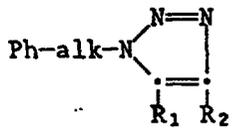
The invention relates to novel fluorinated 1-(α-phenylalkyl)-1H-1,2,3-triazole compounds of formula



(I),

wherein Ph is an o-fluorinated phenyl radical which may be additionally substituted by up to 2 chlorine atoms inclusive, by 1 fluorine atom and 1 chlorine atom, or by up to 2 fluorine atoms inclusive, alk is methylene, R_1 is hydrogen, carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, and R_2 is carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, to processes for the preparation of said compounds, to pharmaceutical compositions comprising said compounds, and to the use of said compounds.

A total of up to 3 halogen substituents inclusive may be present, which halogens may be, in addition to the o-fluoro substituent, 1 or 2 chlorine atom(s), 1 chlorine atom and 1 fluorine atom or 1 or 2 fluorine atom(s). A single additional halogen atom is located especially in the 6-position.

N-(C_2-C_5)alkanoylcarbamoyl is, for example, N-acetyl- or N-pivaloyl-carbamoyl; N,N-di(C_1-C_4)alkylcarbamoyl is, for example, N,N-dimethylcarbamoyl or N,N-diethylcarbamoyl.

The compounds of formula I have valuable pharmacological properties, in particular a pronounced anticonvulsive activity, which may be observed e.g. in mice in the form of a marked metrazole antagonism in the dosage range from about 30 to about 300 mg/kg p.o. as well as in mice and rats in the form of a distinct protective action against convulsions induced by electroshock in the dosage range

from about 1 to about 50, in most cases from about 1 to about 25, mg/kg p.o.. In this assay, the following values were obtained, for example, for the effective dose ED_{50} in mg/kg p.o. (administration 1 hour beforehand):

1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide: 17 (mice) and 8 (rats);
1-(o-fluorobenzyl)-1H-1,2,3-triazole-4-carboxamide: 17 (mice, rats);
1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide: 4 (mice, rats);
1-(6-chloro-2-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide: 7 (mice) and 10 (rats);
1-(o-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide: 6 (mice) and 10 (rats);
1-(6-chloro-2-fluorobenzyl)-1H-1,2,3-triazole-4-carboxamide: 11 (mice);
1-(2,5-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide: 6 (mice).

European Patent Application No. 114 347 discloses 1-phenylalkyl-1H-1,2,3-triazole-4-carboxamides and 1-phenylalkyl-1H-1,2,3-triazole-4,5-dicarboxamides that are substituted in the phenyl moiety by, inter alia, halogen and that have anticonvulsive properties. The 5-unsubstituted compounds mentioned specifically therein without exception contain chlorine as the halogen substituent. If the halogen substituent is fluorine, however, then there is an amino group in the 5-position of the triazole ring. Compared with the prior-known compounds, the 1-benzyl-1H-1,2,3-triazole-4-carboxamides and 1-benzyl-1H-1,2,3-triazole-4,5-dicarboxamides of the invention, which are always substituted in the phenyl moiety by fluorine, have the advantage of greater activity and a longer duration of action. Thus the following ED_{50} values were obtained, for example, in the

above assay:
1-(o-chlorobenzyl)-1H-1,2,3-triazole-4-carboxamide: 26 (mice) and 25 (rats), and
1-(o-chlorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide: 40 (mice) and 43 (rats).

The compounds of the present invention are therefore especially suitable for the treatment of convulsions of various origins, for example epilepsy, and may be used as anticonvulsive, e.g. antiepileptic, agents.

The invention relates especially to compounds of formula (I) wherein Ph is o-fluorinated phenyl which may be additionally substituted by 1 chlorine atom, by 1 fluorine atom and 1 chlorine atom, or by up to 2 fluorine atoms inclusive, and is e.g. o-fluorophenyl, 2,3-, 2,4-, 2,5- or 2,6-difluorophenyl, 2-chloro-6-fluorophenyl, and also 2,4,6-trifluorophenyl; alk is methylene; R_1 is hydrogen or a radical R_2; and R_2 is carbamoyl or, less preferably, N,N-di(C_1-C_4)alkylcarbamoyl such as N,N-dimethylcarbamoyl; for example to compounds of formula (I) wherein Ph is o-fluorophenyl, 2,3-, 2,4-, 2,5- or 2,6-difluorophenyl or 6-chloro-2-fluorophenyl, alk is methylene, R_1 is hydrogen or unsubstituted carbamoyl, and R_2 is unsubstituted carbamoyl.

More particularly, the invention relates to compounds of formula (I) wherein Ph is o-fluorophenyl or 2,6-difluorophenyl, alk is methylene, R_1 is hydrogen or unsubstituted carbamoyl, and R_2 is unsubstituted carbamoyl.

The invention relates preferably to compounds of formula (I) wherein Ph is 2,6-difluorophenyl, alk is methylene, R_1 is hydrogen or a radical R_2, and R_2 is carbamoyl or, less preferably, N-(C_2-C_5)alkanoylcarbamoyl, such as N-acetylcarbamoyl, or is N,N-di(C_1-C_4)alkylcarbamoyl, such

as N,N-dimethylcarbamoyl.

First and foremost, the invention relates to compounds of formula (I) wherein Ph is o-fluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl or 2-chloro-6-fluorophenyl, alk is methylene and R_1 and R_2 are both carbamoyl; and further to compounds of formula (I) wherein Ph is 2,6-difluorophenyl, alk is methylene, R_1 is hydrogen or carbamoyl and R_2 is carbamoyl.

The compounds of formula (I) can be prepared by methods which are known per se, for example by

a) reacting a compound of formula

$$Ph - alk - N_3 \qquad (II)$$

with a compound of formula

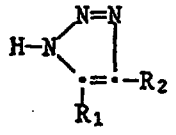
$$R_1 - \underset{Y_1}{C} = \underset{Y_2}{C} - R_2 \qquad (III)$$

wherein Y_1 is hydroxy and Y_2 is hydrogen, or Y_1 and Y_2 together form an additional bond, or with a salt and/or tautomer thereof, or

b) reacting a compound of formula

$$Ph - alk - Z \qquad (IV),$$

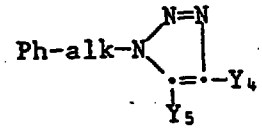
wherein Z is reactive esterified hydroxy, with a 1H-1,2,3-triazole derivative of formula



(V)

or with a salt thereof, or

c) for the preparation of compounds of formula I wherein either R_1 is hydrogen, carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl and R_2 is carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, or R_1 is carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl and R_2 is carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di-(C_1-C_4)alkylcarbamoyl, in a compound of formula



(VI),

wherein Y_4 is a radical Y_A which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl and Y_5 is a group R_1 or a radical Y_B which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, or Y_4 is a group R_2 and Y_5 is a radical Y_B which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, converting Y_A and/or Y_B into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, if necessary separating a resulting mixture of isomers into the individual isomers and isolating the isomer of formula I and, if desired, converting a compound of formula I obtainable by the process of the invention into another compound of formula I and/or resolving a mixture of enantiomers or diastereoisomers obtainable by the process of the invention into the individual components.

Suitable starting materials of formula (III) for process variant a) and tautomers thereof are e.g. compounds of formulae R_1-C≡C-R_2 (IIIa) and R_1-C(=O)-CH_2-R_2 (IIIb). Salts thereof are e.g. alkali metal salts, such as sodium salts, of compounds of formula (IIIa), which can be obtained therefrom and from alkali metal alkanolates,

e.g. sodium methanolate.

The reaction of compound II with compound III is carried out in conventional manner, conveniently in an inert solvent, if necessary in the presence of a condensing agent and/or at elevated temperature. Examples of inert solvents are aromatic or araliphatic hydrocarbons, such as benzene or toluene, or ethers, such as tert-butoxy-methane, tetrahydrofuran or dioxane.

Preferred embodiments of this process are, for example, the reaction of an azide of formula (II) with a compound of formula (IIIa) in benzene or dioxane, in the temperature range of approximately from 60° to 120°C, preferably at boiling temperature.

The starting materials of formula (III) and some of those of formula (II) are known. Novel starting materials of formula (II) can be prepared by methods analogous to those employed for obtaining the known compounds, for example by reacting a compound of formula Ph-alk-Z (IV), wherein Z is reactive esterified hydroxy, such as halogen, e.g. chlorine, bromine or iodine, or sulfonyl-oxy, such as (C_1-C_4)alkanesulfonyloxy or unsubstituted or substituted benzenesulfonyloxy, such as methanesulfonyl-oxy, ethanesulfonyloxy, benzenesulfonyloxy, p-toluene-sulfonyloxy or p-bromobenzenesulfonyloxy, or fluoro-sulfonyloxy, with an alkali metal azide, e.g. with sodium azide, for example in dimethyl sulfoxide or dimethyl-formamide, or by reacting an alcohol corresponding to formula IV (Z = hydroxy) in the presence of triphenyl-phosphane and an azodicarboxylate, e.g. diethyl azo-dicarboxylate, with hydrazoic acid, for example in toluene.

In starting materials IV for process variant b), reactive

esterified hydroxy is e.g. halogen, for example chlorine, bromine or iodine, or sulfonyloxy, such as (C_1-C_4)alkanesulfonyloxy or unsubstituted or substituted benzenesulfonyloxy, such as methanesulfonyloxy, ethanesulfonyloxy, benzenesulfonyloxy, p-toluenesulfonyloxy or p-bromobenzenesulfonyloxy, or fluorosulfonyloxy.

Salts of compounds (V) are e.g. alkali metal salts or alkaline earth metal salts thereof, such as sodium, potassium or calcium salts thereof.

The reaction is carried out in conventional manner, for example in the presence of a basic condensing agent or, conveniently, by using the component of formula (V) in salt form, if necessary with heating, preferably in a solvent or diluent. Examples of basic condensing agents are those that form salts with the component of formula (V), e.g. alkali metal alcoholates, such as sodium methanolate or sodium ethanolate, or alkali metal amides or alkaline earth metal amides, such as sodium amide or lithium diisopropylamide. As already mentioned, the conversion of the component of formula (V) into a salt thereof is best carried out beforehand, e.g. by reaction with one of the above-mentioned bases. Preferred solvents for carrying out the reaction in the presence of an alcoholate are the corresponding alcohols, and preferred solvents for carrying out the reaction in the presence of amides are e.g. aprotic organic solvents, such as (C_1-C_4)alkylamides of phosphoric acid, e.g. hexamethylphosphoramide, alkanoic acid amides, such as dimethylformamide, or di(C_1-C_4)alkyl sulfoxides, such as dimethyl sulfoxide. Isomers obtained as by-products in the process of the invention may be separated from the desired compounds of formula (I) if necessary.

The starting compounds (IV) and (V), if not already

known, may be prepared in conventional manner. Thus compounds of formula (IV) may be obtained, for example, by reactively esterifying an appropriate alcohol (IV; Z = hydroxy), for example with thionyl chloride, phosphorus tribromide or a sulfonyl chloride. Compounds (V) may be prepared by reacting trimethylsilyl azide or hydrazoic acid with a compound of formula

$R_1-C\equiv C-R_2$ (IIIa) or $R_1-C(=O)-CH_2-R_2$ (IIIb),

wherein R_1 is especially carbamoyl or N,N-di(C_1-C_4)-alkylcarbamoyl, and removing the silyl group by mild hydrolysis from a 1-trimethylsilyltriazole derivative, where obtained, if desired after N-alkylating or N-alkanoylating a carbamoyl group R_2 and/or R_1 as described below for compounds of formula I. It is, however, also possible to react trimethylsilyl azide with a compound of formula

$Y_5-C\equiv C-Y_4$ (VIIa) or $R_1-C(=O)-CH_2-Y_4$ (VIIb),

wherein Y_4 is a radical Y_A which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, for example esterified carboxy, such as (C_1-C_4)alkoxycarbonyl, or cyano, and Y_5 is hydrogen or preferably a radical Y_B which is convertible into carbamoyl or N,N-di(C_1-C_4)-alkylcarbamoyl and which is preferably identical with Y_A, and convert Y_A and/or Y_B into carbamoyl or N,N-di(C_1-C_4)-alkylcarbamoyl, in the case of esterified carboxy e.g. by ammonolysis (reaction with ammonia) and in the case of cyano e.g. by hydrolysis, with simultaneous removal of the trimethylsilyl group.

In process variant c), radicals Y_A and/or Y_B which are convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl are, for example, carboxyl groups which are in the free

or salt form or in the anhydride form, or amidino groups or esterified carboxyl groups, or also cyano groups.

Esterified carboxyl groups are e.g. carboxyl groups esterified with a (C_1-C_4)alkanol or a (C_1-C_4)alkylmercaptan, i.e. (C_1-C_4)alkoxycarbonyl or (C_1-C_4)alkylthiocarbonyl groups. However, they may also be esterified with any other alcohol or mercaptan, e.g. with an unsubstituted or substituted phenol or thiophenol.

Carboxyl groups in salt form are e.g. carboxyl groups which are in the form of ammonium salts derived from ammonia or a di(C_1-C_4)alkylamine, and also carboxyl groups in the form of metal salts, e.g. alkali metal salts or alkaline earth metal salts.

Carboxyl groups in anhydride form are e.g. carboxyl groups in halide form, such as chlorocarbonyl, but may also be formed by dehydration with a reactive carboxylic acid and be e.g. alkoxycarbonyloxycarbonyl or trifluoroacetoxycarbonyl.

The conversion of the groups Y_A and/or Y_B into carbamoyl or N,N-di(C_1-C_4)alkylated carbamoyl is effected in conventional manner, starting from carboxyl groups which are free, esterified or in anhydride form, and amidino groups, by solvolysis, i.e. hydrolysis, or by ammonolysis or aminolysis (reaction with ammonia or a di(C_1-C_4)alkylamine, respectively).

For example, by means of hydrolysis cyano groups or amidino groups Y_A and/or Y_B can be converted into carbamoyl. The hydrolysis of cyano groups is carried out e.g. in the presence of a basic hydrolysing agent, such as an alkali metal hydroxide, e.g. sodium or potassium hydroxide, if necessary in the presence of a peroxy

compound, e.g. hydrogen peroxide. The hydrolysis of amidino groups is carried out e.g. in the presence of an acid hydrolysing agent, such as a mineral acid, a sulfonic acid or a carboxylic acid, for example in the presence of sulfuric acid, phosphoric acid, hydrochloric acid or another hydrohalic acid, p-toluenesulfonic acid or another organic sulfonic acid, or of a (C_1-C_4)alkanoic acid, such as acetic acid, preferably in catalytic amounts.

By means of ammonolysis or aminolysis it is possible, for example, to convert carboxyl groups which are free or in salt or anhydride form or are esterified into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl. The reaction is performed, if necessary, in the presence of a condensing agent and especially in an inert solvent. Suitable condensing agents are basic condensing agents, especially an excess of ammonia or of the amine employed for the aminolysis, and when starting from carboxyl in anhydride form they are also alkali metal hydroxides or alkali metal carbonates or tertiary organic nitrogen bases, such as tri(C_1-C_4)alkylamines, or tertiary heteroaromatic nitrogen bases, such as triethylamine or pyridine. Free carboxyl groups can be converted into carbamoyl by dehydration of the ammonium salts obtained as intermediates, e.g. by heating or by treatment with dehydrating agents, such as acid anhydrides, e.g. phosphorus pentoxide and the like, or carbodiimides, e.g. N,N'-dicyclohexylcarbodiimide. A particularly preferred embodiment of this process variant comprises reacting a compound of formula VI, wherein Y_4 is esterified carboxy and Y_5 is hydrogen or is also esterified carboxy, with an excess of ammonia or of a di(C_1-C_4)alkylamine.

The starting materials of formula (VI), if not known, may be prepared in conventional manner, for example by

reacting an azide of formula

$$Ph - alk - N_3 \qquad (II)$$

with a compound of formula

$Y_5-C\equiv C-Y_4$ (VIIa) or $R_1-C(=O)-CH_2-Y_4$ (VIIb),

for example in a manner analogous to that described in process variant a). If necessary, directly obtained esters or nitriles of formula VI (Y_4 and/or Y_5 = esterified carboxy or cyano) can be hydrolysed under basic conditions, e.g. with aqueous alcoholic sodium hydroxide solution, to the corresponding acid, and acids of formula VI (Y_4 and/or Y_5 = carboxy) which are obtained directly or by hydrolysis of corresponding esters or nitriles can be converted into the acid chlorides, e.g. with thionyl chloride.

In compounds of formula (I) obtainable by the process of the invention it is possible to convert N-unsubstituted carbamoyl into N-(C_2-C_5)alkanoylcarbamoyl by treatment with an alkanoylating agent.

Alkanoylating agents are e.g. (C_1-C_4)alkanecarboxylic acid anhydrides, such as acetic anhydride or the mixed anhydride of formic acid and acetic acid, or (C_1-C_4)-alkanecarboxylic acid chlorides, such as acetyl chloride. The reaction with these compounds is carried out in conventional manner, if necessary in the presence of a base, e.g. triethylamine or pyridine, or, if an acid anhydride is used as alkanoylating agent, in the presence of a mineral acid, e.g. sulfuric acid.

The <u>separation of mixtures of isomers</u>, exemplary of which are mixtures of enantiomers and diastereoisomers of

compounds of formula (I) containing at least one asymmetrical carbon atom, as well as mixtures of compounds of formula (I) and isomers thereof formed in accordance with the process, is effected in known manner. Mixtures of diastereoisomers and mixtures of compounds of formula (I) and isomers thereof formed in accordance with the process may be separated e.g. on the basis of the different physical properties of the components by conventional physical methods of separation such as fractional crystallisation, chromatographic methods and the like. A suitable method of separating mixtures of enantiomers is, for example, fractional crystallisation from an optically active solvent or chromatography over an optically active stationary and/or mobile phase. It is, however, also possible to convert a mixture of enantiomers into the corresponding diastereoisomeric acyl derivatives, for example by reaction with an optically active acid chloride, to separate said diastereoisomers into the individual components and to isolate the pure enantiomers therefrom, for example by mild acid treatment.

The compounds of formula (I) may be used, for example, in the form of pharmaceutical compositions that comprise a therapeutically effective amount of active ingredient, optionally together with inorganic or organic, solid or liquid pharmaceutically acceptable carriers that are suitable for enteral, e.g. oral, or parenteral administration. Hence the compositions employed are tablets or gelatin capsules which comprise the active ingredient together with diluents, e.g. lactose, dextrose, saccharose, mannitol, sorbitol, cellulose and/or glycine, and/or lubricants, e.g. silica, talcum, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Tablets may also comprise binders, e.g. magnesium aluminium

silicate, starches such as corn, wheat, rice or arrow-root starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethylcellulose and/or polyvinyl-pyrrolidone, and, if desired, disintegrators, e.g. starches, agar, alginic acid or a salt thereof, such as sodium alginate, and/or effervescent mixtures, or adsorption agents, colourants, flavourings and sweeteners. The compounds of formula (I) may also be used in the form of compositions for parenteral administration or of infusion solutions. Such solutions are preferably isotonic aqueous solutions or suspensions which, e.g. in the case of lyophilised formulations that comprise the active ingredient alone or together with a carrier, e.g. mannitol, may be prepared prior to use. The pharmaceutical compositions may be sterilised and/or may comprise adjuvants, e.g. preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers. The pharmaceutical compositions of the invention, which may, if desired, comprise further pharmacologically active substances, are prepared in a manner known per se, e.g. by conventional mixing, granulating, confectioning, dissolving or lyophilising methods, and comprise from about 0.1 to 100 %, preferably from about 1 to about 50 % (lyophilisates up to 100 %), active ingredient.

The invention also relates to the use of compounds of formula (I), preferably in the form of pharmaceutical compositions. The dosage may depend on various factors, such as the mode of application, species, age and/or the individual condition of the patient. The daily doses for oral administration are in the range from about 1 to about 50 mg/kg, in single doses of about 1 to about 25 mg/kg, and for warm-blooded animals having a body weight of about 70 kg, preferably in daily doses of about 0.070 g to about 3.5 g.

The invention is illustrated by the following Examples; temperatures are given in degrees Celsius.

Example 1: 73.5 g (0.25 mole) of dimethyl 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxylate are dissolved in 1000 ml of methanol. Then 250 g of ammonia are introduced under pressure in an autoclave, and the reaction mixture is kept for 24 hours at 100°. The batch is then cooled and the crystallised product is filtered with suction, washed with methanol and recrystallised from dioxane/toluene, affording 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide with a melting point of 197-199°.

The starting material may be prepared, for example, as follows:
A solution of 40 g (0.282 mole) of dimethyl acetylenedicarboxylate in 500 ml of toluene is added dropwise to a solution of 41.5 g (0.275 mole) of o-fluorobenzyl azide in 50 ml of toluene, which solution has been heated to 90°. After a further 5 hours at 90°, the toluene is stripped off, the reaction mixture is cooled and the crystallised product is filtered with suction. Recrystallisation from a 1:1 mixture of diethyl ether/-petroleum ether yields dimethyl 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxylate with a melting point of 49-51°.

Example 2: 59 g (0.26 mole) of 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid and 300 ml of thionyl chloride are heated for 1 hour to reflux. Excess thionyl chloride is then distilled off in vacuo and the residual 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid chloride is dissolved in 500 ml of toluene. The solution is added dropwise at 5-10° to 500 ml of a concentrated

aqueous ammonia solution. The precipitated product is filtered with suction, washed with water and recrystallised from ethanol, affording 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4-carboxamide with a melting point of 220-222°.

The starting material may be prepared, for example, as follows:
A solution of 50 g (0.33 mole) of o-fluorobenzyl azide, 23.1 g (0.33 mole) of propinecarboxylic acid and 400 ml of toluene is stirred for 24 hours at 70°. After the reaction mixture has cooled to room temperature, the precipitated product is filtered with suction and washed first with toluene and then with diethyl ether, affording 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid with a melting point of 151° (decomp.).

Example 3: Following the procedure described in Example 1, 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide with a melting point of 203-205° (recrystallisation from methanol) is obtained from 2,6-difluorobenzyl azide and dimethyl acetylenedicarboxylate via dimethyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxylate with a melting point of 62-65°.

Example 4: Following the procedure described in Example 2, 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide with a melting point of 237-240° (recystallisation from ethanol) is obtained from 2,6-difluorobenzyl azide via 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid with a melting point of 160-162° (recrystallisation from acetonitrile; decomposition).

Example 5: The following compounds can also be prepared in accordance with the procedures described in Examples 1-4:

1-(2,3-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide,
1-(2,4-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide
and
1-(2,5-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide.

Example 6: Following the procedure described in Example 2, 1-(6-chloro-2-fluorobenzyl)-1H-1,2,3-triazole-4-carboxamide with a melting point of 274-276° (recrystallisation from glacial acetic acid) is obtained from 1-(6-chloro-2-fluorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid.

The starting material may be prepared, for example, as follows:
A mixture of 98 g (0.678 mole) of 6-chloro-2-fluorotoluene, 91.5 g (0.678 mole) of sulfuryl chloride and 0.2 g of dibenzoyl peroxide is stirred for 3 hours at 100-110° and then distilled, affording 6-chloro-2-fluorobenzyl chloride (bp_{15} = 78-82°).

123 g (0.687 mole) of 6-chloro-2-fluorobenzyl chloride are added dropwise at 20-40° to a suspension of 47 g (0.722 mole) of sodium azide in 400 ml of dimethyl sulfoxide. The mixture is stirred for 4 hours at room temperature, then diluted with 1 litre of ice-water and extracted with cyclohexane. The solvent is removed by distillation and the residue is distilled, affording 6-chloro-2-fluorobenzyl azide (bp_{15} = 99-100°).

27.5 g (0.15 mole) of 6-chloro-2-fluorobenzyl azide and 10.5 g (0.15 mole) of propinecarboxylic acid in 300 ml of toluene are heated for 3 hours at 90°C. After cooling, the crystals are filtered with suction and recrystallised from acetonitrile to give 1-(6-chloro-2-fluorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid with a melting point of 182° (decomp.).

Example 7: Following the procedure described in Example 1, 1-(6-chloro-2-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide with a melting point of 214-216° (recrystallisation from glacial acetic acid) is obtained from 6-chloro-2-fluorobenzyl azide and dimethyl acetylenedicarboxylate via dimethyl 1-(6-chloro-2-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxylate with a melting point of 88-90°.

Example 8: Following the procedure described in Example 1, 1-(2,5-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide with a melting point of 191-192° (recrystallisation from dioxane/toluene) is obtained from 2,5-difluorobenzyl azide (bp_{15} = 82-84°) via dimethyl 1-(2,5-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxylate.

Example 9: Following the procedure described in Example 1, 1-(2,4-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide with a melting point of 183-185° (recrystallisation from dioxane/toluene) is obtained from 2,4-difluorobenzyl azide (bp_{15} = 80-83°) via dimethyl 1-(2,4-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxylate with a melting point of 75-76° (recrystallisation from cyclohexane).

Example 10: Following the procedure described in Example 1, N,N-dimethyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide with a melting point of 130-133° (recrystallisation from tert-butoxymethane) is obtained by reaction with dimethylamine.

Example 11: Following the procedure described in Example 1, 1-(2,3-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide with a melting point of 183-185° (recrystallisation from ethyl acetate/benzene) is obtained from 2,3-difluorobenzyl azide and dimethyl acetylenedicarboxylate

via dimethyl 1-(2,3-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxylate.

Example 12: 2.81 g (10 millimoles) of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide, 20 ml of acetic anhydride and 2 drops of sulfuric acid are heated for 3 hours at 80°. After cooling, the mixture is stirred with 100 ml of water for 1 hour at 20-25° and the precipitated product is filtered with suction and washed with water. Recrystallisation from 75 ml of methanol gives 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4,5-di(N-acetyl)carboxamide with a melting point of 136-138°.

Example 13: Following the procedure described in Example 12, 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-(N-acetyl)carboxamide with a melting point of 205-207° (recrystallisation from dioxane/toluene) is also obtained.

Example 14: 1.4 g (12.5 millimoles) of acetylene-dicarboxylic acid diamide are dissolved at 60° in 10 ml of dimethyl sulfoxide. 1.69 g (10 millimoles) of 2,6-difluorobenzyl azide are added, and the mixture is stirred for 16 hours at 80°. The mixture is then diluted with 25 ml of water, filtered with suction, stirred with 50 ml of water, stirred at 50-60° for 30 minutes, again filtered with suction, dried and recrystallised from dioxane/ethanol, affording 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide with a melting point of 203-205°.

Example 15: Tablets which each comprise 50 mg of 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4-carboxamide may be prepared as follows:

Composition (for 10,000 tablets)

active ingredient	500.0 g
lactose	500.0 g
potato starch	352.0 g
gelatin	8.0 g
talcum	60.0 g
magnesium stearate	10.0 g
silica (highly dispersed)	20.0 g
ethanol	q.s.

The active ingredient is mixed with the lactose and 292 g of potato starch and this mixture is moistened with an alcoholic solution of the gelatin and granulated through a sieve. After drying, the granulate is mixed with the remainder of the potato starch, the talcum, the magnesium stearate and the highly dispersed silica, and the mixture is compressed to tablets each weighing 145.0 mg and comprising 50.0 mg of active ingredient. If desired, the tablets may be provided with a breaking notch for a finer adjustment of the dose.

Example 16: Film-coated tablets each comprising 100 mg of 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4-carboxamide may be prepared as follows:

Composition (for 1000 tablets)

active ingredient	100.00 g
lactose	100.00 g
corn starch	70.00 g
talcum	8.50 g
calcium stearate	1.50 g
hydroxypropylmethylcellulose	2.36
shellac	0.64 g
water	q.s.
methylene chloride	q.s.

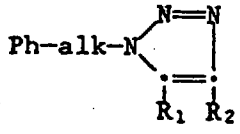
The active ingredient, the lactose and 40 g of the corn starch are mixed and moistened with a paste prepared from 15 g of corn starch and water (with heating), and the mixture is granulated. The granulate is dried and mixed with the remainder of the corn starch, the talcum and the calcium stearate. The mixture is compressed to tablets weighing 280 mg. The tablets are then coated with a solution of the hydroxypropylmethylcellulose and the shellac in methylene chloride. The tablets have a final weight of 283 mg.

Example 17: Tablets and film-coated tablets comprising another compound according to one of Examples 1-14 can also be prepared as described in Examples 15 and 16.

* C L M S *

Patent claims (for Contracting States: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE)

1. Fluorinated 1-(α-phenylalkyl)-1H-1,2,3-triazole compounds of the formula



(I),

wherein Ph is an o-fluorinated phenyl radical which may be additionally substituted by up to 2 chlorine atoms inclusive, by 1 fluorine atom and 1 chlorine atom, or by up to 2 fluorine atoms inclusive, alk is methylene, R_1 is hydrogen, carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, and R_2 is carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl.

2. Compounds according to claim 1, wherein Ph is an o-fluorinated phenyl radical which may be additionally substituted by 1 chlorine atom, by 1 fluorine atom and 1 chlorine atom, or by up to 2 fluorine atoms inclusive, alk is methylene, R_1 is hydrogen or a radical R_2, and R_2 is carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl.

3. Compounds according to claim 1, wherein Ph is o-fluorophenyl, 2,3-, 2,4-, 2,5- or 2,6-difluorophenyl or 6-chloro-2-fluorophenyl, alk is methylene, R_1 is hydrogen or carbamoyl and R_2 is carbamoyl.

4. Compounds according to claim 1, wherein Ph is o-fluorophenyl or 2,6-difluorophenyl, alk is methylene, R_1 is hydrogen or carbamoyl and R_2 is carbamoyl.

5. Compounds according to claim 1, wherein Ph is 2,6-difluorophenyl, alk is methylene, R_1 is hydrogen or a

radical R_2, and R_2 is carbamoyl, N-(C_2-C_5)alkanoyl-carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl.

6. Compounds according to claim 1, wherein Ph is o-fluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl or 2-chloro-6-fluorophenyl, alk is methylene and R_1 and R_2 are both carbamoyl.

7. Compounds according to claim 1, wherein Ph is 2,6-difluorophenyl, alk is methylene, R_1 is hydrogen or carbamoyl and R_2 is carbamoyl.

8. 1-(o-Fluorobenzyl)-1H-1,2,3-triazole-4-carboxamide according to claim 1.

9. 1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide according to claim 1.

10. 1-(o-Fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide according to claim 1.

11. 1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide according to claim 1.

12. 1-(6-Chloro-2-fluorobenzyl)-1H-1,2,3-triazole-4-carboxamide according to claim 1.

13. 1-(6-Chloro-2-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide according to claim 1.

14. 1-(2,5-Difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide according to claim 1.

15. 1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4,5-di-(N,N-dimethyl)carboxamide according to claim 1.

16. 1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4-(N-acetyl)carboxamide according to claim 1.

17. 1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4,5-di(N-acetyl)carboxamide according to claim 1.

18. 1-(2,3-Difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide according to claim 1.

19. 1-(2,3-Difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide according to claim 1.

20. 1-(2,4-Difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide according to claim 1.

21. A compound according to any one of claims 1, 2, 5 and 15 to 20 for use in a therapeutic method of treating the human or animal body, for example as an anticonvulsive agent.

22. A compound according to any one of claims 3, 4 and 6 to 14 for use in a therapeutic method of treating the human or animal body, for example as an anticonvulsive agent.

23. Pharmaceutical compositions comprising a compound according to any one of claims 1, 2, 5 and 15 to 21, together with conventional pharmaceutical excipients and/or carriers.

24. Pharmaceutical compositions comprising a compound according to any one of claims 3, 4, 6 to 14 and 22, together with conventional pharmaceutical excipients and/or carriers.

25. A process for the preparation of compounds of

formula I according to claim 1, which comprises

a) reacting a compound of formula

$$Ph - alk - N_3 \qquad (II)$$

with a compound of formula

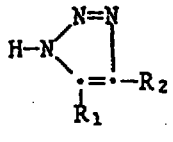
$$R_1 - \underset{Y_1}{C} = \underset{Y_2}{C} - R_2 \qquad (III),$$

wherein Y_1 is hydroxy and Y_2 is hydrogen, or Y_1 and Y_2 together form an additional bond, or with a salt and/or tautomer thereof, or

b) reacting a compound of formula

$$Ph - alk - Z \qquad (IV),$$

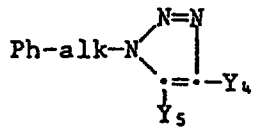
wherein Z is reactive esterified hydroxy, with a 1H-1,2,3-triazole derivative of formula



(V)

or with a salt thereof, or

c) for the preparation of compounds of formula I wherein either R_1 is hydrogen, carbamoyl, N-(C_2-C_5)alkanoyl-carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl and R_2 is carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, or R_1 is carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl and R_2 is carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di-(C_1-C_4)alkylcarbamoyl, in a compound of formula



(VI),

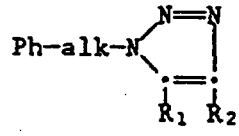
wherein Y_4 is a radical Y_A which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl and Y_5 is a group R_1 or a radical Y_B which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, or Y_4 is a group R_2 and Y_5 is a radical Y_B which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, converting Y_A and/or Y_B into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, if necessary separating a resulting mixture of isomers into the individual isomers and isolating the isomer of formula I and, if desired, converting a compound of formula I obtainable by the process of the invention into another compound of formula I and/or resolving a mixture of enantiomers or diastereoisomers obtainable by the process of the invention into the individual components.

26. The use of a compound according to any one of claims 1 to 22 for the preparation of an anticonvulsive medicament.

* C L M S *

Patent claims (for designated Contracting State AT)

1. A process for the preparation of fluorinated 1-(α-phenylalkyl)-1H-1,2,3-triazole compounds of the formula



(I),

wherein Ph is an o-fluorinated phenyl radical which may be additionally substituted by up to 2 chlorine atoms inclusive, by 1 fluorine atom and 1 chlorine atom, or by up to 2 fluorine atoms inclusive, alk is methylene, R_1 is hydrogen, carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, and R_2 is carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, which process comprises

a) reacting a compound of formula

$$Ph - alk - N_3 \qquad (II)$$

with a compound of formula

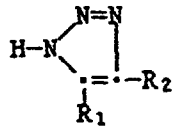
$$R_1 - \underset{Y_1}{C} = \underset{Y_2}{C} - R_2 \qquad (III),$$

wherein Y_1 is hydroxy and Y_2 is hydrogen, or Y_1 and Y_2 together form an additional bond, or with a salt and/or tautomer thereof, or

b) reacting a compound of formula

$$Ph - alk - Z \qquad (IV),$$

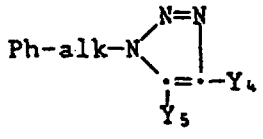
wherein Z is reactive esterified hydroxy, with a 1H-1,2,3-triazole derivative of formula



(V)

or with a salt thereof, or

c) for the preparation of compounds of formula I wherein either R_1 is hydrogen, carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl and R_2 is carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, or R_1 is carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl and R_2 is carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di-(C_1-C_4)alkylcarbamoyl, in a compound of formula



(VI),

wherein Y_4 is a radical Y_A which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl and Y_5 is a group R_1 or a radical Y_B which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, or Y_4 is a group R_2 and Y_5 is a radical Y_B which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, converting Y_A and/or Y_B into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, if necessary separating a resulting mixture of isomers into the individual isomers and isolating the isomer of formula I and, if desired, converting a compound of formula I obtained by the process of the invention into another compound of formula I and/or resolving a mixture of enantiomers or diastereoisomers obtained by the process of the invention into the individual components.

2. A process according to claim 1, wherein a compound of formula VI wherein Y_4 is esterified carboxy and Y_5 is hydrogen or is also esterified carboxy is reacted with an excess of ammonia or of a di(C_1-C_4)alkylamine.

3. A process according to claim 1 or 2, wherein compounds of formula I wherein Ph is an o-fluorinated phenyl radical which may be additionally substituted by 1 chlorine atom, by 1 fluorine atom and 1 chlorine atom, or by up to 2 fluorine atoms inclusive, alk is methylene, R_1 is hydrogen or a radical R_2, and R_2 is carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl are prepared.

4. A process according to claim 1 or 2, wherein compounds of formula I wherein Ph is o-fluorophenyl, 2,3-, 2,4-, 2,5- or 2,6-difluorophenyl or 6-chloro-2-fluorophenyl, alk is methylene, R_1 is hydrogen or carbamoyl and R_2 is carbamoyl are prepared.

5. A process according to claim 1 or 2, wherein compounds of formula I wherein Ph is o-fluorophenyl or 2,6-difluorophenyl, alk is methylene, R_1 is hydrogen or carbamoyl and R_2 is carbamoyl are prepared.

6. A process according to claim 1 or 2, wherein compounds of formula I wherein Ph is o-fluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl or 6-chloro-2-fluorophenyl, alk is methylene and R_1 and R_2 are both carbamoyl are prepared.

7. A process according to claim 1 or 2, wherein compounds of formula I wherein Ph is 2,6-difluorophenyl, alk is methylene, R_1 is hydrogen or carbamoyl and R_2 is carbamoyl are prepared.

8. A process according to claim 1 or 2, wherein 1-(o-

* C L M S *

fluorobenzyl)-1H-1,2,3-triazole-4-carboxamide is prepared.

9. A process according to claim 1 or 2, wherein 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide is prepared.

10. A process according to claim 1 or 2, wherein 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide is prepared.

11. A process according to claim 1 or 2, wherein 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide is prepared.

12. A process according to claim 1 or 2, wherein 1-(6-chloro-2-fluorobenzyl)-1H-1,2,3-triazole-4-carboxamide is prepared.

13. A process according to claim 1 or 2, wherein 1-(6-chloro-2-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide is prepared.

14. A process according to claim 1 or 2, wherein 1-(2,5-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide is prepared.

15. A process according to claim 1 or 2, wherein 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4,5-di(N,N-dimethyl)-carboxamide is prepared.

16. A process according to claim 1 or 2, wherein 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-(N-acetyl)carboxamide is prepared.

17. A process according to claim 1 or 2, wherein 1-(2,6-



difluorobenzyl)-1H-1,2,3-triazole-4,5-di(N-acetyl)-carboxamide is prepared.

18. A process according to claim 1 or 2, wherein 1-(2,3-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide is prepared.

19. A process according to claim 1 or 2, wherein 1-(2,3-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide is prepared.

20. A process according to claim 1 or 2, wherein 1-(2,4-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide is prepared.

21. A process for the preparation of pharmaceutical compositions, which comprises mixing a compound of formula I, obtainable according to any one of claims 1 to 20, with conventional pharmaceutical excipients and/or carriers.