CF ₃	NO ₂	thiazol-2-yl	131—132
CF ₃	NO ₂	4-methylthiazol-2-yl	160—162
CF ₃	NO ₂	5-methyl-1,3,4-thiadiazol-2-yl	109—111
CF ₃	CN	4-chlorophenyl	137—138
CF ₃	CN	4-fluorophenyl	116—117
CF ₃	CN	4-methylthiophenyl	125—126
CF ₃	CN	pyrid-2-yl	137—139
CF ₃	CN	pyrid-3-yl	135—136
CF ₃	CN	5-chloropyrid-2-yl	113—115
CF ₃	CN	thien-2-yl	101—103
CF ₃	CN	thiazol-2-yl	107—109
CF ₃	CN	4,5-dihydrothiazol-2-yl	110—111
CF ₃	CN	1-methylimidazol-2-yl	112
CF ₃	CN	benzthiazol-2-yl	178—180
CF ₃	CN	pyrimidin-2-yl	120—121

Similarly, by using the appropriate thiol and the appropriate *N*-(2,3-epoxy-2-methylbutyryl)aniline there were obtained:—

4-cyano-3-trifluoromethyl-*N*-[(2*SR*,3*RS*)-3-*p*-fluorophenylthio-2-hydroxy-2-methylbutyryl]aniline, m.p. 114—116°C. and 4-nitro-3-trifluoromethyl-*N*-[(2*SR*,3*RS*)-2-hydroxy-2-methyl-3-phenylthiobutyryl]aniline, m.p. 143—145°C.

The *N*-(2,3-epoxy-2-methylpropionyl or butyryl)anilines used as starting material were obtained by the epoxidation of the appropriate *N*-methacryloyl or *N*-methylcrotonoylaniline by a similar process to that described in the second part of Example 3. *N*-Methacryloyl-4-nitro-3-trifluoromethylaniline had m.p. 102—104°C. and the corresponding epoxy compound had m.p. 119—121°C.;

4-cyano-*N*-methacryloyl-3-trifluoromethylaniline had m.p. 137—139°C. and the corresponding epoxy-compound had m.p. 149—150°C.

N-(2-methylcrotonoyl)-4-nitro-3-trifluoromethylaniline had m.p. 65—67°C. and the corresponding epoxy compound had m.p. 99—102°C.;

4-cyano-*N*-(2-methylcrotonoyl)-3-trifluoromethylaniline had m.p. 127—128°C. and the corresponding epoxy compound had m.p. 100—103°C.

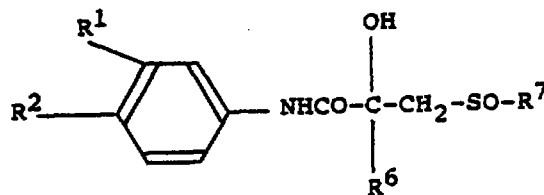
(The last two compounds are derived from *trans*-tiglic acid as opposed to *cis*-angelic acid).

Example 5

A solution of sodium metaperiodate (0.407 g.) in water (15 ml.) was added dropwise to a stirred solution of 4-cyano-3-trifluoromethyl-*N*-(3-ethylthio-2-hydroxy-2-trifluoromethylpropionyl)aniline (0.6 g.) in methanol (25 ml.) and the mixture was stirred at laboratory temperature for 48 hours and then filtered. The solid was washed with methanol (25 ml.) and the mixture was filtered, and the combined filtrates were evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (150 ml.) and the solution was washed successively with water (15 ml.), saturated aqueous sodium sulphite solution (25 ml.) and saturated aqueous sodium chloride solution (25 ml.), dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel (Merck 7734) using a 1:1 v/v mixture of ethyl acetate and petroleum ether (b.p. 60—80°C.) as eluant, and the two

diastereoisomers of 4-cyano-3-trifluoromethyl-*N*-(3-ethylsulphonyl-2-hydroxy-2-trifluoromethylpropionyl)-aniline were obtained by evaporation of the appropriate fractions of the eluate. These had m.p. 141—143°C. (more polar isomer) and 160—162°C. (less polar isomer).

The process described above was repeated using the appropriate thiopropionylaniline as starting material, and there were thus obtained the compounds described in the following table:—

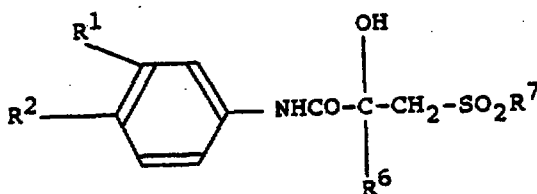


R ¹	R ²	R ⁶	R ⁷	Diastereoisomer	m.p. (°C.)
CF ₃	NO ₂	CH ₃	phenyl	more polar	126.5—127.5
CF ₃	CN	CH ₃	phenyl	more polar	164—165
CF ₃	CN	CH ₃	phenyl	mixed	175—176
CF ₃	CN	CH ₃	phenyl	mixed	110—112

Example 6

A solution of *m*-chloroperbenzoic acid (0.40 g.) in methylene chloride (80 ml.) was added to a stirred solution of 4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-3-phenylthio-2-trifluoromethylpropionyl)aniline (0.38 g.) in methylene chloride (100 ml.) during 30 minutes and the reaction mixture was then stirred at laboratory temperature for 18 hours. Aqueous 10% w/v sodium sulphite gel solution (15 ml.) was added, the mixture was stirred and the organic layer was separated, washed successively twice with aqueous 10% w/v sodium carbonate solution (15 ml. each time) and once with saturated aqueous sodium chloride solution (15 ml.), dried over anhydrous magnesium sulphate and evaporated to dryness. The residue was dissolved in a 1:1 v/v mixture of ethyl acetate and petroleum ether (b.p. 60—80°C.) and the solution was chromatographed on a silica gel column (Merck 7734) using a 1:1 v/v mixture of ethyl acetate and petroleum ether (b.p. 60—80°C.) as eluant. There was thus obtained 4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-3-phenylsulphonyl-2-trifluoromethylpropionyl)aniline, m.p. 175—176°C.

The process described above was repeated using the appropriate thiopropionylaniline as starting material and there were thus obtained the compounds described in the following table:—



24

R ¹	R ²	R ⁶	R ⁷	m.p. (°C)
CF ₃	NO ₂	CH ₃	phenyl	149—151
CF ₃	NO ₂	CH ₃	4-fluorophenyl	188—189
CF ₃	NO ₂	CH ₃	pyrid-2-yl	148—150
CF ₃	NO ₂	CH ₃	ethyl	135—136
CF ₃	NO ₂	CH ₃	n-propyl	118—119
CF ₃	NO ₂	CH ₃	n-pentyl	104—105
CF ₃	CN	CH ₃	phenyl	172—173.5
CF ₃	CN	CH ₃	4-fluorophenyl	189—191
CF ₃	CN	CH ₃	ethyl	116—118
CF ₃	CN	CH ₃	n-propyl	117—119
CF ₃	CN	CH ₃	ethyl	164—165
Cl	NO ₂	CH ₃	ethyl	145—146
Cl	NO ₂	CH ₃	n-butyl	116—118
Cl	CN	CH ₃	ethyl	135—136
CH ₃ O	CN	CH ₃	phenyl	172—173

Example 7

(-)-Camphanoyl chloride (4.33 g.) was added portionwise during 5 minutes to a solution of 4-cyano-3-trifluoromethyl-N-(2-hydroxy-3-phenylthio-2-trifluoromethylpropionyl)aniline (5.8 g.) in pyridine (35 ml.) and the mixture was heated at 95°C. for 150 minutes and then evaporated to dryness. Toluene (50 ml.) was added and the mixture was again evaporated to dryness. The residue was dissolved in ethyl acetate (200 ml.) and the solution was washed with water (30 ml.) and then twice with saturated aqueous sodium chloride solution (20 ml. each time), dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was dissolved in methylene chloride (10 ml.) and the solution was flash chromatographed on silica gel (Merck 9385) using methylene chloride as eluant. There were thus obtained the two diastereoisomers of 4-cyano-3-trifluoromethyl-N-[2-(-)-camphanoyloxy-3-phenylthio-2-trifluoromethylpropionyl]aniline, the less polar isomer having m.p. 121—123°C. and the more polar isomer having m.p. 140—143°C.

A mixture of a solution of the less polar isomer (2.0 g.) in methanol (30 ml.) and aqueous 4% w/v sodium hydroxide solution (3.5 ml.) was stirred at laboratory temperature for 30 minutes and then evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (160 ml.) and the solution was washed successively with water (25 ml.), saturated aqueous sodium chloride solution (25 ml.), and saturated aqueous sodium chloride solution (25 ml.), dried over magnesium sulphate and evaporated to dryness. The residue was dissolved in methylene chloride (5 ml.) and flash-chromatographed on silica gel (Merck 9385) using methylene chloride as eluant. The product was crystallised from petroleum ether (b.p. 60—80°C.) and there was thus obtained (-)-4-cyano-3-trifluoromethyl-N-(2-hydroxy-3-phenylthio-2-trifluoromethylpropionyl)aniline, m.p. 156—157°C., $[\alpha]_D^{23} = 43.8^\circ$ (C, 1% in methanol).

The process described in the preceding paragraph was repeated using the more polar isomer of the camphanoyl ester, and the product obtained was crystallised from a 5:1 v/v mixture of toluene and petroleum ether (b.p. 60—80°C.). There was thus obtained (+)-4-cyano-3-trifluoromethyl-N-(2-hydroxy-3-phenylthio-2-trifluoromethylpropionyl)aniline, m.p. 159—160°C., $[\alpha]_D^{23} = +45.5^\circ$ (C, 1% in methanol).

Example 8

The process described in Example 7 was repeated using 4-cyano-3-trifluoromethyl-N-(3-p-fluorophenylthio-2-hydroxy-2-methylpropionyl)aniline as the compound to be resolved. There were thus obtained the (-)-isomer, m.p. 94—96°C., $[\alpha]_D^{24} = -3.06^\circ$ (C, 1% in methanol) and the (+)-isomer, m.p. 95—97°C., $[\alpha]_D^{24} = +2.42^\circ$ (C, 1% in methanol).

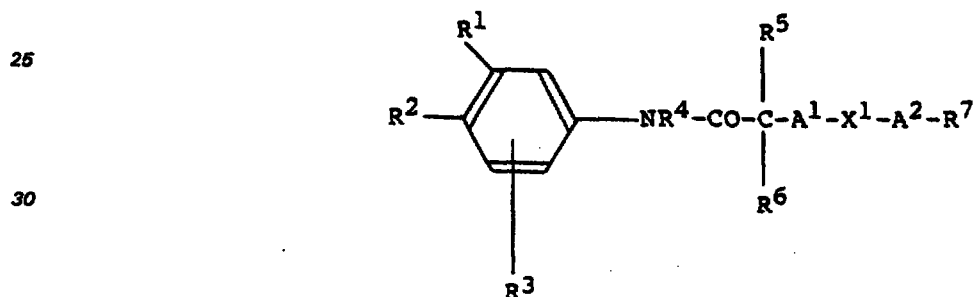
Example 9

n-Butyl-lithium (4.7 ml. of a 1.6 molar solution in hexane) was added during 2 minutes to a stirred solution of methylthiobenzene (0.82 ml.) and 1,4-diazabicyclo[2,2,2]octane (0.78 g.) in tetrahydrofuran (20 ml.) which was maintained at $-2^{\circ}\text{C}.$ under an atmosphere of argon. The mixture was allowed to warm up to $+2^{\circ}\text{C}.$, stirred at that temperature for 2 hours, cooled to $-65^{\circ}\text{C}.$ and a solution of *N*-(3,4-dichlorophenyl)pyruvamide (0.81 g.) in tetrahydrofuran (5 ml) was added during 5 minutes. The mixture was stirred and allowed to warm up to $-30^{\circ}\text{C}.$ during 90 minutes, aqueous 2N-hydrochloric acid (25 ml.) was added, the tetrahydrofuran was removed by evaporation under reduced pressure and the residue was extracted three times with diethyl ether (40 ml. each time). The combined extracts were washed with saturated aqueous sodium chloride solution, dried and evaporated to dryness and the residue was purified by flash chromatography on a silica gel column (Merck 9385) using a 5:2 v/v mixture of petroleum ether (b.p. $60-80^{\circ}\text{C}.$) and ethyl acetate as eluant. The product was crystallised from petroleum ether (b.p. $60-80^{\circ}\text{C}.$) and there was thus obtained 3,4-dichloro-*N*-(2-hydroxy-2-methyl-3-phenylthiopropionyl)aniline, m.p. $85-86^{\circ}\text{C}.$

The process described above was repeated using 4-bromo-2-methylsulphonylthiophen as starting material in place of methylthiobenzene. There was thus obtained *N*-[3-(4-bromothiophen-2-ylsulphonyl)-2-hydroxy-2-methylpropionyl]-3,4-dichloroaniline, m.p. $170-171^{\circ}\text{C}.$

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. An acylanilide of the formula:—



wherein R^1 is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo or hydrogen, or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;

wherein R^2 is cyano, carbamoyl, nitro, fluoro, chloro, bromo or iodo, or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;

wherein R^3 is hydrogen or halogen;

wherein R^4 is hydrogen or alkyl of up to 4 carbon atoms, or is joined to R^5 as stated below;

wherein R^5 is hydroxy or alkoxy or acyloxy each of up to 15 carbon atoms, or is joined to R^4 to form an oxycarbonyl group such that together with the $-\text{N}-\text{CO}-\text{C}-$ part of the molecule it forms an oxazolidinedione group;

wherein R^6 is alkyl or halogenoalkyl of up to 4 carbon atoms, or has the formula $-\text{A}^3-\text{R}^8$ or $-\text{A}^4-\text{X}^2-\text{A}^5-\text{R}^9$;

wherein A^1 and A^4 , which may be the same or different, each is alkylene of up to 6 carbon atoms;

wherein A^2 , A^3 and A^5 , which may be the same or different, each is a direct link or alkylene of up to 6 carbon atoms;

wherein X^1 and X^2 , which may be the same or different, each is sulphur, sulphinyl ($-\text{SO}-$) or sulphonyl ($-\text{SO}_2-$);

wherein R^7 and R^9 , which may be the same or different, each is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbon atoms, or R^7 or R^9 is phenyl which bears one, two or three substituents selected from hydrogen, halogen, nitro, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxycarbonyl and *N*-alkylcarbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or R^7 or R^9 is naphthyl; or R^7 or R^9 is 5- or 6-membered saturated or unsaturated heterocyclic which contains one, two or three heteroatoms selected from oxygen, nitrogen and sulphur, which heterocyclic may be a single ring or may be fused to a benzo-ring, and which heterocyclic is unsubstituted or bears one or two halogen, cyano or amino, or alkyl, alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl each of up to 4 carbon atoms, or oxy or hydroxy substituents, or which if sufficiently saturated may bear one or two oxo substituents; and wherein R^8 is phenyl, naphthyl or heterocyclic as defined above for R^7 or R^9 .

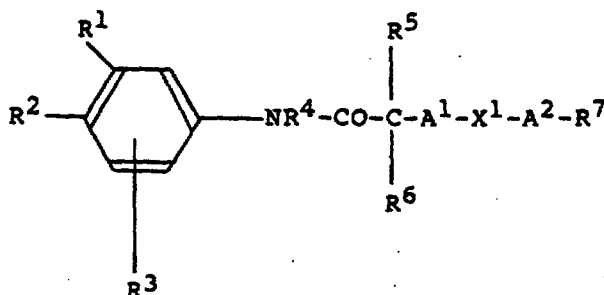
Example 9

n-Butyl-lithium (4.7 ml. of a 1.6 molar solution in hexane) was added during 2 minutes to a stirred solution of methylthiobenzene (0.82 ml.) and 1,4-diazabicyclo[2,2,2]octane (0.78 g.) in tetrahydrofuran (20 ml.) which was maintained at -2°C . under an atmosphere of argon. The mixture was allowed to warm up to $+2^{\circ}\text{C}$., stirred at that temperature for 2 hours, cooled to -65°C . and a solution of *N*-(3,4-dichlorophenyl)pyruvamide (0.81 g.) in tetrahydrofuran (5 ml) was added during 5 minutes. The mixture was stirred and allowed to warm up to -30°C . during 90 minutes, aqueous 2N-hydrochloric acid (25 ml.) was added, the tetrahydrofuran was removed by evaporation under reduced pressure and the residue was extracted three times with diethyl ether (40 ml. each time). The combined extracts were washed with saturated aqueous sodium chloride solution, dried and evaporated to dryness and the residue was purified by flash chromatography on a silica gel column (Merck 9385) using a 5:2 v/v mixture of petroleum ether (b.p. $60-80^{\circ}\text{C}$.) and ethyl acetate as eluant. The product was crystallised from petroleum ether (b.p. $60-80^{\circ}\text{C}$.) and there was thus obtained 3,4-dichloro-*N*-(2-hydroxy-2-methyl-3-phenylthiopropionyl)aniline, m.p. $85-86^{\circ}\text{C}$.

The process described above was repeated using 4-bromo-2-methylsulphonylthiophen as starting material in place of methylthiobenzene. There was thus obtained *N*-[3-(4-bromothiophen-2-ylsulphonyl)-2-hydroxy-2-methylpropionyl]-3,4-dichloroaniline, m.p. $170-171^{\circ}\text{C}$.

' Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. An acylanilide of the formula:—



wherein R^1 is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo or hydrogen, or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;

wherein R^2 is cyano, carbamoyl, nitro, fluoro, chloro, bromo or iodo, or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;

wherein R^3 is hydrogen or halogen;

wherein R^4 is hydrogen or alkyl of up to 4 carbon atoms, or is joined to R^5 as stated below;

wherein R^5 is hydroxy or alkoxy or acyloxy each of up to 15 carbon atoms, or is joined to R^4 to form an oxycarbonyl group such that together with the $-\text{N}-\text{CO}-\text{C}-$ part of the molecule it forms an oxazolidinedione group;

wherein R^6 is alkyl or halogenoalkyl of up to 4 carbon atoms, or has the formula $-\text{A}^3-\text{R}^8$ or $-\text{A}^4-\text{X}^2-\text{A}^5-\text{R}^9$;

wherein A^1 and A^4 , which may be the same or different, each is alkylene of up to 6 carbon atoms;

wherein A^2 , A^3 and A^5 , which may be the same or different, each is a direct link or alkylene of up to 6 carbon atoms;

wherein X^1 and X^2 , which may be the same or different, each is sulphur, sulphinyl ($-\text{SO}-$) or sulphonyl ($-\text{SO}_2-$);

wherein R^7 and R^9 , which may be the same or different, each is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbon atoms, or R^7 or R^9 is phenyl which bears one, two or three substituents selected from hydrogen, halogen, nitro, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxycarbonyl and *N*-alkylcarbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or R^7 or R^9 is naphthyl; or R^7 or R^9 is 5- or 6-membered saturated or unsaturated heterocyclic which contains one, two or three heteroatoms selected from oxygen, nitrogen and sulphur, which heterocyclic may be a single ring or may be fused to a benzo-ring, and which heterocyclic is unsubstituted or bears one or two halogen, cyano or amino, or alkyl, alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl each of up to 4 carbon atoms, or oxy or hydroxy substituents, or which if sufficiently saturated may bear one or two oxo substituents; and wherein R^8 is phenyl, naphthyl or heterocyclic as defined above for R^7 or R^9 .



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2. An acylanilide as claimed in claim 1 wherein R¹ is cyano, nitro, trifluoromethyl, chloro, methyl or methoxy, R² is cyano, nitro, trifluoromethyl or chloro, R³ and R⁴ are both hydrogen, R⁵ is hydroxy, R⁶ is methyl or trifluoromethyl, A¹ is methylene, ethylene or ethylidene, X¹ is sulphur, sulphonyl or sulphonyl, A² is a direct link or methylene and R⁷ is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbon atoms, or phenyl which is unsubstituted or which bears one fluoro, chloro, cyano, nitro, methoxy or methylthio substituent, or thienyl, imidazolyl, thiazolyl, benzothiazolyl, thiadiazolyl, pyridyl or pyrimidinyl which is unsubstituted or which bears one chloro, bromo or methyl substituent.

3. An acylanilide as claimed in claim 1 wherein R¹ is trifluoromethyl, R² is cyano or nitro, R³ and R⁴ are both hydrogen, R⁵ is hydroxy, R⁶ is methyl, A¹ is methylene, X¹ is sulphur, sulphonyl or sulphonyl, A² is a direct link and R⁷ is alkyl of up to 3 carbon atoms, or is allyl, phenyl, *p*-fluorophenyl, thiazol-2-yl, 4-methylthiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl or 2-pyridyl.

4. The compound

3-chloro-4-cyano-*N*-(3-ethylthio-2-hydroxy-2-methylpropionyl)-aniline;

3-chloro-4-cyano-*N*-(3-ethylsulphonyl-2-hydroxy-2-methylpropionyl)-aniline;

4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-phenylsulphonylpropionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-phenylsulphonylpropionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-phenylsulphonylpropionyl)-aniline;

3-chloro-4-nitro-*N*-(2-hydroxy-2-methyl-3-phenylthio-2-methylpropionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(thiazol-2-ylthio)propionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(3-allylthio-2-hydroxy-2-methylpropionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(3-*p*-fluorophenylthio-2-hydroxy-2-methylpropionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(pyrid-2-ylthio)propionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(5-methyl-1,3,4-thiadiazol-2-

ylthio)propionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(4-methylthiazol-2-ylthio)propionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(pyrid-2-ylsulphonyl)propionyl)-aniline;

4-nitro-3-trifluoromethyl-*N*-(3-*p*-fluorophenylsulphonyl-2-hydroxy-2-methylpropionyl)-aniline;

4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(thiazol-2-ylthio)propionyl)-aniline;

4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-(pyrid-2-ylthio)propionyl)-aniline;

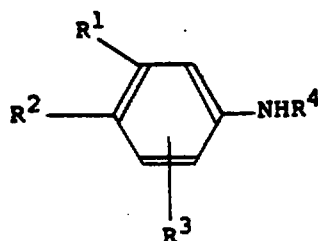
4-cyano-3-trifluoromethyl-*N*-(2-hydroxy-2-methyl-3-methylthiopropionyl)-aniline;

4-cyano-3-trifluoromethyl-*N*-(3-*p*-fluorophenylthio-2-hydroxy-2-methylpropionyl)-aniline.

5. The compound 4-cyano-3-trifluoromethyl-*N*-(3-*p*-fluorophenylsulphonyl-2-hydroxy-2-methylpropionyl)-aniline.

6. A process for the manufacture of an acylanilide, claimed in claim 1, which comprises

(a) the reaction of an amine of the formula:—

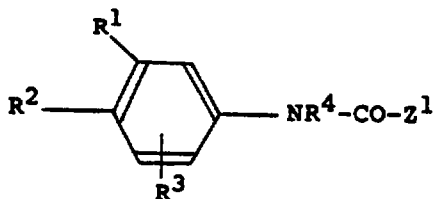


wherein R¹, R², R³ and R⁴ have the meanings stated in claim 1, with an acid of the formula:—



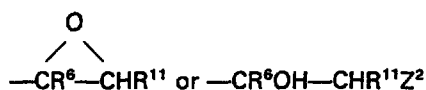
wherein R⁵, R⁶, R⁷, X¹, A¹ and A² have the meanings stated in claim 1, or with a reactive derivative of said acid; or

(b) for the manufacture of an acylanilide wherein R⁵ is hydroxy and X¹ is sulphur, the reaction of an epoxide of the formula:—

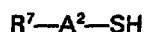


wherein R¹, R², R³ and R⁴ have the meanings stated above and wherein Z¹ has the formula



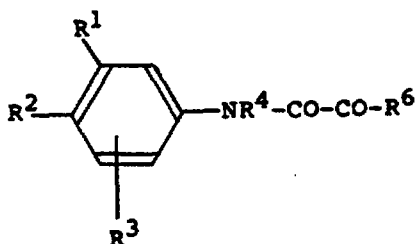


5 wherein R^6 has the meaning stated above, wherein Z^2 is a displaceable group and wherein R^{11} is such that $-\text{CHR}^{11}-$ is $-\text{A}^1-$ as stated above, with a thiol of the formula:—

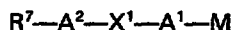


10 wherein R^7 and A^2 have the meanings stated above; or

(c) for the manufacture of an acylanilide wherein R^5 is hydroxy, the reaction of a compound of the formula:—

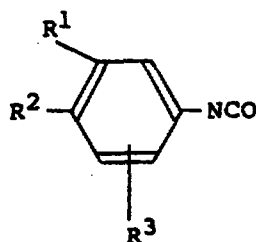


15 wherein R^1 , R^2 , R^3 , R^4 and R^6 have the meanings stated above, with an organometallic compound of the formula:—

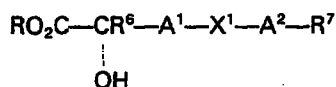


20 wherein A^1 , A^2 , R^7 and X^1 have the meanings stated above and M is a metal radical; or

25 (d) for the manufacture of an acylanilide of the invention wherein R^4 and R^5 are joined together to form a carbonyloxy group, the reaction of an isocyanate of the formula:—



30 wherein R^1 , R^2 and R^3 have the meanings stated above, with an ester of the formula:—



35 wherein R^6 , R^7 , X^1 , A^1 and A^2 have the meanings stated above, and wherein R is alkyl of up to 6 carbon atoms: whereafter

(i) an acylanilide wherein R^5 is hydroxy may be prepared by the hydrolysis of the corresponding acylanilide wherein R^5 is acyloxy; or

(ii) an acylanilide wherein R^5 is hydroxy and R^4 is hydrogen may be prepared by the hydrolysis of the corresponding oxazolidinedione, which may be prepared as described in paragraph (d) above; or

40 (iii) an acylanilide wherein R^4 is alkyl may be prepared by the alkylation of the corresponding acylanilide wherein R^4 is hydrogen; or

(iv) an acylanilide wherein R^5 is acyloxy may be prepared by the acylation of the corresponding acylanilide wherein R^5 is hydroxy; or

45 (v) an oxazolidinedione wherein R^4 and R^5 are joined together to form a carbonyloxy group may be prepared by the reaction of the corresponding acylanilide wherein R^4 is hydrogen and R^5 is hydroxy with phosgene (COCl_2); or

50 (vi) an acylanilide wherein X^1 or X^2 is sulphonyl or sulphinyl or wherein one or more of R^1 , R^2 and a substituent in the phenyl or heterocyclic group R^7 , R^8 or R^9 is alkylsulphonyl, perfluoroalkylsulphonyl or phenylsulphonyl, or is alkylsulphinyl, perfluoroalkylsulphinyl or phenylsulphinyl, may be prepared by the oxidation of the corresponding acylanilide wherein X^1 or X^2 is sulphur or wherein one or more of R^1 , R^2 and



a substituent in the phenyl or heterocyclic group R^7 , R^8 or R^9 is alkylthio, perfluoroalkylthio or phenylthio, respectively; or (vi) a racemic acylanilide wherein R^5 is hydroxy may be separated into its optical isomers by forming an ester of the hydroxy group R^5 with an optically-active acid, separating the diastereoisomeric esters thus obtained, and then hydrolysing each separate ester to the alcohol.

7. A pharmaceutical or veterinary composition which comprises an acylanilide, claimed in claim 1, in association with a pharmaceutically-acceptable diluent or carrier.

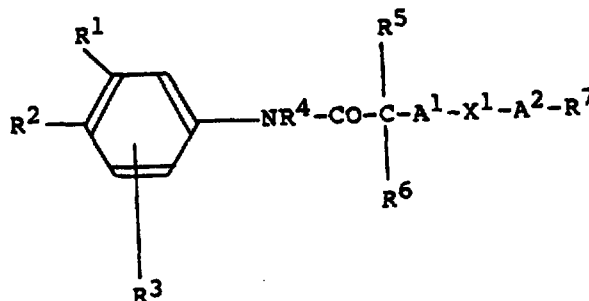
8. A composition as claimed in claim 7 which is in a form suitable for oral dosage, as a tablet, capsule, aqueous or oily solution or suspension or emulsion; or in the form of a sterile solution or suspension suitable for parenteral administration; or in the form of an ointment or lotion for topical administration, or in the form of a suppository for anal or vaginal administration.

9. A composition as claimed in claim 7 which additionally contains one or more drugs selected from anti-oestrogens, aromatase inhibitors, progestins, inhibitors of gonadotrophin secretion, LH—RH— analogues, cytotoxic agents, antibiotics and anti-inflammatory agents.

10. The use of a compound, claimed in any of claims 1 to 5 for the manufacture of a medicament for producing an antiandrogenic effect in a warm blooded animal.

Claims for the Contracting State: AT

1. A process for the manufacture of an acylanilide of the formula:—



wherein R^1 is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo or hydrogen, or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;

wherein R^2 is cyano, carbamoyl, nitro, fluoro, chloro, bromo or iodo, or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;

wherein R^3 is hydrogen or halogen;

wherein R^4 is hydrogen or alkyl of up to 4 carbon atoms, or is joined to R^5 as stated below;

wherein R^5 is hydroxy or alkoxy or acyloxy each of up to 15 carbon atoms, or is joined to R^4 to form an oxycarbonyl group such that together with the $-N-CO-C-$ part of the molecule it forms an oxazolidinedione group;

wherein R^6 is alkyl or halogenoalkyl of up to 4 carbon atoms, or has the formula $-A^3-R^8$ or $-A^4-X^2-A^5-R^9$;

wherein A^1 and A^4 , which may be the same or different, each is alkylene of up to 6 carbon atoms;

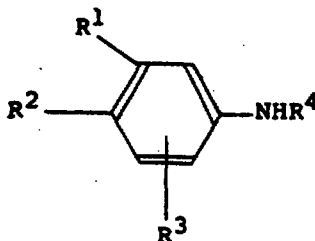
wherein A^2 , A^3 and A^5 , which may be the same or different, each is a direct link or alkylene of up to 6 carbon atoms;

wherein X^1 and X^2 , which may be the same or different, each is sulphur, sulphinyl ($-SO-$) or sulphonyl ($-SO_2-$);

wherein R^7 and R^9 , which may be the same or different, each is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbon atoms, or R^7 or R^9 is phenyl which bears one, two or three substituents selected from hydrogen, halogen, nitro, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxycarbonyl and *N*-alkylcarbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or R^7 or R^9 is naphthyl; or R^7 or R^9 is 5- or 6-membered saturated or unsaturated heterocyclic which contains one, two or three heteroatoms selected from oxygen, nitrogen and sulphur, which heterocyclic may be a single ring or may be fused to a benzo-ring, and which heterocyclic is unsubstituted or bears one or two halogen, cyano or amino, or alkyl, alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl each of up to 4 carbon atoms, or oxy or hydroxy substituents, or which if sufficiently saturated may bear one or two oxo substituents; and wherein R^8 is phenyl, naphthyl or heterocyclic as defined above for R^7 or R^9 , characterised by:—



(a) the reaction of an amine of the formula:—

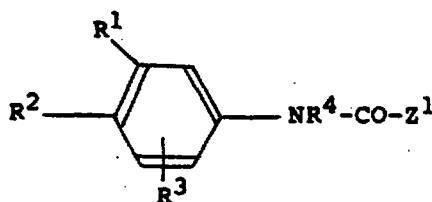


wherein R¹, R², R³ and R⁴ have the meanings stated above, with an acid of the formula:—

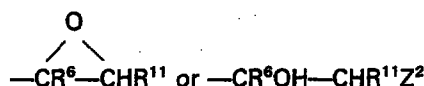


wherein R⁵, R⁶, R⁷, X¹, A¹ and A² have the meanings stated above, or with a reactive derivative of said acid; or

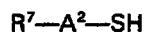
(b) for the manufacture of an acylanilide wherein R⁵ is hydroxy and X¹ is sulphur, the reaction of an epoxide of the formula:—



wherein R¹, R², R³ and R⁴ have the meanings stated above and wherein Z¹ has the formula

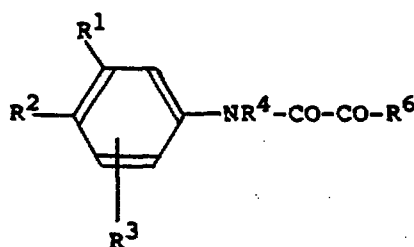


wherein R⁶ has the meaning stated above, wherein Z² is a displaceable group and wherein R¹¹ is such that —CHR¹¹— is —A¹— as stated above, with a thiol of the formula:—

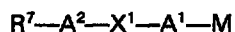


wherein R⁷ and A² have the meanings stated above; or

(c) for the manufacture of an acylanilide wherein R⁵ is hydroxy, the reaction of a compound of the formula:—



wherein R¹, R², R³, R⁴ and R⁶ have the meanings stated above, with an organometallic compound of the formula:—

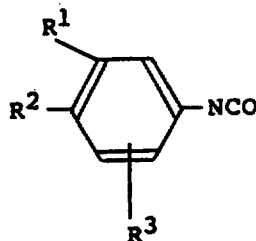


wherein A¹, A², R⁷ and X¹ have the meanings stated above and M is a metal radical; or

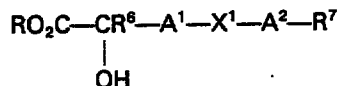
(d) for the manufacture of an acylanilide of the invention wherein R⁴ and R⁵ are joined together to form a carbonyloxy group, the reaction of an isocyanate of the formula:—



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wherein R¹, R² and R³ have the meanings stated above, with an ester of the formula:—



wherein R⁶, R⁷, X¹, A¹ and A² have the meanings stated above, and wherein R is alkyl of up to 6 carbon atoms: whereafter

(i) an acylanilide wherein R⁵ is hydroxy may be prepared by the hydrolysis of the corresponding acylanilide wherein R⁵ is acyloxy; or

(ii) an acylanilide wherein R⁵ is hydroxy and R⁴ is hydrogen may be prepared by the hydrolysis of the corresponding oxazolidinedione, which may be prepared as described in paragraph (d) above; or

(iii) an acylanilide wherein R⁴ is alkyl may be prepared by the alkylation of the corresponding acylanilide wherein R⁴ is hydrogen; or

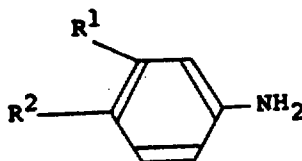
(iv) an acylanilide wherein R⁵ is acyloxy may be prepared by the acylation of the corresponding acylanilide wherein R⁵ is hydroxy; or

(v) an oxazolidinedione wherein R⁴ and R⁵ are joined together to form a carbonyloxy group may be prepared by the reaction of the corresponding acylanilide wherein R⁴ is hydrogen and R⁵ is hydroxy with phosgene (COCl₂); or

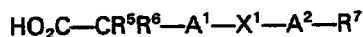
(vi) an acylanilide wherein X¹ or X² is sulphinyl or sulphonyl, or wherein one or more of R¹, R² and a substituent in the phenyl or heterocyclic group R⁷, R⁸ or R⁹ is alkylsulphinyl, perfluoroalkylsulphinyl or phenylsulphinyl, or is alkylsulphonyl, perfluoroalkylsulphonyl or phenylsulphonyl, may be prepared by the oxidation of the corresponding acylanilide wherein X¹ or X² is sulphur, or wherein more of R¹, R², and a substituent in the phenyl or heterocyclic group R⁷, R⁸ or R⁹ is alkylthio, perfluoroalkylthio or phenylthio, respectively; or (vi) a racemic acylanilide wherein R⁵ is hydroxy may be separated into its optical isomers by forming an ester of the hydroxy group R⁵ with an optically-active acid, separating the diastereoisomeric esters thus obtained, and then hydrolysing each separate ester to the alcohol.

2. A process for the manufacture of an acylanilide of the formula stated in claim 1 wherein R¹ is cyano, nitro, trifluoromethyl, chloro, methyl or methoxy, R² is cyano, nitro, trifluoromethyl or chloro, R³ and R⁴ are both hydrogen, R⁵ is hydroxy, R⁶ is methyl or trifluoromethyl, A¹ is methylene, ethylene or ethylidene, X¹ is sulphur, sulphinyl or sulphonyl, A² is a direct link or methylene and R⁷ is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbon atoms, or phenyl which is unsubstituted or which bears one fluoro, chloro, cyano, nitro, methoxy or methylthio substituent, or thienyl, imidazolyl, thiazolyl, benzothiazolyl, thiadiazolyl, pyridyl or pyrimidinyl which is unsubstituted or which bears one chloro, bromo or methyl substituent, characterised by:—

(a) the reaction of an amine of the formula:—



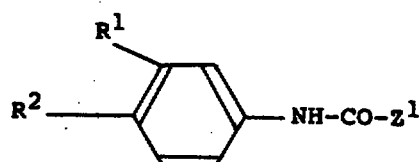
wherein R¹ and R² have the meanings stated above, with an acid of the formula:—



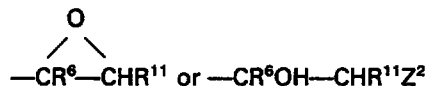
wherein R⁶, R⁷, X¹, A¹ and A² have the meanings stated above and R⁶ is hydroxy or acyloxy as stated in claim 1, or with a reactive derivative of said acid; or

(b) for the manufacture of an acylanilide wherein X¹ is sulphur, the reaction of an epoxide of the formula:—

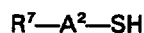




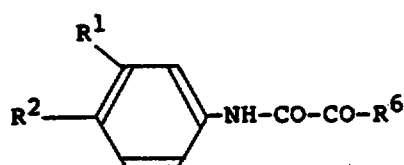
wherein R^1 and R^2 have the meanings stated above and wherein Z^1 has the formula



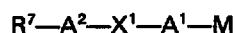
wherein R^6 has the meaning stated above, wherein Z^2 is a displaceable group and wherein R^{11} is such that $\text{—CHR}^{11}\text{—}$ is $\text{—A}^1\text{—}$ as stated above, with a thiol of the formula:—



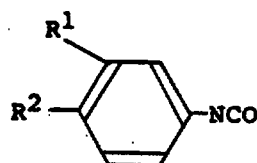
wherein R^7 and A^2 have the meanings stated above; or
(c) the reaction of a compound of the formula:—



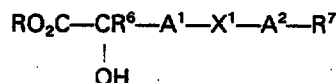
wherein R^1 , R^2 and R^6 have the meanings stated above, with an organometallic compound of the formula:—



wherein A^1 , A^2 , R^7 and X^1 have the meanings stated above and M is a metal radical; or
(d) the reaction of an isocyanate of the formula:—



wherein R^1 and R^2 have the meanings stated above, with an ester of the formula:—



wherein R^6 , R^7 , X^1 , A^1 and A^2 have the meanings stated above, and wherein R is alkyl of up to 6 carbon atoms, followed by hydrolysis of the oxazolidinedione thus obtained; whereafter

(i) an acylanilide wherein R^5 is hydroxy may be prepared by the hydrolysis of the corresponding acylanilide wherein R^5 is acyloxy; or

(ii) an acylanilide wherein X^1 is sulphonyl or sulphonyl may be prepared by the oxidation of the corresponding acylanilide wherein X^1 is sulphur; or

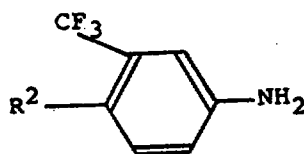
(iii) a racemic acylanilide may be separated into its optical isomers by forming an ester of the hydroxy group R^5 with an optically-active acid, separating the diastereoisomeric esters thus obtained, and then hydrolysing each separate ester to the alcohol.

3. A process for the manufacture of an acylanilide of the formula stated in claim 1 wherein R^1 is trifluoromethyl, R^2 is cyano or nitro, R^3 and R^4 are both hydrogen, R^5 is hydroxy, R^6 is methyl, A^1 is methylene, X^1 is sulphur, sulphonyl or sulphonyl, A^2 is a direct link and R^7 is alkyl of up to 3 carbon atoms, or is allyl, phenyl, *p*-fluorophenyl, thiazol-2-yl, 4-methylthiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl or 2-pyridyl, characterised by:—



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(a) the reaction of an amine of the formula:—

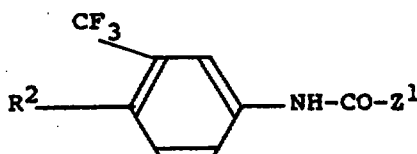


wherein R² has the meaning stated above, with an acid of the formula:—

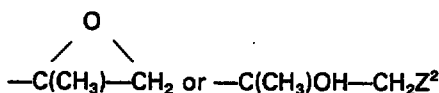


wherein R⁷ and X¹ have the meanings stated above and R⁵ is hydroxy or acyloxy as stated in claim 1, or with a reactive derivative of said acid; or

(b) for the manufacture of an acylanilide wherein X¹ is sulphur, the reaction of an epoxide of the formula:—



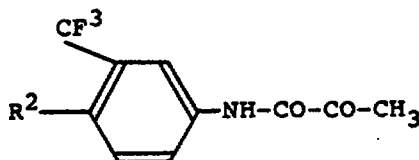
wherein R² has the meaning stated above and wherein Z¹ has the formula



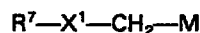
wherein Z² is a displaceable group, with a thiol of the formula:—

wherein R⁷ has the meaning stated above; or

(c) reaction of a compound of the formula:—



wherein R² has the meaning stated above, with an organometallic compound of the formula:—



wherein R⁷ and X¹ have the meanings stated above and M is a metal radical; whereafter

(i) an acylanilide wherein R⁵ is hydroxy may be prepared by the hydrolysis of the corresponding acylanilide wherein R⁵ is acyloxy; or

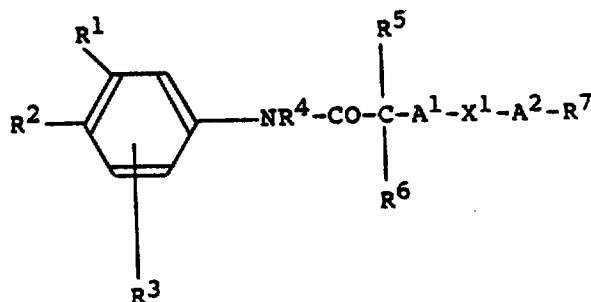
(ii) an acylanilide wherein X¹ is sulphonyl or sulphonyl may be prepared by the oxidation of the corresponding acylanilide wherein X¹ is sulphur; or

(iii) a racemic acylanilide may be separated into its optical isomers by forming an ester of the hydroxy group R⁵ with an optically-active acid, separating the diastereoisomeric esters thus obtained, and then hydrolysing each separate ester to the alcohol.

4. A process as claimed in claim 1, 2 or 3 wherein in the starting materials R¹ is trifluoromethyl, R² is cyano, R³ and R⁴ are both hydrogen, R⁵ is hydroxy or acyloxy, R⁶ is methyl, A¹ is methylene, X¹ is sulphur or sulphonyl, A² is a direct link and R⁷ is *p*-fluorophenyl, whereafter if R⁵ is acyloxy the compound is hydrolysed to the corresponding compound wherein R⁵ is hydroxy, and if X¹ is sulphur the compound is oxidised to the corresponding compound wherein X¹ is sulphonyl.



1. Acylanilid der Formel



worin R¹ für Cyano, Carbamoyl, Nitro, Fluoro, Chloro, Bromo, Jodo oder Wasserstoff oder Alkyl, Alkoxy, Alkanoyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Perfluoroalkyl, Perfluoroalkylthio, Perfluoroalkylsulfinyl oder Perfluoroalkylsulfonyl mit jeweils bis zu 4 Kohlenstoffatomen oder Phenylthio, Phenylsulfinyl oder Phenylsulfonyl steht;

worin R² für Cyano, Carbamoyl, Nitro, Fluoro, Chloro, Bromo oder Jodo oder Alkanoyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Perfluoroalkyl, Perfluoroalkylthio, Perfluoroalkylsulfinyl oder Perfluoroalkylsulfonyl mit jeweils bis zu 4 Kohlenstoffatomen oder Phenylthio, Phenylsulfinyl oder Phenylsulfonyl steht;

worin R³ für Wasserstoff oder Halogen steht;

worin R⁴ für Wasserstoff oder Alkyl mit bis zu 4 Kohlenstoffatomen steht oder mit R⁵ verbunden ist, wie es nachstehend angegeben ist;

worin R⁵ für Hydroxy oder Alkoxy oder Acyloxy mit jeweils bis zu 15 Kohlenstoffatomen steht oder mit R⁴ unter Bildung einer Oxycarbonylgruppe verbunden ist, so daß es zusammen mit dem —N—CO—C— Teil des Moleküls eine Oxazolidindiongruppe bildet;

worin R⁶ für Alkyl oder Halogenoalkyl mit bis zu 4 Kohlenstoffatomen steht oder die Formel —A³—R⁸ oder —A⁴—X²—A⁵—R⁹ aufweist;

worin A¹ und A⁴, welche gleich oder verschieden sein können, jeweils für Alkylen mit bis zu 6 Kohlenstoffatomen stehen;

worin A², A³ und A⁵, welche gleich oder verschieden sein können, jeweils für eine direkte Bindung oder Alkylen mit bis zu 6 Kohlenstoffatomen stehen;

worin X¹ und X², welche gleich oder verschieden sein können, jeweils für Schwefel, Sulfinyl (—SO—) oder Sulfonyl (—SO₂—) stehen;

worin R⁷ und R⁹, welche gleich oder verschieden sein können, jeweils für Alkyl, Alkenyl, Hydroxyalkyl oder Cycloalkyl mit jeweils bis zu 6 Kohlenstoffatomen stehen oder R⁷ oder R⁹ für Phenyl steht, das einen, zwei oder drei Substituenten trägt, die ausgewählt sind aus Wasserstoff, Halogen, Nitro, Carboxy, Carbamoyl und Cyano und Alkyl, Alkoxy, Alkanoyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Perfluoroalkyl, Perfluoroalkylthio, Perfluoroalkylsulfinyl, Perfluoroalkylsulfonyl, Alkoxycarbonyl und N-Alkylcarbamoyl mit jeweils bis zu 4 Kohlenstoffatomen und Phenyl, Phenylthio, Phenylsulfinyl und Phenylsulfonyl, oder R⁷ oder R⁹ für Naphthyl steht oder R⁷ oder R⁹ für einen 5- oder 6-gliedrigen, gesättigten oder ungesättigten Heterozyklus steht, der ein, zwei oder drei Heteroatome enthält, die ausgewählt sind aus Sauerstoff, Stickstoff und Schwefel, welcher Heterozyklus ein einzelner Ring sein kann oder an einen Benzoring kondensiert sein kann und welcher Heterozyklus unsubstituiert ist oder einen oder zwei Halogen-, Cyano- oder Aminosubstituenten oder Alkyl-, Alkoxy-, Alkylthio-, Alkylsulfinyl- oder Alkylsulfonylsubstituenten mit jeweils bis zu 4 Kohlenstoffatomen oder Oxy- oder Hydroxysubstituenten trägt, oder welcher, sofern er ausreichend gesättigt ist, einen oder zwei Oxosubstituenten tragen kann; und

worin R⁸ für Phenyl, Naphthyl oder einen Heterozyklus, wie er oben für R⁷ oder R⁹ definiert ist, steht.

2. Acylanilid nach Anspruch 1, worin R¹ für Cyano, Nitro, Trifluoromethyl, Chloro, Methyl oder Methoxy steht, R² für Cyano, Nitro, Trifluoromethyl oder Chloro steht, R³ und R⁴ beide für Wasserstoff stehen, R⁵ für Hydroxy steht, R⁶ für Methyl oder Trifluoromethyl steht, A¹ für Methylen, Ethylen oder Ethylen steht, X¹ für Schwefel, Sulfinyl oder Sulfonyl steht, A² für eine direkte Bindung oder Methylen steht und R⁷ für Alkyl, Alkenyl, Hydroxyalkyl oder Cycloalkyl mit jeweils bis zu 6 Kohlenstoffatomen oder Phenyl, das unsubstituiert ist oder einen Fluoro-, Chloro-, Cyano-, Nitro-, Methoxy- oder Methylthiosubstituenten trägt, oder Thienyl, Imidazolyl, Thiazolyl, Benzothiazolyl, Thiadiazolyl, Pyridyl oder Pyrimidinyl, das unsubstituiert ist oder einen Chloro-, Bromo- oder Methylsubstituenten trägt, steht.

3. Acylanilid nach Anspruch 1, worin R¹ für Trifluoromethyl steht, R² für Cyano oder Nitro steht, R³ und R⁴ beide für Wasserstoff stehen, R⁵ für Hydroxy steht, R⁶ für Methyl steht, A¹ für Methylen steht, X¹ für Schwefel, Sulfinyl oder Sulfonyl steht, A² für eine direkte Bindung steht und R⁷ für Alkyl mit bis zu 3 Kohlenstoffatomen oder Allyl, Phenyl, p-Fluorophenyl, Thiazol-2-yl, 4-Methylthiazol-2-yl, 5-Methyl-1,3,4-thiadiazol-2-yl oder 2-Pyridyl steht.

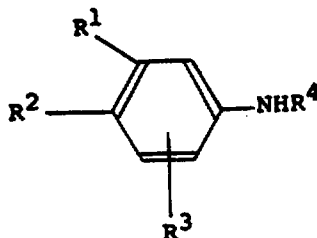


4. Die Verbindungen

3-Chloro-4-cyano-N-(2-ethylthio-2-hydroxy-2-methylpropionyl)anilin,
 3-Chloro-4-cyano-N-(3-ethylsulfonyl-2-hydroxy-2-methylpropionyl)anilin,
 4-Cyano-3-trifluoromethyl-N-(2-hydroxy-2-methyl-3-phenylsulfonylpropionyl)anilin,
 4-Cyano-3-trifluoromethyl-N-(3-ethylsulfonyl-2-hydroxy-2-methylpropionyl)anilin,
 4-Nitro-3-trifluoromethyl-N-(2-hydroxy-3-phenylsulfonyl-2-methylpropionyl)anilin,
 4-Nitro-3-trifluoromethyl-N-(3-ethylsulfonyl-2-hydroxy-2-methylpropionyl)anilin,
 3-Chloro-4-nitro-N-(2-hydroxy-3-phenylthio-2-methylpropionyl)anilin,
 4-Nitro-3-trifluoromethyl-N-[2-hydroxy-2-methyl-3-(thiazol-2-ylthio)propionyl]anilin,
 4-Nitro-3-trifluoromethyl-N-(3-allylthio-2-hydroxy-2-methylpropionyl)anilin,
 4-Nitro-3-trifluoromethyl-N-(3-p-fluorophenylthio-2-hydroxy-2-methylpropionyl)anilin,
 4-Nitro-3-trifluoromethyl-N-[2-hydroxy-2-methyl-3-(pyrid-2-ylthio)propionyl]anilin,
 4-Nitro-3-trifluoromethyl-N-[2-hydroxy-2-methyl-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)propionyl]anilin,
 4-Nitro-3-trifluoromethyl-N-[2-hydroxy-2-methyl-3-(4-methylthiazol-2-ylthio)propionyl]anilin,
 4-Nitro-3-trifluoromethyl-N-[2-hydroxy-2-methyl-3-(pyrid-2-ylsulfonyl)propionyl]anilin,
 4-Nitro-3-trifluoromethyl-N-(3-p-fluorophenylsulfonyl-2-hydroxy-2-methylpropionyl)anilin,
 4-Cyano-3-trifluoromethyl-N-[2-hydroxy-2-methyl-3-(thiazol-2-ylthio)propionyl]anilin,
 4-Cyano-3-trifluoromethyl-N-[2-hydroxy-2-methyl-3-(pyrid-2-ylthio)propionyl]anilin,
 4-Cyano-3-trifluoromethyl-N-(2-hydroxy-2-methyl-3-methylthiopropionyl)anilin und
 4-Cyano-3-trifluoromethyl-N-(3-p-fluorophenylthio-2-hydroxy-2-methylpropionyl)anilin.

5. Die Verbindung 4-Cyano-3-trifluoromethyl-N-(3-p-fluorophenylsulfonyl-2-hydroxy-2-methylpropionyl)anilin.

6. Verfahren zur Herstellung eines Acylanilids nach Anspruch 1, bei welchem
 (a) ein Amin der Formel

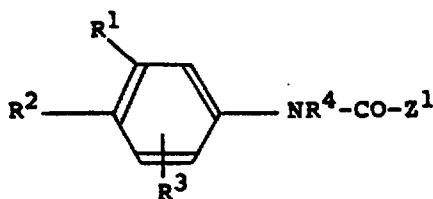


worin R^1 , R^2 , R^3 und R^4 die in Anspruch 1 angegebenen Bedeutungen besitzen, mit einer Säure der Formel

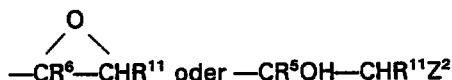


worin R^5 , R^6 , R^7 , X^1 , A^1 und A^2 die in Anspruch 1 angegebenen Bedeutungen besitzen, oder mit einem reaktiven Derivat dieser Säure umgesetzt wird oder

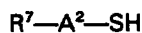
(b) zur Herstellung eines Acylanilids, worin R^6 für Hydroxy steht und X^1 für Schwefel steht, ein Epoxid der Formel



worin R^1 , R^2 , R^3 und R^4 die oben angegebenen Bedeutungen besitzen und worin Z^1 die Formel



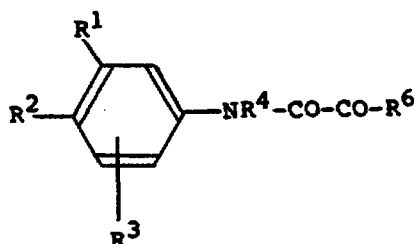
aufweist, worin R^6 die oben angegebene Bedeutung besitzt, worin Z^2 für eine ersetzbare Gruppe steht und worin R^{11} so ausgebildet ist, daß $-\text{CHR}^{11}-$ für $-\text{A}^1-$, wie es oben angegeben ist, steht, mit einem Thiol der Formel



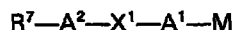
worin R^7 und A^2 die oben angegebenen Bedeutungen besitzen, umgesetzt wird, oder



(c) zur Herstellung eines Acylanilids, worin R⁵ für Hydroxy steht, eine Verbindung der Formel

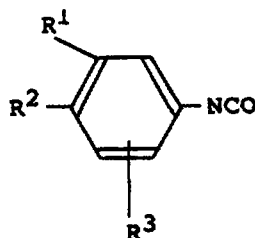


worin R¹, R², R³, R⁴ und R⁶ die oben angegebenen Bedeutungen besitzen, mit einer Organometallverbindung der Formel

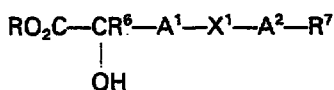


worin A¹, A², R⁷ und X¹ die oben angegebenen Bedeutungen besitzen und M für ein Metallradikal steht, umgesetzt wird oder

(d) zur Herstellung eines Acylanilids, worin R⁴ und R⁵ unter Bildung einer Carbonyloxygruppe miteinander verbunden sind, ein Isocyanat der Formel



worin R¹, R² und R³ die oben angegebenen Bedeutungen besitzen, mit einem Ester der Formel



worin R⁶, R⁷, X¹, A¹ und A² die oben angegebenen Bedeutungen besitzen und worin R für Alkyl mit bis zu 6 Kohlenstoffatomen steht, umgesetzt wird, worauf

(i) ein Acylanilid, worin R⁵ für Hydroxy steht, durch Hydrolyse des entsprechenden Acylanilids, worin R⁵ für Acyloxy steht, hergestellt werden kann oder

(ii) ein Acylanilid, worin R⁵ für Hydroxy steht und R⁴ für Wasserstoff steht, durch Hydrolyse des entsprechenden Oxazolidindions, das wie oben im Absatz (d) angegeben herstellbar ist, hergestellt werden kann oder

(iii) ein Acylanilid, worin R⁴ für Alkyl steht, durch Alkylierung des entsprechenden Acylanilids, worin R⁴ für Wasserstoff steht, hergestellt werden kann oder

(iv) ein Acylanilid, worin R⁵ für Acyloxy steht, durch Acylierung des entsprechenden Acylanilids, worin R⁵ für Hydroxy steht, hergestellt werden kann oder

(v) ein Oxazolidindion, worin R⁴ und R⁵ miteinander unter Bildung einer Carbonyloxygruppe verbunden sind, durch Umsetzung des entsprechenden Acylanilids, worin R⁴ für Wasserstoff steht und R⁵ für Hydroxy steht, mit Phosgen (COCl₂) hergestellt werden kann oder

(vi) ein Acylanilid, worin X¹ oder X² für Sulfinyl oder Sulfonyl steht oder worin einer oder mehrere der Substituenten R¹ und R² und der Substituenten in der Phenyl- oder heterocyclischen Gruppe R⁷, R⁸ oder R⁹ für Alkylsulfinyl, Perfluoroalkylsulfinyl oder Phenylsulfinyl oder für Alkylsulfonyl, Perfluoroalkylsulfonyl oder Phenylsulfonyl stehen, durch Oxidation des entsprechenden Acylanilids, worin X¹ oder X² für Schwefel steht oder worin einer oder mehrere der Substituenten R¹ und R² und der Substituenten in der Phenyl- oder heterocyclischen Gruppe R⁷, R⁸ oder R⁹ für Alkylthio, Perfluoroalkylthio bzw. Phenylthio stehen, hergestellt werden kann oder

(vii) ein racemisches Acylanilid, worin R⁵ für Hydroxy steht, in optische Isomere getrennt werden kann durch Herstellen eines Esters an der Hydroxygruppe R⁵ mit einer optisch aktiven Säure, Trennen der so erhaltenen diastereoisomeren Ester und anschließendes Hydrolysieren jedes gesonderten Esters zum Alkohol.

7. Pharmazeutische oder veterinäre Zusammensetzung, welche ein Acylanilid nach Anspruch 1 gemeinsam mit einem pharmazeutisch zulässigen Verdünnungs- oder Trägermittel enthält.



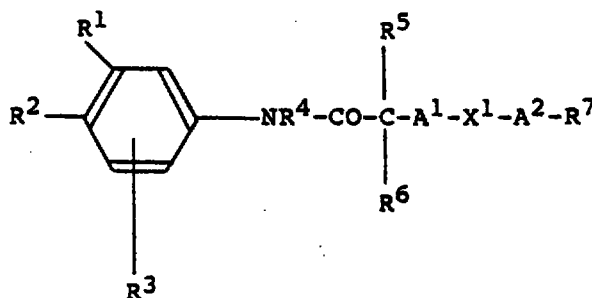
8. Zusammensetzung nach Anspruch 7, welche eine für orale Dosierung geeignete Form, wie z.B. einer Tablette, Kapsel, wäßrigen oder öligen Lösung oder Suspension oder Emulsion, oder die Form einer für parenterale Verabreichung geeigneten sterilen Lösung oder Suspension oder die Form einer für topische Verabreichung geeigneten Salbe oder Lotion oder die Form eines für anale oder vaginale Verabreichung geeigneten Suppositoriums aufweist.

9. Zusammensetzung nach Anspruch 7, welche zusätzlich einem oder mehrere Wirkstoffe enthält, die ausgewählt sind aus Antiöstrogenen, Aromataseinhibitoren, Progestinen, Inhibitoren der Gonadotrophinsekretion, LH—RH-Analogen, cytotoxischen Mitteln, Antibiotika und antiinflammatorischen Mitteln.

10. Die Verwendung einer Verbindung nach einem der Ansprüche 1 bis 5 für die Herstellung eines Medikaments zur Erzeugung eines antiandrogenen Effekts bei Warmblütern.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung eines Acylanilids der Formel



worin R¹ für Cyano, Carbamoyl, Nitro, Fluoro, Chloro, Bromo, Jodo oder Wasserstoff oder Alkyl, Alkoxy, Alkanoyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Perfluoroalkyl, Perfluoroalkylthio, Perfluoroalkylsulfinyl oder Perfluoroalkylsulfonyl mit jeweils bis zu 4 Kohlenstoffatomen oder Phenylthio, Phenylsulfinyl oder Phenylsulfonyl steht;

worin R² für Cyano, Carbamoyl, Nitro, Fluoro, Chloro, Bromo oder Jodo oder Alkanoyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Perfluoroalkyl, Perfluoroalkylthio, Perfluoroalkylsulfinyl oder Perfluoroalkylsulfonyl mit jeweils bis zu 4 Kohlenstoffatomen oder Phenylthio, Phenylsulfinyl oder Phenylsulfonyl steht;

worin R³ für Wasserstoff oder Halogen steht;

worin R⁴ für Wasserstoff oder Alkyl mit bis zu 4 Kohlenstoffatomen steht oder mit R⁵ verbunden ist, wie es nachstehend angegeben ist;

worin R⁵ für Hydroxy oder Alkoxy oder Acyloxy mit jeweils bis zu 15 Kohlenstoffatomen steht oder mit R⁴ unter Bildung einer Oxycarbonylgruppe verbunden ist, so daß es zusammen mit dem —N—CO—C— Teil des Moleküls eine Oxazolidindiongruppe bildet;

worin R⁶ für Alkyl oder Halogenoalkyl mit bis zu 4 Kohlenstoffatomen steht oder die Formel —A³—R⁸ oder —A⁴—X²—A⁵—R⁹ aufweist;

worin A¹ und A⁴, welche gleich oder verschieden sein können, jeweils für Alkylen mit bis zu 6 Kohlenstoffatomen stehen;

worin A², A³ und A⁵, welche gleich oder verschieden sein können, jeweils für eine direkte Bindung oder Alkylen mit bis zu 6 Kohlenstoffatomen stehen;

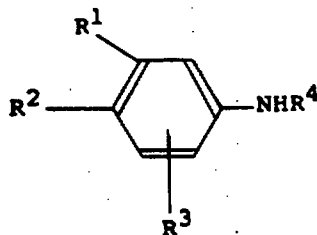
worin X¹ und X², welche gleich oder verschieden sein können, jeweils für Schwefel, Sulfinyl (—SO—) oder Sulfonyl (—SO₂—) stehen;

worin R⁷ und R⁹, welche gleich oder verschieden sein können, jeweils für Alkyl, Alkenyl, Hydroxyalkyl oder Cycloalkyl mit jeweils bis zu 6 Kohlenstoffatomen stehen oder R⁷ oder R⁹ für Phenyl steht, das einen, zwei oder drei Substituenten trägt, die ausgewählt sind aus Wasserstoff, Halogen, Nitro, Carboxy, Carbamoyl und Cyano und Alkyl, Alkoxy, Alkanoyl, Alkylthio, Alkylsulfinyl, Alkylsulfonyl, Perfluoroalkyl, Perfluoroalkylthio, Perfluoroalkylsulfinyl, Perfluoroalkylsulfonyl, Alkoxycarbonyl und N-Alkylcarbamoyl mit jeweils bis zu 4 Kohlenstoffatomen und Phenyl, Phenylthio, Phenylsulfinyl und Phenylsulfonyl, oder R⁷ oder R⁹ für Naphthyl steht oder R⁷ oder R⁹ für einen 5- oder 6-gliedrigen, gesättigten oder ungesättigten Heterozyklus steht, der ein, zwei oder drei Heteroatome enthält, die ausgewählt sind aus Sauerstoff, Stickstoff und Schwefel, welcher Heterozyklus ein einzelner Ring sein kann oder an einen Benzoring kondensiert sein kann und welcher Heterozyklus unsubstituiert ist oder einen oder zwei Halogen-, Cyano- oder Aminosubstituenten oder Alkyl-, Alkoxy-, Alkylthio-, Alkylsulfinyl- oder Alkylsulfonylsubstituenten mit jeweils bis zu 4 Kohlenstoffatomen oder Oxy- oder Hydroxysubstituenten trägt, oder welcher, sofern er ausreichend gesättigt ist, einen oder zwei Oxosubstituenten tragen kann; und

worin R⁸ für Phenyl, Naphthyl oder einen Heterozyklus, wie er oben für R⁷ oder R⁹ definiert ist, steht, dadurch gekennzeichnet, daß



(a) ein Amin der Formel

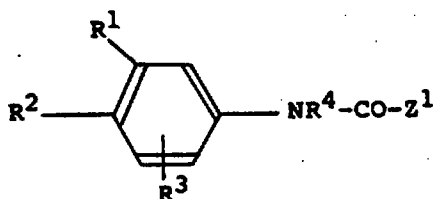


worin R¹, R², R³ und R⁴ die in oben angegebenen Bedeutungen besitzen, mit einer Säure der Formel

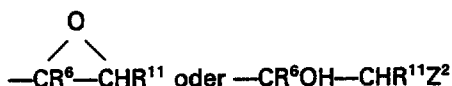


worin R⁵, R⁶, R⁷, X¹, A¹ und A² die in oben angegebenen Bedeutungen besitzen, oder mit einem reaktiven Derivat dieser Säure umgesetzt wird oder

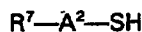
(b) zur Herstellung eines Acylanilids, worin R⁵ für Hydroxy steht und X¹ für Schwefel steht, ein Epoxid der Formel



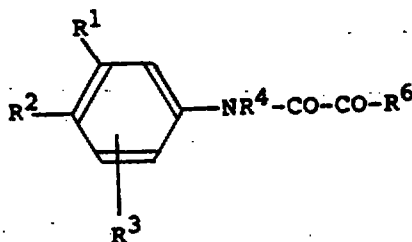
worin R¹, R², R³ und R⁴ die oben angegebenen Bedeutungen besitzen und worin Z¹ die Formel



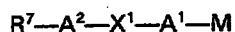
aufweist, worin R⁶ die oben angegebene Bedeutung besitzt, worin Z² für eine ersetzbare Gruppe steht und worin R¹¹ so ausgebildet ist, daß -CHR¹¹- für -A¹-, wie es oben angegeben ist, steht, mit einem Thiol der Formel



worin R⁷ und A² die oben angegebenen Bedeutungen besitzen, umgesetzt wird oder
(c) zur Herstellung eines Acylanilids, worin R⁵ für Hydroxy steht, eine Verbindung der Formel



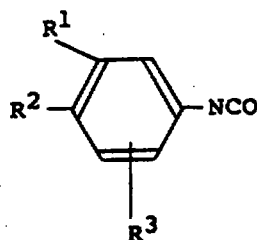
worin R¹, R², R³, R⁴ und R⁶ die oben angegebenen Bedeutungen besitzen, mit einer Organometallverbindung der Formel



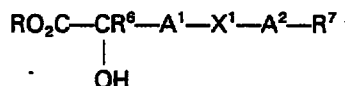
worin A¹, A², R⁷ und X¹ die oben angegebenen Bedeutungen besitzen und M für ein Metallradikal steht, umgesetzt wird oder

(d) zur Herstellung eines Acylanilids, worin R⁴ und R⁵ unter Bildung einer Carbonyloxygruppe miteinander verbunden sind, ein Isocyanat der Formel





worin R¹, R² und R³ die oben angegebenen Bedeutungen besitzen, mit einem Ester der Formel



worin R⁶, R⁷, X¹, A¹ und A² die oben angegebenen Bedeutungen besitzen und worin R für Alkyl mit bis zu 6 Kohlenstoffatomen steht, umgesetzt wird, worauf

(i) ein Acylanilid, worin R⁵ für Hydroxy steht, durch Hydrolyse des entsprechenden Acylanilids, worin R⁵ für Acyloxy steht, hergestellt werden kann oder

(ii) ein Acylanilid, worin R⁵ für Hydroxy steht und R⁴ für Wasserstoff steht, durch Hydrolyse des entsprechenden Oxazolidindions, das wie oben im Absatz (d) angegeben herstellbar ist, hergestellt werden kann oder

(iii) ein Acylanilid, worin R⁴ für Alkyl steht, durch Alkylierung des entsprechenden Acylanilids, worin R⁴ für Wasserstoff steht, hergestellt werden kann oder

(iv) ein Acylanilid, worin R⁵ für Acyloxy steht, durch Acylierung des entsprechenden Acylanilids, worin R⁵ für Hydroxy steht, hergestellt werden kann oder

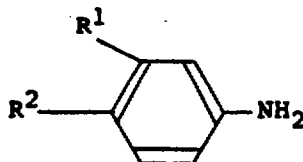
(v) ein Oxazolidindion, worin R⁴ und R⁵ miteinander unter Bildung einer Carbonyloxygruppe verbunden sind, durch Umsetzung des entsprechenden Acylanilids, worin R⁴ für Wasserstoff steht und R⁵ für Hydroxy steht, mit Phosgen (COCl₂) hergestellt werden kann oder

(vi) ein Acylanilid, worin X¹ oder X² für Sulfinyl oder Sulfonyl steht oder worin einer oder mehrere der Substituenten R¹ und R² und der Substituenten in der Phenyl- oder heterocyclischen Gruppe R⁷, R⁸ oder R⁹ für Alkylsulfinyl, Perfluoroalkylsulfinyl oder Phenylsulfinyl oder für Alkylsulfonyl, Perfluoroalkylsulfonyl oder Phenylsulfonyl stehen, durch Oxidation des entsprechenden Acylanilids, worin X¹ oder X² für Schwefel steht oder worin einer oder mehrere der Substituenten R¹ und R² und der Substituenten in der Phenyl- oder heterocyclischen Gruppe R⁷, R⁸ oder R⁹ für Alkylthio, Perfluoroalkylthio bzw. Phenylthio stehen, hergestellt werden kann oder

(vii) ein racemisches Acylanilid, worin R⁵ für Hydroxy steht, in optische Isomere getrennt werden kann durch Herstellen eines Esters an der Hydroxygruppe R⁵ mit einer optisch aktiven Säure, Trennen der so erhaltenen diastereoisomeren Ester und anschließendes Hydrolysieren jedes gesonderten Esters zum Alkohol.

2. Verfahren zur Herstellung eines Acylanilids der Formel von Anspruch 1, worin R¹ für Cyano, Nitro, Trifluoromethyl, Chloro, Methyl oder Methoxy steht, R² für Cyano, Nitro, Trifluoromethyl oder Chloro steht, R³ und R⁴ beide für Wasserstoff stehen, R⁵ für Hydroxy steht, R⁶ für Methyl oder Trifluoromethyl steht, A¹ für Methylen, Ethylen oder Ethylen steht, X¹ für Schwefel, Sulfinyl oder Sulfonyl steht, A² für eine direkte Bindung oder Methylen steht und R⁷ für Alkyl, Alkenyl, Hydroxyalkyl oder Cycloalkyl mit jeweils bis zu 6 Kohlenstoffatomen oder Phenyl, das unsubstituiert ist oder einen Fluoro-, Chloro-, Cyano-, Nitro-, Methoxy- oder Methylthiosubstituenten trägt, oder Thienyl, Imidazolyl, Thiazolyl, Benzthioazolyl, Thiadiazolyl, Pyridyl oder Pyrimidinyl, das unsubstituiert ist oder einen Chloro-, Bromo- oder Methylsubstituenten trägt, steht, dadurch gekennzeichnet, daß

(a) ein Amin der Formel



worin R¹ und R² die oben angegebenen Bedeutungen besitzen, mit einer Säure der Formel

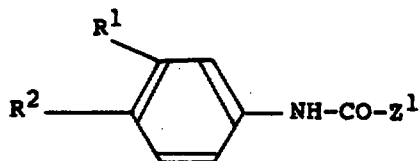


worin R⁶, R⁷, X¹, A¹ und A² die oben angegebenen Bedeutungen besitzen und R⁵ für Hydroxy oder Acyloxy,

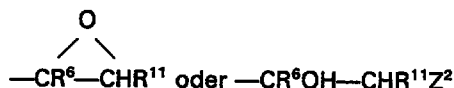


wie es in Anspruch 1 angegeben ist, steht, oder mit einem reaktiven Derivat dieser Säure umgesetzt wird oder

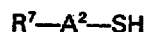
(b) zur Herstellung eines Acylanilids, worin X^1 für Schwefel steht, ein Epoxid der Formel



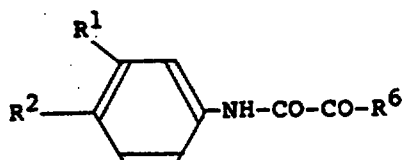
worin R^1 und R^2 die oben angegebenen Bedeutungen besitzen und worin Z^1 die Formel



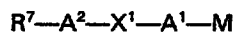
aufweist, worin R^6 die oben angegebene Bedeutung besitzt, worin Z^2 für eine ersetzbare Gruppe steht und worin R^{11} so ausgebildet ist, daß $-CHR^{11}-$ für $-A^1-$, wie es oben angegeben ist, steht, mit einem Thiol der Formel



worin R^7 und A^2 die oben angegebenen Bedeutungen besitzen, umgesetzt wird, oder
(c) eine Verbindung der Formel

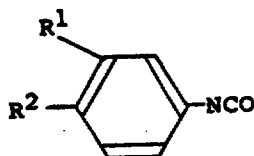


worin R^1 , R^2 und R^6 die oben angegebenen Bedeutungen besitzen, mit einer Organometallverbindung der Formel

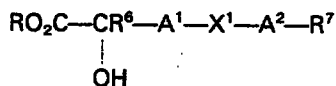


worin A^1 , A^2 , R^7 und X^1 die oben angegebenen Bedeutungen besitzen und M für ein Metallradikal steht, umgesetzt wird, oder

(d) ein Isocyanat der Formel



worin R^1 und R^2 die oben angegebenen Bedeutungen besitzen, mit einem Ester der Formel



worin R^6 , R^7 , X^1 , A^1 und A^2 die oben angegebenen Bedeutungen besitzen und worin R für Alkyl mit bis zu 6 Kohlenstoffatomen steht, umgesetzt wird und hierauf das so erhaltene Oxazolidindion hydrolysiert wird, worauf

(i) ein Acylanilid, worin R^5 für Hydroxy steht, durch Hydrolyse des entsprechenden Acylanilids, worin R^5 für Acyloxy steht, hergestellt werden kann oder

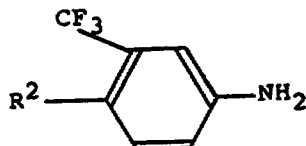
(ii) ein Acylanilid, worin X^1 für Sulfinyl oder Sulfonyl steht, durch Oxidation des entsprechenden Acylanilids, worin X^1 für Schwefel steht, hergestellt werden kann oder

(iii) ein racemisches Acylanilid in seine optischen Isomeren getrennt werden kann durch Herstellen eines Esters an der Hydroxygruppe R^5 mit einer optisch aktiven Säure, Trennen der so erhaltenen



diastereoisomeren Ester und anschließendes Hydrolysieren jedes gesonderten Esters zum Alkohol.

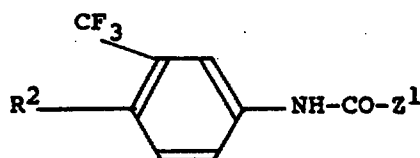
3. Verfahren zur Herstellung eines Acylanilids der Formel von Anspruch 1, worin R¹ für Trifluoromethyl steht, R² für Cyano oder Nitro steht, R³ und R⁴ beide für Wasserstoff stehen, R⁵ für Hydroxy steht, R⁶ für Methyl steht, A¹ für Methylen steht, X¹ für Schwefel, Sulfinyl oder Sulfonyl steht, A² für eine direkte Bindung steht und R⁷ für Alkyl mit bis zu 3 Kohlenstoffatomen oder Allyl, Phenyl, p-Fluorophenyl, Thiazol-2-yl, 4-Methylthiazol-2-yl, 5-Methyl-1,3,4-thiadiazol-2-yl oder 2-Pyridyl steht, dadurch gekennzeichnet, daß
- (a) ein Amin der Formel



15. worin R² die oben angegebene Bedeutung besitzt, mit einer Säure der Formel



20. worin R⁷ und X¹ die oben angegebenen Bedeutungen besitzen und R⁵ für Hydroxy oder Acyloxy, wie es in Anspruch 1 angegeben ist, steht, oder mit einem reaktiven Derivat dieser Säure umgesetzt wird oder
- (b) zur Herstellung eines Acylanilids, worin X¹ für Schwefel steht, ein Epoxid der Formel



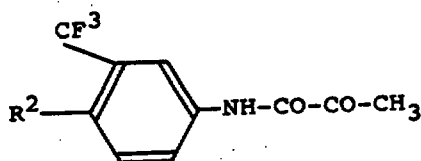
30. worin R² die oben angegebene Bedeutung besitzt und worin Z¹ die Formel



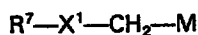
35. aufweist, worin Z² für eine ersetzbare Gruppe steht, mit einem Thiol der Formel



40. worin R⁷ die oben angegebene Bedeutung besitzt, umgesetzt wird oder
- (c) eine Verbindung der Formel



50. worin R² die oben angegebene Bedeutung besitzt, mit einer Organometallverbindung der Formel



55. worin R⁷ und X¹ die oben angegebenen Bedeutungen besitzen und M für ein Metallradikal steht, umgesetzt wird, worauf

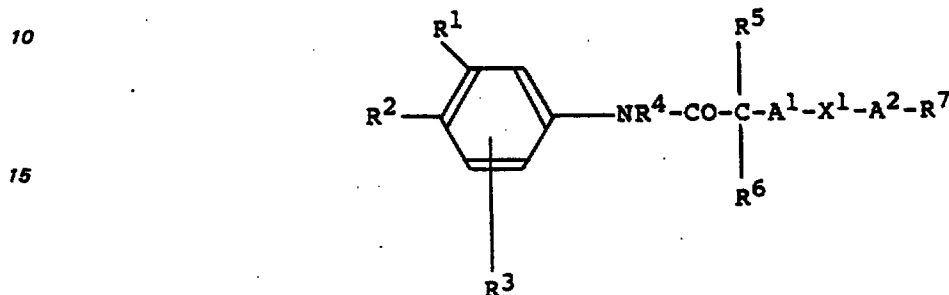
- (i) ein Acylanilid, worin R⁵ für Hydroxy steht, durch Hydrolyse des entsprechenden Acylanilids, worin R⁵ für Acyloxy steht, hergestellt werden kann oder
- (ii) ein Acylanilid, worin X¹ für Sulfinyl oder Sulfonyl steht, durch Oxidation des entsprechenden Acylanilids, worin X¹ für Schwefel steht, hergestellt werden kann oder
60. (iii) ein racemisches Acylanilid in seine optischen Isomere getrennt werden kann durch Herstellen eines Esters an der Hydroxygruppe R⁵ mit einer optisch aktiven Säure, Trennen der so erhaltenen diastereoisomeren Ester und anschließendes Hydrolysieren jedes gesonderten Esters zum Alkohol.

4. Verfahren nach Anspruch 1, 2 oder 3, worin im Ausgangsmaterial R¹ für Trifluoromethyl steht, R² für Cyano steht, R³ und R⁴ beide für Wasserstoff stehen, R⁵ für Hydroxy oder Acyloxy steht, R⁶ für Methyl steht, A¹ für Methylen steht, X¹ für Schwefel oder Sulfonyl steht, A² für eine direkte Bindung steht und R⁷ für p-
- 65.

Fluorophenyl steht, worauf, wenn R⁵ für Acyloxy steht, die Verbindung zur entsprechenden Verbindung, worin R⁵ für Hydroxy steht, hydrolysiert wird und, wenn X¹ für Schwefel steht, die Verbindung zur entsprechenden Verbindung, worin X¹ für Sulfonyl steht, oxidiert wird.

5 Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Acylanilide de formule:



dans laquelle

R¹ est un groupe cyano, carbamoyle, nitro, fluoro, chloro, bromo, iodo ou un atome d'hydrogène, ou un groupe alkyle, alkoxy, alcanoyle, alkylthio, alkylsulfinyle, alkylsulfonyle, perfluoralkyle, perfluoralkylthio, perfluoralkylsulfinyle ou perfluoralkylsulfonyle ayant chacun jusqu'à 4 atomes de carbone, ou phénylthio, phénylsulfinyle ou phénylsulfonyle;

R² est un groupe cyano, carbamoyle, nitro, fluoro, chloro, bromo ou iodo, ou un groupe alcanoyle, alkylthio, alkylsulfinyle, alkylsulfonyle, perfluoralkyle, perfluoralkylthio, perfluoralkylsulfinyle ou perfluoralkylsulfonyle ayant chacun jusqu'à 4 atomes de carbone, ou phénylthio, phénylsulfinyle ou phénylsulfonyle;

R³ est l'hydrogène ou un halogène;

R⁴ est l'hydrogène ou un groupe alkyle ayant jusqu'à 4 atomes de carbone, ou est associé à R⁵ comme indiqué ci-dessous;

R⁵ est un groupe hydroxy or alkoxy ou un groupe acyloxy, chacun ayant jusqu'à 15 atomes de carbone, ou s'associe avec R⁴ pour former un groupe oxycarbonyle de manière à former avec la partie —N—CO—C— de la molécule un groupe oxazolidinedione;

R⁶ est un groupe alkyle ou halogénalkyle ayant jusqu'à 4 atomes de carbone ou répond à la formule —A³—R⁸ ou —A⁴—X²—A⁵—R⁹;

A¹ et A⁴, qui peuvent être identiques ou différents, représentent chacun un groupe alkylène ayant jusqu'à 6 atomes de carbone;

A², A³ et A⁵, qui peuvent être identiques ou différents, représentent chacun une liaison directe ou un groupe alkylène ayant jusqu'à 6 atomes de carbone;

X¹ et X², qui peuvent être identiques ou différents, représentent chacun le soufre, un groupe sulfinyle (—SO—) ou sulfonyle (—SO₂—);

R⁷ et R⁹, qui peuvent être identiques ou différents, représentent chacun un groupe alkyle, alcényle, hydroxyalkyle ou cycloalkyle ayant chacun jusqu'à 6 atomes de carbone, ou bien R⁷ ou R⁹ est un groupe phényle qui porte un, deux ou trois substituants choisis entre l'hydrogène, un halogène, les groupes nitro, carboxy, carbamoyle et cyano, et des groupes alkyle, alkoxy, alcanoyle, alkylthio, alkylsulfinyle, alkylsulfonyle, perfluoralkyle, perfluoralkylthio, perfluoralkylsulfinyle, perfluoralkylsulfonyle, alkoxycarbonyle et N-alkylcarbamoyle ayant chacun jusqu'à 4 atomes de carbone, et les groupes phényle, phénylthio, phénylsulfinyle et phénylsulfonyle; ou bien R⁷ ou R⁹ est un groupe naphthyle; ou bien R⁷ ou R⁹ est un noyau hétérocyclique saturé ou insaturé pentagonal ou hexagonal qui contient un, deux ou trois hétéro-atomes choisis entre des atomes d'oxygène, d'azote et de soufre, ce noyau hétérocyclique pouvant être un noyau simple ou un noyau condensé à un noyau benzénique, et ce noyau hétérocyclique n'étant pas substitué ou portant un ou deux substituants halogéno, cyano ou amino, ou alkyle, alkoxy, alkylthio, alkylsulfinyle ou alkylsulfonyle ayant chacun jusqu'à 4 atomes de carbone, ou des substituants oxy ou hydroxy, ou qui peut porter, s'il est suffisamment saturé, un ou deux substituants oxo; et R⁸ est un groupe phényle, naphthyle ou un noyau hétérocyclique tel que défini ci-dessus pour R⁷ ou R⁹.

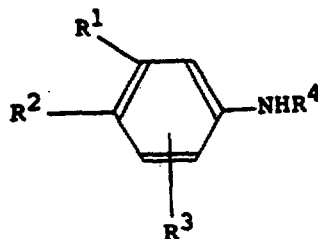
2. Acylanilide suivant la revendication 1, dans lequel R¹ est un groupe cyano, nitro, trifluorométhyle, chloro, méthyle ou méthoxy, R² est un groupe cyano, nitro, trifluorométhyle ou chloro, R³ et R⁴ sont tous deux de l'hydrogène, R⁵ est un groupe hydroxy, R⁶ est un groupe méthyle ou trifluorométhyle, A¹ est un groupe méthylène, éthylène ou éthylidène, X¹ est le soufre, un groupe sulfinyle ou sulfonyle, A² est une liaison directe ou un groupe méthylène et R⁷ est un groupe alkyle, alcényle, hydroxyalkyle ou cycloalkyle, chacun ayant jusqu'à 6 atomes de carbone, ou un groupe phényle qui n'est pas substitué ou qui porte un substituant fluoro, chloro, cyano, nitro, méthoxy ou méthylthio, ou un groupe thiénylène, imidazolyle,



thiazolyle, benzothiazolyle, thiadiazolyle, pyridyle ou pyrimidinyle qui n'est pas substitué ou qui porte un substituant chloro, bromo ou méthyle.

3. Acylanilide suivant la revendication 1, dans lequel R^1 est un groupe trifluorométhyle, R^2 est un groupe cyano ou nitro, R^3 et R^4 sont tous deux de l'hydrogène, R^5 est un groupe hydroxy, R^6 est un groupe méthyle, A^1 est un groupe méthylène, X^1 est le soufre, un groupe sulfinyle ou sulfonyle, A^2 est une liaison directe et R^7 est un groupe alkyle ayant jusqu'à 3 atomes de carbone, ou est un groupe allyle, phényle, *p*-fluorophényle, thiazole-2-yle, 4-méthylthiazole-2-yle, 5-méthyl-1,3,4-thiadiazole-2-yle ou 2-pyridyle.

4. La 3-chloro-4-cyano-*N*-(3-éthylthio-2-hydroxy-2-méthylpropionyl)-aniline;
 la 3-chloro-4-cyano-*N*-(3-éthylsulfonyl-2-hydroxy-2-méthylpropionyl)-aniline;
 la 4-cyano-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-phénylsulfonylpropionyl)-aniline;
 la 4-cyano-3-trifluorométhyl-*N*-(3-éthylsulfonyl-2-hydroxy-2-méthylpropionyl)-aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(2-hydroxy-3-phénylsulfonyl-2-méthylpropionyl)-aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(3-éthylsulfonyl-2-hydroxy-2-méthylpropionyl)-aniline;
 la 3-chloro-4-nitro-*N*-(2-hydroxy-3-phénylthio-2-méthylpropionyl)-aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-(thiazole-2-ylthio)propionyl)-aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(3-allylthio-2-hydroxy-2-méthylpropionyl)-aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(3-*p*-fluorophénylthio-2-hydroxy-2-méthylpropionyl)-aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-(pyrid-2-ylthio)propionyl)-aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-(5-méthyl-1,3,4-thiadiazole-2-ylthio)propionyl)-aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-(4-méthylthiazole-2-ylthio)propionyl)-aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-(pyrid-2-ylsulfonyl)propionyl)-aniline;
 la 4-nitro-3-trifluorométhyl-*N*-(3-*p*-fluorophénylsulfonyl-2-hydroxy-2-méthylpropionyl)-aniline;
 la 4-cyano-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-(thiazole-2-ylthio)propionyl)-aniline;
 la 4-cyano-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-(pyrid-2-ylthio)propionyl)-aniline;
 la 4-cyano-3-trifluorométhyl-*N*-(2-hydroxy-2-méthyl-3-méthylthiopropionyl)-aniline;
 la 4-cyano-3-trifluorométhyl-*N*-(3-*p*-fluorophénylthio-2-hydroxy-2-méthylpropionyl)-aniline.
 5. La 4-cyano-3-trifluorométhyl-*N*-(3-*p*-fluorophénylsulfonyl-2-hydroxy-2-méthylpropionyl)-aniline.
 6. Procédé de production d'un acylanilide suivant la revendication 1, qui comprend
 (a) la réaction d'une amine de formule:

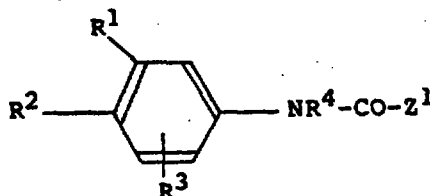


dans laquelle R^1 , R^2 , R^3 et R^4 ont les définitions données dans la revendication 1, avec un acide de formule:

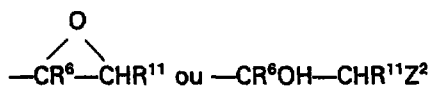


dans laquelle R^5 , R^6 , R^7 , X^1 , A^1 et A^2 ont les définitions indiquées dans la revendication 1, ou avec un dérivé réactif de cet acide; ou bien

(b) pour la production d'un acylanilide dans lequel R^5 est un groupe hydroxy et X^1 est le soufre, la réaction d'un époxyde de formule:



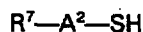
dans laquelle R^1 , R^2 , R^3 et R^4 ont les définitions indiquées ci-dessus et Z^1 répond à la formule



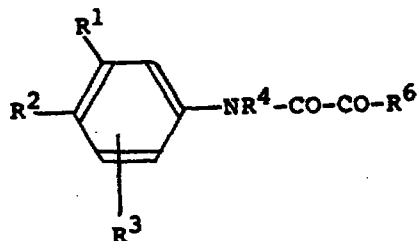
dans laquelle R^6 a la définition indiquée ci-dessus, Z^2 est un groupe déplaçable et R^{11} est choisi de manière



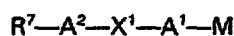
que $\text{—CHR}^{11}\text{—}$ représente $\text{—A}^1\text{—}$ tel que défini ci-dessus, avec un thiol de formule:



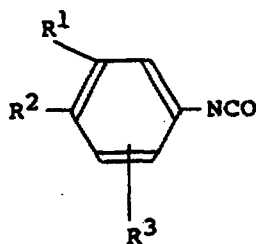
- 5 dans laquelle R^7 et A^2 ont les définitions données ci-dessus; ou
 (c) pour la production d'un acylanilide dans lequel R^5 est un groupe hydroxy, la réaction d'un composé de formule:



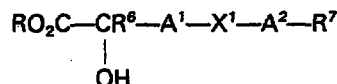
10 dans laquelle R^1 , R^2 , R^3 , R^4 et R^6 ont les définitions indiquées ci-dessus, avec un composé organométallique de formule:



15 dans laquelle A^1 , A^2 , R^7 et X^1 ont les définitions indiquées ci-dessus et M est un métal alcalin; ou bien
 (d) pour la production d'un acylanilide de l'invention dans lequel R^4 et R^5 forment conjointement un groupe carbonyloxy, la réaction d'un isocyanate de formule:



20 dans laquelle R^1 , R^2 et R^3 ont les définitions indiquées ci-dessus, avec un ester de formule:



25 dans laquelle R^6 , R^7 , X^1 , A^1 et A^2 ont les définitions indiquées ci-dessus, et R est un groupe alkyle ayant jusqu'à 6 atomes de carbone; après quoi

(i) un acylanilide dans lequel R^5 est un groupe hydroxy peut être préparé par l'hydrolyse de l'acylanilide correspondant dans lequel R^5 est un groupe acyloxy; ou bien

(ii) un acylanilide dans lequel R^5 est un groupe hydroxy et R^4 est l'hydrogène peut être préparé par l'hydrolyse de l'oxazolidinedione correspondante, qui peut être préparée comme décrit dans le paragraphe (d) ci-dessus; ou bien

(iii) ou acylanilide dans lequel R^4 est un groupe alkyle peut être préparé par alkylation de l'acylanilide correspondant dans lequel R^4 est l'hydrogène; ou bien

(iv) un acylanilide dans lequel R^5 est un groupe acyloxy peut être préparé par acylation de l'acylanilide correspondant dans lequel R^5 est un groupe hydroxy; ou bien

(v) une oxazolidinedione dans laquelle R^4 et R^5 forment conjointement un groupe carbonyloxy peut être préparée par réaction de l'acylanilide correspondant dans lequel R^4 est l'hydrogène et R^5 est un groupe hydroxy, avec le phosgène (COCl_2); ou bien

(vi) un acylanilide dans lequel X^1 ou X^2 est un groupe sulfinyle ou sulfonyle ou dans lequel ou un plusieurs de R^1 , R^2 et un substituant du groupe phényle ou hétérocyclique R^7 , R^8 ou R^9 , sont un groupe alkylsulfinyle, perfluoralkylsulfinyle ou phénylsulfinyle, ou un groupe alkylsulfonyle, perfluoralkylsulfonyle ou phénylsulfonyle, peut être préparé par l'oxydation de l'acylanilide correspondant dans lequel X^1 ou X^2 est le soufre ou dans lequel un ou plusieurs de R^1 , R^2 et un substituant du groupe phényle ou hétérocyclique R^7 , R^8 ou R^9 sont, respectivement, un groupe alkylthio, perfluoralkylthio ou phénylthio; ou bien

(vi) un acylanilide racémique dans lequel R^5 est un groupe hydroxy peut être divisé en ses isomères



optiques par formation d'un ester du groupe hydroxy R⁵ avec un acide optiquement actif, séparation des esters diastéro-isomériques ainsi obtenus, puis hydrolyse de chaque ester séparé en l'alcool.

7. Composition pharmaceutique ou vétérinaire, qui comprend un acylanilide suivant la revendication 1 en association avec un diluant ou support pharmaceutiquement acceptable.

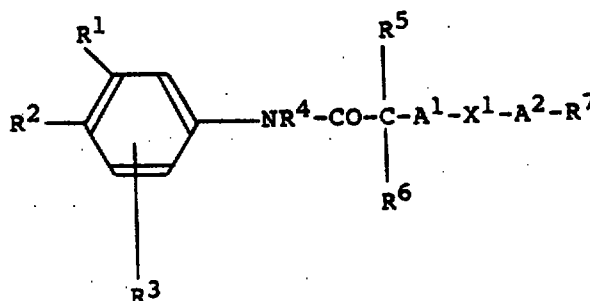
8. Composition suivant la revendication 7, qui est sous une forme qui convient pour l'administration orale, telle qu'un comprimé, une capsule, une solution ou suspension ou émulsion aqueuse ou huileuse; ou sous la forme d'une solution ou suspension stérile qui convient pour l'administration parentérale; ou sous la forme d'une pommade ou d'une lotion pour l'administration topique, ou sous la forme d'un suppositoire pour l'administration anale ou vaginale.

9. Composition suivant la revendication 7, qui contient en outre un ou plusieurs médicaments choisis entre des anti-œstrogènes, des inhibiteurs d'aromatase, des progestines, des inhibiteurs de sécrétion gonadotrope, des analogues de l'hormone libérant l'hormone lutéinisante, des agents cytotoxiques, des antibiotiques et des agents anti-inflammatoires.

10. Utilisation d'un composé suivant l'une quelconque des revendications 1 à 5 pour la préparation d'un médicament destiné à produire un effet anti-androgénique chez un animal à sang chaud.

Revendications pour l'Etat contractant: AT

1. Procédé de production d'un acylanilide de formule:



dans laquelle

R¹ est un groupe cyano, carbamoyle, nitro, fluoro, chloro, bromo, iodo ou un atome d'hydrogène, ou un groupe alkyle, alkoxy, alcanoyle, alkylthio, alkylsulfinyle, alkylsulfonyle, perfluoralkyle, perfluoralkylthio, perfluoralkylsulfinyle ou perfluoralkylsulfonyle ayant chacun jusqu'à 4 atomes carbone, ou phénylthio, phénylsulfinyle ou phénylsulfonyle;

R² est un groupe cyano, carbamoyle, nitro, fluoro, chloro, bromo ou iodo, ou un groupe alcanoyle, alkylthio, alkylsulfinyle, alkylsulfonyle, perfluoralkyle, perfluoralkylthio, perfluoralkylsulfinyle ou perfluoralkylsulfonyle ayant chacun jusqu'à 4 atomes de carbone, ou phénylthio, phénylsulfinyle ou phénylsulfonyle;

R³ est l'hydrogène ou un halogène;

R⁴ est l'hydrogène ou un groupe alkyle ayant jusqu'à 4 atomes de carbone, ou est associé à R⁵ comme indiqué ci-dessous;

R⁵ est un groupe hydroxy or alkoxy ou un groupe acyloxy, chacun ayant jusqu'à 15 atomes de carbone, ou s'associe avec R⁴ pour former un groupe oxycarbonyl de manière à former avec la partie —N—CO—C— de la molécule un groupe oxazolidinedione;

R⁶ est un groupe alkyl ou halogénalkyle ayant jusqu'à 4 atomes de carbone ou répond à la formule —A³—R⁸ ou —A⁴—X²—A⁵—R⁹;

A¹ et A⁴, qui peuvent être identiques ou différents, représentent chacun un groupe alkylène ayant jusqu'à 6 atomes de carbone;

A², A³ et A⁵, qui peuvent être identiques ou différents, représentent chacun une liaison directe ou un groupe alkylène ayant jusqu'à 6 atomes de carbone;

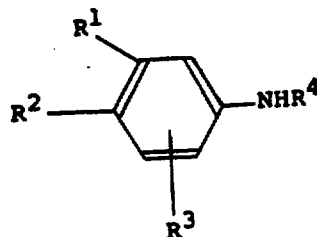
X¹ et X², qui peuvent être identiques ou différents, représentent chacun le soufre, un groupe sulfinyle (—SO—) ou sulfonyle (—SO₂—);

R⁷ et R⁸, qui peuvent être identiques ou différents, représentent chacun un groupe alkyle, alcényle, hydroxyalkyle ou cycloalkyle ayant chacun jusqu'à 6 atomes de carbone, ou bien R⁷ ou R⁸ est un groupe phényle qui porte un, deux ou trois substituants choisis entre l'hydrogène, un halogène, les groupes nitro, carboxy, carbamoyle et cyano, et des groupes alkyle, alkoxy, alcanoyle, alkylthio, alkylsulfinyle, alkylsulfonyle, perfluoralkyle, perfluoralkylthio, perfluoralkylsulfinyle, perfluoralkylsulfonyle, alkoxy-carbonyl et N-alkylcarbamoyl ayant chacun jusqu'à 4 atomes de carbone, et les groupes phényle, phénylthio, phénylsulfinyle et phénylsulfonyl; ou bien R⁷ ou R⁸ est un groupe naphthyle; ou bien R⁷ ou R⁸ est un noyau hétérocyclique saturé ou insaturé pentagonal ou hexagonal qui contient un, deux ou trois hétéro-atomes choisis entre des atomes d'oxygène, d'azote et de soufre, ce noyau hétérocyclique pouvant être un noyau

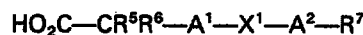


simple ou un noyau condensé à un noyau benzénique, et ce noyau hétérocyclique n'étant pas substitué ou portant ou un deux substituants halogéno, cyano ou amino, ou alkyle, alkoxy, alkylthio, alkylsulfinyle ou alkylsulfonyl ayant chacun jusqu'à 4 atomes de carbone, ou des substituants oxy ou hydroxy, ou qui peut porter, s'il est suffisamment saturé, un ou deux substituants oxo; et R^8 est un groupe phényle, naphtyle ou un noyau hétérocyclique tel que défini ci-dessus pour R^7 ou R^9 , caractérisé par:

(a) la réaction d'une amine de formule:

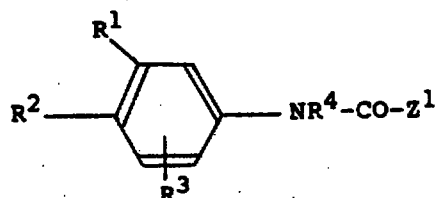


dans laquelle R^1 , R^2 , R^3 et R^4 ont les définitions indiquées, avec un acide de formule:

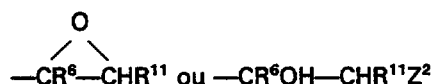


dans laquelle R^5 , R^6 , R^7 , X^1 , A^1 et A^2 ont les définitions indiquées ci-dessus ou avec un dérivé réactif d'un tel acide; ou bien

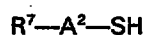
(b) pour la production d'un acylanilide dans lequel R^5 est un groupe hydroxy et X^1 est le soufre, la réaction d'un époxyde de formule:



dans laquelle R^1 , R^2 , R^3 et R^4 ont les définitions indiquées ci-dessus et Z^1 répond à la formule

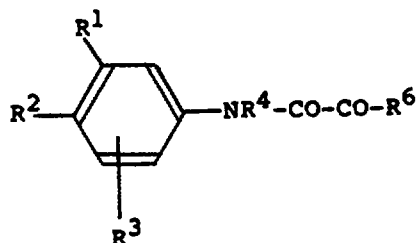


dans laquelle R^6 a la définition indiquée ci-dessus, Z^2 est un groupe déplaçable et R^{11} est choisi de manière que $-CHR^{11}-$ représente $-A^1-$ tel que défini ci-dessus, avec un thiol de formule:

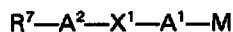


dans laquelle R^7 et A^2 ont les définitions données ci-dessus; ou

(c) pour la production d'un acylanilide dans lequel R^5 est un groupe hydroxy, la réaction d'un composé de formule:



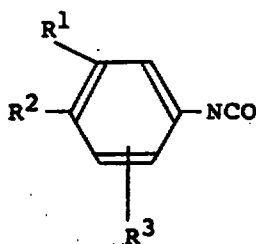
dans laquelle R^1 , R^2 , R^3 , R^4 et R^6 ont les définitions indiquées ci-dessus, avec un composé organométallique de formule;



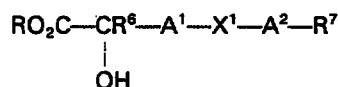
dans laquelle A^1 , A^2 , R^7 et X^1 ont les définitions indiquées ci-dessus et M est un métal alcalin; ou bien



(d) pour la production d'un acylanilide de l'invention dans lequel R⁴ et R⁵ forment conjointement un groupe carbonyloxy, la réaction d'un isocyanate de formule:



dans laquelle R¹, R² et R³ ont les définitions indiquées ci-dessus, avec un ester de formule:



dans laquelle R⁶, R⁷, X¹, A¹ et A² ont les définitions indiquées ci-dessus, et R est un groupe alkyle ayant jusqu'à 6 atomes de carbone; après quoi

(i) un acylanilide dans lequel R⁵ est un groupe hydroxy peut être préparé par l'hydrolyse de l'acylanilide correspondant dans lequel R⁵ est un groupe acyloxy; ou bien

(ii) un acylanilide dans lequel R⁵ est un groupe hydroxy et R⁴ est l'hydrogène peut être préparé par l'hydrolyse de l'oxazolidinedione correspondante, qui peut être préparée comme décrit dans le paragraphe (d) ci-dessus; ou bien

(iii) ou acylanilide dans lequel R⁴ est un groupe alkyle peut être préparé par alkylation de l'acylanilide correspondant dans lequel R⁴ est l'hydrogène; ou bien

(iv) un acylanilide dans lequel R⁵ est un groupe acyloxy peut être préparé par acylation de l'acylanilide correspondant dans lequel R⁵ est un groupe hydroxy; ou bien

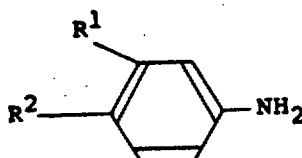
(v) une oxazolidinedione dans laquelle R⁴ et R⁵ forment conjointement un groupe carbonyloxy peut être préparée par réaction de l'acylanilide correspondant dans lequel R⁴ est l'hydrogène et R⁵ est un groupe hydroxy, avec le phosgène (COCl₂); ou bien

(vi) un acylanilide dans lequel X¹ ou X² est un groupe sulfinyle ou sulfonyle ou dans lequel un ou plusieurs de R¹, R² et un substituant du groupe phényle ou hétérocyclique R⁷, R⁸ ou R⁹, sont un groupe alkylsulfinyle, perfluoralkylsulfinyle ou phénylsulfinyle, ou un groupe alkylsulfonyle, perfluoralkylsulfonyle ou phénylsulfonyle, peut être préparé par l'oxydation de l'acylanilide correspondant dans lequel X¹ ou X² est le soufre ou dans lequel un ou plusieurs de R¹, R² et un substituant du groupe phényle ou hétérocyclique R⁷, R⁸ ou R⁹ sont, respectivement, un groupe alkylthio, perfluoralkylthio ou phénylthio; ou bien

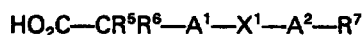
(vi) un acylanilide racémique dans lequel R⁵ est un groupe hydroxy peut être divisé en ses isomères optiques par formation d'un ester du groupe hydroxy R⁵ avec un acide optiquement actif, séparation des esters diastéreo-isomériques ainsi obtenus, puis hydrolyse de chaque ester séparé en l'alcool.

2. Procédé de production d'un acylanilide de formule suivant la revendication 1, dans laquelle R¹ est un groupe cyano, nitro, trifluorométhyle, chloro, méthyle ou méthoxy, R² est un groupe cyano, nitro, trifluorométhyle ou chloro, R³ et R⁴ sont tous deux de l'hydrogène, R⁵ est un groupe hydroxy, R⁶ est un groupe méthyle ou trifluorométhyle, A¹ est un groupe méthylène, éthylène ou éthylidène, X¹ est le soufre, un groupe sulfinyle ou sulfonyle, A² est une liaison directe ou un groupe méthylène et R⁷ est un groupe alkyle, alcényle, hydroxyalkyle ou cycloalkyle ayant chacun jusqu'à 6 atomes de carbone, ou un groupe phényle qui n'est pas substitué ou qui porte un substituant fluoro, chloro, cyano, nitro, méthoxy ou méthylthio, ou un groupe thiénylène, imidazolyle, thiazolyle, benzothiazolyle, thiadiazolyle, pyridyle ou pyrimidinyle qui n'est pas substitué ou qui porte un substituant chloro, bromo ou méthyle, caractérisé par:

(a) la réaction d'une amine de formule:

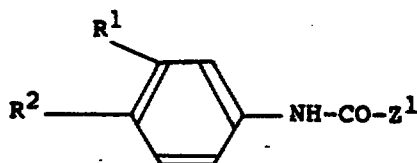


dans laquelle R¹ et R² ont les définitions indiquées ci-dessus, avec un acide de formule:

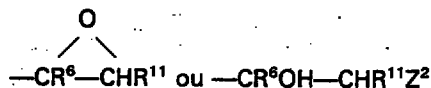


dans laquelle R^6 , R^7 , X^1 , A^1 et A^2 ont les définitions indiquées ci-dessus et R^5 est un groupe hydroxy ou acyloxy tel que défini dans la revendication 1, ou avec un dérivé réactif dudit acide; ou bien

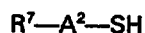
(b) pour la production d'un acylanilide dans lequel X^1 est le soufre, la réaction d'un époxyde de formule:



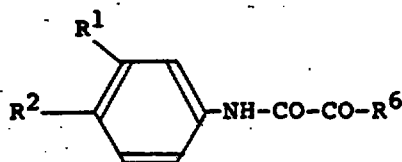
dans laquelle R^1 et R^2 ont les définitions indiquées ci-dessus et Z^1 répond à la formule



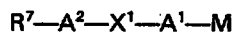
dans laquelle R^6 a la définition indiquée ci-dessus, Z^2 est un groupe déplaçable et R^{11} est choisi de manière que $-CHR^{11}-$ représente $-A^1-$ comme indiqué ci-dessus, avec un thiol de formule:



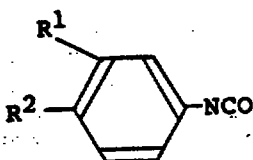
dans laquelle R^7 et A^2 ont les définitions indiquées ci-dessus; ou bien
(c) la réaction d'un composé de formule:



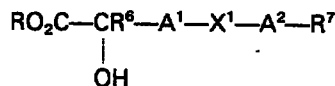
dans laquelle R^1 , R^2 et R^6 ont les définitions indiquées ci-dessus, avec un composé organométallique de formule:



dans laquelle A^1 , A^2 , R^7 et X^1 ont les définitions indiquées ci-dessus et M est un radical métallique; ou bien
(d) la réaction d'un isocyanate de formule:



dans laquelle R^1 et R^2 ont les définitions indiquées ci-dessus, avec un ester de formule:



dans laquelle R^6 , R^7 , X^1 , A^1 et A^2 ont les définitions indiquées ci-dessus, et dans laquelle R est un groupe alkyle ayant jusqu'à 6 atomes de carbone, suivie de l'hydrolyse de l'oxazolidinedione ainsi obtenue; après quoi

(i) un acylanilide dans lequel R^5 est un groupe hydroxy peut être préparé par l'hydrolyse de l'acylanilide correspondant dans lequel R^5 est un groupe acyloxy; ou bien

(ii) un acylanilide dans lequel X^1 est un groupe sulfinyle ou sulfonyle peut être préparé par l'oxydation de l'acylanilide correspondant dans lequel X^1 est le soufre; ou bien

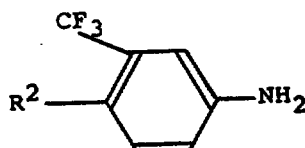
(iii) un acide acylanilide racémique peut être divisé en ses isomères optiques par formation d'un ester du groupe hydroxy R^5 avec un acide optiquement actif, séparation des esters diastéro-isomériques ainsi obtenus, puis hydrolyse de chaque ester séparé en l'alcool.

3. Procédé de production d'un acylanilide de formule indiquée dans la revendication 1, dans laquelle R^1 est un groupe trifluorométhyle, R^2 est un groupe cyano ou nitro, R^3 et R^4 sont tous deux de l'hydrogène, R^5 est un groupe hydroxy, R^6 est un groupe méthyle, A^1 est un groupe méthylène, X^1 est le soufre, un groupe



sulfinyle ou sulfonyle, A² est une liaison directe et R⁷ est un groupe alkyle ayant jusqu'à 3 atomes de carbone, ou est un groupe allyle, phényle, *p*-fluorophényle, thiazole-2-yle, 4-méthylthiazole-2-yle, 5-méthyl-1,3,4-thiadiazole-2-yle ou 2-pyridyle, caractérisé par:

(a) la réaction d'une amine de formule:

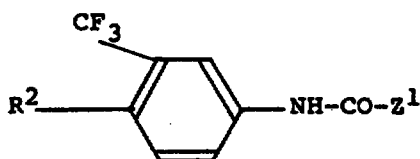


dans laquelle R², a la définition indiquée ci-dessus, avec un acide de formule:

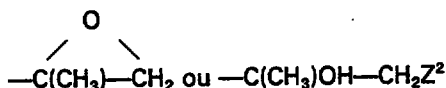


dans laquelle R⁷ et X¹ ont les définitions indiquées ci-dessus et R⁵ est un groupe hydroxy ou acyloxy comme indiqué dans la revendication 1, ou avec un dérivé réactif dudit acide; ou bien

(b) pour la production d'un acylanilide dans lequel X¹ est le soufre, la réaction d'un époxyde de formule:



dans laquelle R² a la définition indiquée ci-dessus et Z¹ répond à la formule

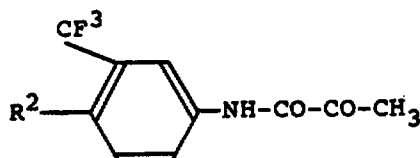


dans laquelle Z² est un groupe déplaçable, avec un thiol de formule:

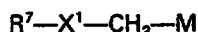


dans laquelle R⁷ a la définition indiquée ci-dessus; ou bien

(c) la réaction d'un composé de formule:



dans laquelle R² a la définition indiquée ci-dessus, avec un composé organométallique de formule:



dans laquelle R⁷ et X¹ ont les définitions indiquées ci-dessus et M est un radical métallique; après quoi

(i) un acylanilide dans lequel R⁵ est un groupe hydroxy peut être préparé par l'hydrolyse de l'acylanilide correspondant dans lequel R⁵ est un groupe acyloxy; ou bien

(ii) un acylanilide dans lequel X¹ est un groupe sulfinyle ou sulfonyle peut être préparé par oxydation de l'acylanilide correspondant dans lequel X¹ est le soufre; ou bien

(iii) un acylanilide racémique peut être divisé en ses isomères optiques par formation d'un ester du groupe hydroxy R⁵ avec un acide optiquement actif, séparation des esters diastéro-isomériques ainsi obtenus, puis hydrolyse en l'alcool de chaque ester séparé.

4. Procédé suivant la revendication 1, 2 ou 3, dans les matières de départ duquel R¹ est un groupe trifluorométhyle, R² est un groupe cyano, R³ et R⁴ sont chacun un atome d'hydrogène, R⁵ est un groupe hydroxy ou acyloxy, R⁶ est un groupe méthyle, A¹ est un groupe méthylène, X¹ est le soufre ou un groupe sulfonyle, A² est une liaison directe et R⁷ est un groupe *p*-fluorophényle, après quoi si R⁵ est un groupe acyloxy, le composé est hydrolysé en le composé correspondant dans lequel R⁵ est un groupe hydroxy, et si X¹ est le soufre, le composé est oxydé en le composé correspondant dans lequel X¹ est un groupe sulfonyle.

