

PATENT SPECIFICATION

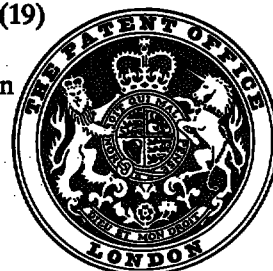
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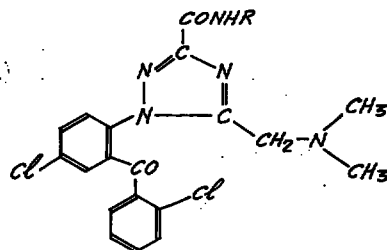
C2C	1450	215	220	22Y	250	252	25Y
	280	313	316	31Y	323	32Y	338
	342	34Y	351	355	35X	366	367
	440	584	620	625	628	62X	650
	678	699	802	80Y	AA	KS	LZ
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(54) NOVEL TRIAZOLE DERIVATIVES AND PROCESSES FOR THEIR PRODUCTION

(71) We, CIBA-GEIGY AG, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

The present invention relates to an improvement in, or modification of the invention of our co-pending application No. 24616/75 (Serial No. 1476116), and in particular to processes for the production of novel triazole derivatives and their acid addition salts, to these novel substances themselves, and to pharmaceutical compositions containing them, as well as to the therapeutic application of the novel substances.

The novel triazole derivatives according to the invention correspond to the formula I



wherein

R represents straight-chain alkyl having 2 or 3 carbon atoms.

The invention relates also to the addition salts of the triazole derivatives of the formula I with inorganic and organic acids.

In the triazole derivatives of the formula I, R is ethyl or propyl.

The triazole derivatives of the formula I and their addition salts with inorganic and organic acids possess valuable pharmacological properties. They have, in particular, an anticonvulsive action, as can be verified, for example, on the mouse in the pentetrazole convulsion test after administration of oral doses of upwards of about 0.3 mg/kg, as well as in the strychnine convulsion test and in the electroshock test after administration in each case of oral doses of upwards of about 1 mg/kg of N-propyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[dimethylamino]-methyl]-1H-1,2,4-triazole-3-carboxamide or N-ethyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[dimethylamino]-methyl]-1H-1,2,4-triazole-3-carboxamide. Furthermore, the triazole derivatives of the formula I and their acid addition salts also have a moderate central depressant action. This and also the atactic properties are however slight in proportion to the strong anticonvulsive and anxiolytic activity. The stated properties, together with others that can be demonstrated by selected standard tests [see W. Theobald and H.A. Kunz, *Arzneimittelforsch.* 13, 122 (1963) as well as W. Theobald et al., *Arzneimittelforsch.* 17, 561 (1967)], as well as good compatibility characterise the triazole

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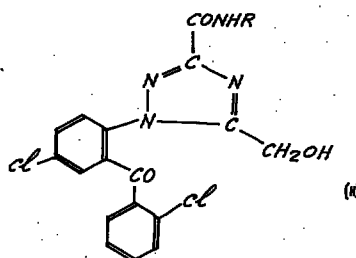
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derivatives of the formula I and their pharmaceutically acceptable addition salts with inorganic and organic acids as being active substances for anticonvulsants and tranquillisers, with at most only a slight sedative action, which are usable for the treatment of epilepsy and of conditions of tension and agitation.

5 The data given in the foregoing relate likewise to the addition salts of the stated triazole derivatives, embraced by the formula I, with inorganic and organic acids, especially to the pharmaceutically acceptable acid addition salts.

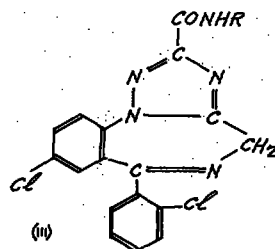
10 The novel triazole derivatives of the formula I and their acid addition salts are produced according to the invention by a process wherein

a) a reactive ester of a compound of the formula II



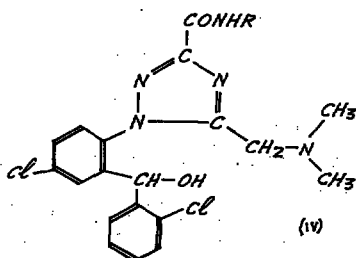
wherein R has the meaning given under the formula I, is reacted with dimethylamine or with an alkali metal derivative thereof; or

25 b) a compound of the formula III



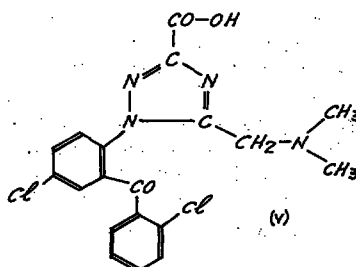
wherein R has the meaning given under formula I, is reacted with formaldehyde and formic acid; or

40 c) a compound of the formula IV



50 wherein R has the meaning given under formula I, is oxidised; or

d) the carboxylic acid of the formula V



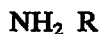
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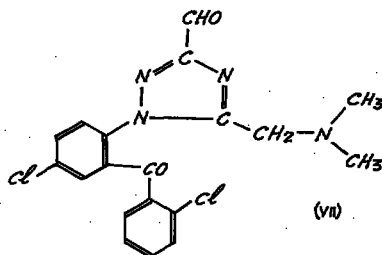
or a reactive functional derivative thereof, is reacted with a compound of the formula VI



(VI),

wherein R has the meaning given under the formula I, or with a reactive functional derivative of such a compound; or

e) the compound of the formula VII



is reacted with a compound of the formula VI given in the foregoing, wherein R has the meaning given under the formula I, in the presence of an alkali metal cyanide and of a selective oxidising agent; and, optionally, a triazole derivative of the formula I obtained by any one of the processes given under a) to e) is converted into an addition salt with an inorganic or organic acid.

For the process a), suitable reactive esters of hydroxy compounds of the formula II are, for example, hydrohalic acid esters, such as chlorides and bromides, as well as the iodides produced from these, optionally in situ not till immediately before the subsequent reaction. Further suitable reactive esters of compounds of the formula II are the sulphonic acid esters thereof, particularly lower alkanesulphonic acid esters such as the methanesulphonic acid esters, and arenesulphonic acid esters, such as the o- or p-toluenesulphonic acid esters, the o- or p-nitrobenzenesulphonic acid esters or the o- or p-chlorobenzenesulphonic acid esters. The reactions with dimethylamine are preferably performed in the presence of an acid-binding agent. As the acid-binding agent, it is possible to use an excess of dimethylamine, or, e.g., a tertiary organic base, such as ethyl-diisopropylamine or collidine, or an inorganic basic substance such as potassium carbonate. The reaction medium used can be, e.g., an inert, optionally hydrous, solvent, e.g. a lower alkanol such as methanol, ethanol, propanol, isopropanol or butanol, a ketone such as acetone or methyl ethyl ketone, also, e.g., dioxane, tetrahydrofuran, dimethylformamide or dimethylsulphoxide, or an excess of dimethylamine, as such or as an aqueous or organic solution. When the word "lower" is used in this specification in relation to alkyl groups or alkanols, it is intended to refer to alkyl groups or alkanols of at most 7 carbon atoms, preferably 4 carbon atoms.

If there is used as reactant instead of dimethylamine an alkali metal derivative thereof, e.g. the sodium, lithium or potassium derivative, then as solvent are preferably used hydrocarbons such as benzene, toluene or xylene, ethereal liquids such as 1,2-dimethoxyethane, tetrahydrofuran or dioxane, acid amides such as dimethylformamide or N,N,N',N',N'',N''-hexamethyl-phosphoric acid triamide, or sulfoxides such as dimethylsulphoxide. The alkali metal derivatives of dimethylamine are preferably formed in situ, e.g. by the addition of at least the equimolar amount of alkali metal hydride such as sodium hydride, alkali metal amide such as sodium or lithium amide, or of an alkali-metalorganic compound such as phenyl- or butyllithium. The reaction temperatures are preferably between 0° and 120°C, or the boiling temperature of the employed reaction medium is used.

Chlorides of compounds of the formula II are described, as intermediates, in the German Offenlegungsschriften Nos. 2,159,527, 2,215,943 and 2,304,307. Other reactive esters of compounds of the formula II can be produced analogously.

The splitting of the diazepine ring according to process b) by means of formaldehyde and formic acid is performed at elevated temperature, preferably at from 80°C up to the boiling temperature of the reaction mixture. Although not absolutely necessary with regard to the overall balance of the reaction, an appreciable content of water in the reaction mixture is advantageous; it is therefore possible to use not only, for example, a 30 to 36% aqueous formaldehyde solution but also, for example, an 85 to 95% aqueous formic acid. The formaldehyde is preferably used in a considerable excess, e.g. two to five times the theoretical amount of 2 to 4 moles per mole of starting material of the formula III, and the formic acid in an even greater excess, e.g. two to five times the molar amount relative to the formaldehyde. The starting materials of the formula III are described in the German

Offenlegungsschrift No. 2,304,307.

The oxidation according to process c) is performed, for example, by means of a higher metal oxide such as chromium trioxide, e.g. dissolved in acetic acid, or dissolved in dilute sulphuric acid as oxidation solution according to Jones and gradually added to the solution of the starting material in acetone, at a temperature between 0° and 60°C, preferably at 20-30°C; or with manganese dioxide, particularly in the activated form described by J. Attenburrow et al., J. Chem. Soc. 1952, 1104, in an inert organic solvent such as benzene or dioxane, at temperatures of between room temperature and the boiling temperature of the reaction medium.

The starting materials of the formula IV are obtained, for example, by reduction of reactive esters of compounds of the formula II, especially of chlorides, with an alkali metal boron hydride, such as sodium boron hydride, in a lower alkanol such as methanol, or in another suitable organic solvent such as tetrahydrofuran, at low temperatures, preferably between -20°C and 0°C, and reaction of the resulting reduction products with dimethylamine analogously to the process a).

Process d) is performed, for example, by reacting the carboxylic acid of the formula V with a compound of the formula VI in the presence of a carbodiimide, such as dicyclohexyl-carbodiimide, in an inert solvent such as tetrahydrofuran. Furthermore, the carboxylic acid of the formula V can be reacted with an ethyl- or propylisocyanate or ethyl- or propylisothiocyanate as a reactive functional derivative of a compound of the formula VI; and the immediate reaction product heated until the evolution of carbon dioxide or carbon oxysulphide ceases.

Suitable reactive functional derivatives of the carboxylic acids of the formula V are, for example, their lower alkyl esters, which can be reacted with compounds of the formula VI in some cases at room temperature, or if necessary with heating, and in a closed vessel if required, depending on the reactivity and boiling temperature of the employed compound of the formula VI. As the reaction medium it is possible to use, e.g. a lower alkanol such as methanol or ethanol, or another inert organic solvent such as tetrahydrofuran or dioxane, optionally together with an excess of the compound to be reacted of the formula VI.

Further suitable reactive functional derivatives of carboxylic acid of the formula V are halides thereof, especially chlorides, particularly in the form of their hydrohalides, such as hydrochlorides. These are produced preferably directly before the subsequent reaction with the compounds of the formula VI from the free carboxylic acids and suitable acid halides such as thionyl chloride, oxalyl chloride or phosphorus tribromide, and further reacted without purification. The carboxylic acid halides or their hydrohalides are reacted with compounds of the formula VI, preferably in the presence of at least the equivalent or at least double-equivalent amount of an acid-binding agent, e.g. of a strong tertiary organic base such as triethylamine, N-ethyl-diisopropylamine, pyridine or *s*-collidine, which in excess can also serve as reaction medium, or in the presence of a corresponding excess of the compound of the formula VI to be reacted, in the presence or absence of an inert organic solvent, such as dioxane, tetrahydrofuran, benzene or dimethylformamide, at a temperature of between 0°C and 100°C, or at the boiling temperature of the reaction medium in the case where this is lower. It is possible under analogous reaction conditions to react also mixed anhydrides of the carboxylic acid of the formula V, especially the mixed anhydrides with carbonic acid semi-esters obtainable, e.g., by reaction of alkali metal salts of the carboxylic acid with chloroformic acid esters, preferably chloroformic acid lower alkyl esters, with compounds of formula VI.

Further suitable reactive functional derivatives of the carboxylic acid of the formula V are, for example, reactive esters such as *p*-nitrophenyl esters and cyanomethyl esters, which can be reacted with compounds of the formula VI in inert organic solvents, if necessary with heating. Under the same conditions are reacted the 1-imidazolides of the carboxylic acid of the formula V with compounds of the formula VI.

The carboxylic acid of the formula V and its ethyl ester can be obtained, for example, from the 6-(*o*-chlorophenyl)-8-chloro-4H-*s*-triazolo[1,5-*a*] [1,4]benzodiazepine-2-carboxylic acid described in the German Offenlegungsschrift No. 2,159,527, or from its ethyl ester, described in the German Offenlegungsschriften Nos. 2,234,652 and 2,304,307, by treatment with formaldehyde and formic acid analogously to process b), or from 1-[2-(*o*-chlorobenzoyl)-4-chlorophenyl]-5-(chloromethyl)-1H-1,2,4-triazole-2-carboxylic acid or its ethyl ester, which are likewise described in the aforementioned Offenlegungsschriften, by reaction with dimethylamine, e.g. in the presence of a small amount of sodium iodide, analogously to process a). Other lower alkyl esters, such as the methyl ester, and further reactive functional derivatives can be obtained e.g. from the free carboxylic acid by a process known per se.

As reactive functional derivatives of compounds of the formula VI there may be mentioned the ethyl and propyl isocyanates and ethyl and propyl isothiocyanates. The

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reactions thereof with the carboxylic acid of the formula V can be performed in the presence of absence of an inert organic solvent having a sufficiently high boiling point and boiling range, e.g. in toluene or in xylene or in an xylene mixture. To be mentioned as further reactive functional derivatives of compounds of the formula VI are also, e.g., N-tri-(lower alkyl)-silyl derivatives obtainable by the reaction of these compounds with tri-(lower alkyl)-silyl chlorides, such as trimethylsilyl chloride, in inert, anhydrous organic solvents. The reaction of these derivatives with reactive functional derivatives of the carboxylic acid of the formula V in inert organic solvents yields N-tri-(lower alkyl)-silyl derivatives of carboxamides embraced by the formula I, from which are liberated the desired carboxamides by means of decomposition with water or with lower alkanols.

For the process e) are used, as alkali metal cyanide, for example potassium cyanide and particularly sodium cyanide. By selective oxidising agents are meant those which under the reaction conditions do not attack the aldehyde group of the starting material of the formula VII, but which on the other hand are able to oxidise the hydroxymethylene group of the intermediately formed cyanohydrin to the carbonyl group. A suitable oxidising agent is manganese dioxide, particularly in the active form described by J. Attenburrow et al., J. Chem. Soc. 1952, 1104. The reactions with manganese dioxide are preferably performed in isopropanol, or in another lower secondary alkanol, to which can be added a further organic solvent inert under the reaction conditions, preferably such a solvent having a good dissolving capacity for the starting material of the formula VII, for example, dioxane, in the cold state between -10°C and $+10^{\circ}\text{C}$, preferably around 0°C . Relative to the compound of the formula VI, there is used, for example, a considerable excess of the compound of the general formula VI and also of alkali metal cyanide, e.g. about the 5-fold molar amount of the last-mentioned and an ever greater excess, e.g. about the 20-fold molar amount of manganese dioxide, with a reaction duration of 2 to 6 hours, preferably about 4 hours. The triazole derivative of the formula VII used as starting material is produced, for example, starting with the 6-(o-chlorophenyl)-8-chloro-4H-s-triazolo[1,5-a][1,4]benzodiazepine-2-methanol, described in the German Offenlegungsschrift No. 2,234,652, by treatment with formaldehyde and formic acid analogously to the aforementioned process b), and oxidation of the resulting 1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]1H-1,2,4-triazole-3-methanol under mild conditions, e.g. with the chromium trioxide solution according to Jones, mentioned under process c), at 0°C , or with activated manganese dioxide, mentioned there as well as in the foregoing, in boiling benzene.

The present invention relates also to such modifications of the processes above-mentioned wherein a starting material is used in the form of a salt. If the required starting materials are optically active, then both the racemates and the isolated antipodes can be used, or in the case of diastereomeric compounds either mixtures of racemates or specific racemates, or likewise isolated antipodes can be used. Also such starting materials can optionally, be used in the form of salts.

Depending on the conditions of the process and on the starting materials, the products are obtained in the free form, or in the form, likewise included in the invention, of their acid addition salts, or in some cases in the form of hydrates of the last-mentioned. The acid addition salts of the new compounds of the formula I can be converted in a known manner into the free bases, e.g. with basic agents, such as alkalies or ion exchangers. Alternatively, the compounds of the formula I obtained by the process according to the invention can, optionally, be converted in the usual manner into their addition salts with inorganic or organic salts. For example, the acid desired as salt component is added to a solution of a compound of the formula I in an organic solvent. Solvents preferably used for the reaction are those in which the occurring salt is difficultly soluble, so that the salt can be separated by filtration. Such solvents are, for example, ethyl acetate, methanol, ether, acetone, methyl ethyl ketone, acetone/ether, acetone/ethanol, methanol/ether and ethanol/ether.

It is possible to use as pharmaceutically active substances, instead of free bases, pharmaceutically acceptable acid addition salts, i.e. salts with acids of which the anions are not toxic in the dosage amounts concerned. Moreover, it is of advantage if the salts to be used as pharmaceutically active substances readily crystallise, and are not, or only slightly, hygroscopic. For salt formation with compounds of the formula I, it is possible to use, e.g., hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, acetic acid, lactic acid, succinic acid, fumaric acid, maleic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid, phenylacetic acid, mandelic acid and embonic acid.

The new compounds can be present, depending on the choice of starting materials and working procedures, as optical antipodes or racemates or, if they have at least two asymmetric carbon atoms, also as mixtures of isomers (racemate mixtures). The mixtures of isomers (racemate mixtures) obtained can, by virtue of the physical-chemical differences in the constituents, be separated in a known manner into the two stereoisomeric (di-

astereomeric) pure racemates, e.g. by chromatography and/or fractional crystallisation.

Resulting racemates can be resolved by known methods, for example by recrystallisation from an optically active solvent, with the aid of microorganisms, or by reaction with an optically active acid forming salts with the racemic compound, and separation of the salts obtained in this manner, e.g. by virtue of their different degrees of solubility, into the diastereomers from which the antipodes can be liberated by the action of suitable agents. Particularly suitable optically active acids are, for example, the D- and L-forms of tartaric acid, di-o-toluytartaric acid, malic acid, mandelic acid, camphorsulphonic acid or quinic acid. It is of advantage to isolate the more effective of the two antipodes.

The new compounds are administered orally, rectally or parenterally. The dosage amount depends on the mode of administration, on the species, on the age and on the individual condition. The daily doses of the free bases or of pharmaceutically acceptable salts thereof vary between 0.1 mg/kg and 3 mg/kg for warm-blooded animals. Suitable dosage units, such as dragées, tablets, suppositories or ampoules, preferably contain 0.5 - 50 mg of an active substance according to the invention.

Dosage units for oral administration contain as active substance preferably between 0.5 and 50% of a compound of the formula I, or of a pharmaceutically acceptable salt thereof. The said dosage units are produced by combination of the active substance with, e.g., solid pulverulent carriers such as lactose, saccharose, sorbitol or mannitol; starches such as a potato starch, maize starch or amylopectin, also laminaria powder or citrus pulp powder; cellulose derivatives or gelatine, optionally with the addition of lubricants, such as magnesium stearate or calcium stearate or polyethylene glycols, to form tablets or dragée cores. The dragée cores are coated for example with concentrated sugar solutions which can also contain, e.g., gum arabic, talcum and/or titanium dioxide, or with a lacquer dissolved in readily volatile organic solvents or solvent mixtures.

Dyestuffs may be added to these coatings, e.g. for identification of the various dosage amounts.

Further suitable oral dosage units are hard gelatine capsules, as well as soft closed capsules made from gelatine and a softener such as glycerin. The hard gelatine capsules contain the active substance preferably as a granulate, e.g. in admixture with fillers such as maize starch, and/or lubricants such as talcum or magnesium stearate, and optionally stabilisers such as sodium metabisulphite ($\text{Na}_2\text{S}_2\text{O}_5$) or ascorbic acid. In soft capsules, the active substance is preferably dissolved or suspended in suitable liquids, such as in liquid polyethylene glycols, to which likewise stabilisers may be added.

Suitable dosage units for rectal administration are, e.g., suppositories consisting of a combination of an active substance with a suppository foundation substance. Suppository foundation substances that can be used are, e.g., natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. Also suitable are gelatine rectal capsules consisting of a combination of the active substance with a foundation substance. Suitable foundation substances are, e.g., liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Ampoules for parenteral administration, especially intramuscular administration, preferably contain a water-soluble salt of an active substance at a concentration preferably of 0.2 - 5%, optionally together with suitable stabilisers and buffer substances, in aqueous solution.

The following working examples further illustrate the production of tablets, dragées, suppositories and ampoules:

a) 50.0 g of N-propyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-(dimethylaminomethyl)-1H-1,2,4-triazole-3-carboxamide is mixed with 500 g of lactose and 292 g of potato starch; the mixture is moistened with an alcoholic solution of 8 g of gelatine, and then granulated through a sieve. After drying of the granulate, 60 g of potato starch, 60 g of talcum, 10 g of magnesium stearate and 20 g of highly dispersed silicon dioxide are mixed in, and the mixture is subsequently pressed out to form 10,000 tablets each weighing 105.0 mg and each containing 5.0 mg of active substance; the tablets can be provided with grooves to effect a more precise adjustment of the dosage amount.

b) 2.50 g of N-ethyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-(dimethylamino)-methyl-1H-1,2,4-triazole-3-carboxamide is well mixed with 16 g of maize starch and 6 g of highly dispersed silicon dioxide. The mixture is moistened with a solution of 2 g of stearic acid, 6 g of ethylcellulose and 6 g of stearin in about 70 ml of isopropyl alcohol, and is then granulated through a sieve III (Ph.Helv. V). The granulate is dried for about 14 hours and is subsequently put through sieve III-IIIa. It is then mixed with 16 g of maize starch, 16 g of talcum and 2 g of magnesium stearate and the mixture is pressed out to form 1000 dragée cores. These are coated with a concentrated syrup of 2 g of lacca, 7.5 g of gum arabic, 0.15 g of dyestuff, 2 g of highly dispersed silicon dioxide, 25 g of talcum and 53.35 g of sugar, and finally dried. The dragées obtained each weigh 162.5 mg and each contain 2.5 mg of active substance.

c) 10.0 g of N-propyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxamide and 1990 g of finely ground suppository foundation substance (e.g. cocoa butter) are thoroughly mixed and then melted. From the melt, maintained homogeneous by stirring, are formed 1000 suppositories each weighing 2 g and each containing 10 mg of active substance.

d) A solution of 2.0 g of N-ethyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxamide-hydrochloride in one litre of water is filled into 1000 ampoules and sterilised. Each ampoule contains 2 mg of active substance as a 0.2% solution.

The following Examples further illustrate the production of the novel compounds of the formula I as well as of starting materials not hitherto known, but they are not intended to limit in any way the scope of the invention. Temperatures are given in degrees Centigrade.

Example 1

4.0 ml of a 33% ethanolic dimethylamine solution is added to a mixture of 4.37 g (0.01 mole) of crude N-ethyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-(chloromethyl)-1H-1,2,4-triazole-3-carboxamide and 0.15 g of sodium iodide in 80 ml of methanol, and the mixture is refluxed, with stirring, for 4 hours. The reaction mixture is thereupon concentrated in vacuo. Water and saturated sodium carbonate solution are added to the residue until the pH value has reached 10 and extraction is performed twice with ethyl acetate. The organic phase is washed with water and saturated sodium chloride solution, dried over sodium sulphate and then concentrated in vacuo. The residue is recrystallised from isopropanol to obtain, after drying in vacuo, N-ethyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxamide, m.p. 131-133°.

In an analogous manner is obtained, from 4.51 g of crude N-propyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-(chloromethyl)-1H-1,2,4-triazole-3-carboxamide: N-propyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxamide, m.p. 110-113° (from ether).

The starting material is produced as follows:

8.95 g (0.02 mole) of 1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-(chloromethyl)-1H-1,2,4-triazole-3-carboxylic acid (contains one molecule of crystal methanol; see DOS 2,159,527, p. 32) is covered over with 40 ml of oxalyl chloride and refluxed for one hour. The clear yellow solution is concentrated at 40° in vacuo, and, to effect the complete removal of the oxalyl chloride, 100 ml of toluene is added and the solution is again concentrated at 40° in vacuo.

The resulting crude 1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-(chloromethyl)-1H-1,2,4-triazole-3-carbonyl chloride is dissolved in 80 ml of dioxane, and to the solution is added dropwise at room temperature, in the course of 30 minutes, a solution of 1.98 g (0.044 mole) of ethylamine in 30 ml of dioxane. The ethylamine hydrochloride gradually precipitates out. The reaction mixture is concentrated in vacuo to dryness. Ice water and ether are added to the residue; the organic phase is separated and is washed successively with cold 1N hydrochloric acid, with cold 0.1N sodium hydroxide solution and with saturated sodium chloride solution. After drying, and concentration in vacuo, is obtained crude N-ethyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-(chloromethyl)-1H-1,2,4-triazole-3-carboxamide.

In an analogous manner there is obtained, from 8.95 g of 1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-(chloromethyl)-1H-1,2,4-triazole-3-carboxylic acid (contains one molecule of crystal methanol), by way of the acid chloride with the use of 2.60 g of n-propylamine: crude N-propyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-(chloromethyl)-1H-1,2,4-triazole-3-carboxamide.

Example 2

23 ml of 36% aqueous formaldehyde solution is added to the solution of 11.5 g (0.03 mole) of N-ethyl-6-(o-chlorophenyl)-8-chloro-4H-s-triazolo[1,5-a] [1,4]benzodiazepine-2-carboxamide in 39 ml of 85% commercial formic acid, and the mixture is heated, with stirring, for 4 hours at 100°. The reaction solution is thereupon poured into ice water, and undesired neutral constituents are extracted with ether. To the acid aqueous phase is added concentrated sodium hydroxide solution until the pH value has reached 11. The precipitated crude product is taken up in ether. The organic extracts are washed twice with water and once with saturated sodium chloride solution; they are dried over sodium sulphate and concentrated in vacuo. The residue is recrystallised from isopropanol to obtain, after drying in vacuo, N-ethyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxamide, m.p. 131-133°C.

In an analogous manner there is obtained, from 11.9 g of N-propyl-6-(o-chlorophenyl)-8-chloro-4H-s-triazolo[1,5-a] [1,4]benzodiazepine-2-carboxamide: N-propyl-1-[2-(o-



chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxamide, m.p. 110-113° (from ether).

Example 3

35.0 g (0.0835 mole) of 1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxylic acid is refluxed in 175 ml of thionyl chloride for 90 minutes. The clear solution is concentrated at 40° in vacuo and the residue, for complete removal of the thionyl chloride, is dissolved in 100 ml of absolute toluene and the solution is again concentrated by evaporation. The resulting crude acid chloride hydrochloride is dissolved in 350 ml of dioxane; an addition is made at room temperature, with stirring, of 56.7 ml (0.417 mole) of 33% ethanolic ethylamine solution, and stirring is continued at room temperature for 18 hours. The reaction mixture is thereupon concentrated in vacuo to dryness. To the residue is added ice water, and 2N sodium hydroxide solution is added until the pH value has reached 11. The precipitated crude product is taken up in methylene chloride. The separated organic extracts are washed twice with water and once with saturated sodium chloride solution; they are then dried over sodium sulphate and concentrated in vacuo. The solid residue is recrystallised from 500 ml of isopropanol. After drying in vacuo, the resulting N-ethyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxamide melts at 131-133°.

The starting material is produced as follows:

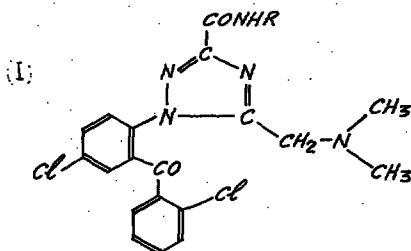
310 ml (0.226 mole) of a 33% ethanolic dimethylamine solution is added to a suspension of 45.0 g (0.11 mole) of 1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-(chloromethyl)-1H-1,2,4-triazole-3-carboxylic acid (see DT-OS 2,159,527, page 32) and 0.5 g (0.0033 mole) of sodium iodide in 250 ml of methanol, and the mixture is stirred for 6 hours at room temperature. The clear reaction solution is concentrated in vacuo; the residue is dissolved in 200 ml of water, and 2N hydrochloric acid solution is slowly added until the pH value of 5 is reached. After 16 hours' standing at 0-5°, the precipitated aminic acid is filtered off and well washed with water and then with ether. Upon drying, there is obtained 1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxylic acid, m.p. 222-225° with decomposition.

In an analogous manner there is obtained:

N-propyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxamide, m.p. 110-113° (from ether).

WHAT WE CLAIM IS:

1. Triazole derivatives of the formula I



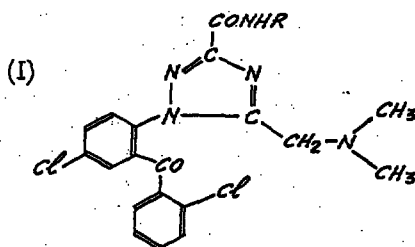
wherein

R represents a straight-chain alkyl having 2 or 3 carbon atoms, and their addition salts with inorganic and organic acids.

2. N-Ethyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxamide and its addition salts with inorganic and organic acids.

3. N-Propyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxamide and its addition salts with inorganic and organic acids.

4. Process for the production of novel triazole derivatives of the formula I



chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxamide, m.p. 110-113° (from ether).

Example 3

35.0 g (0.0835 mole) of 1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxylic acid is refluxed in 175 ml of thionyl chloride for 90 minutes. The clear solution is concentrated at 40° in vacuo and the residue, for complete removal of the thionyl chloride, is dissolved in 100 ml of absolute toluene and the solution is again concentrated by evaporation. The resulting crude acid chloride hydrochloride is dissolved in 350 ml of dioxane; an addition is made at room temperature, with stirring, of 56.7 ml (0.417 mole) of 33% ethanolic ethylamine solution, and stirring is continued at room temperature for 18 hours. The reaction mixture is thereupon concentrated in vacuo to dryness. To the residue is added ice water, and 2N sodium hydroxide solution is added until the pH value has reached 11. The precipitated crude product is taken up in methylene chloride. The separated organic extracts are washed twice with water and once with saturated sodium chloride solution; they are then dried over sodium sulphate and concentrated in vacuo. The solid residue is recrystallised from 500 ml of isopropanol. After drying in vacuo, the resulting N-ethyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxamide melts at 131-133°.

The starting material is produced as follows:

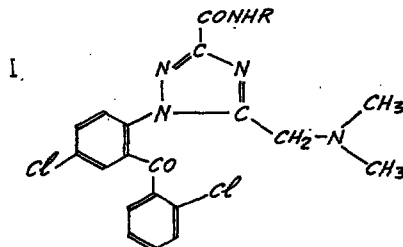
310 ml (0.226 mole) of a 33% ethanolic dimethylamine solution is added to a suspension of 45.0 g (0.11 mole) of 1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-(chloromethyl)-1H-1,2,4-triazole-3-carboxylic acid (see DT-OS 2,159,527, page 32) and 0.5 g (0.0033 mole) of sodium iodide in 250 ml of methanol, and the mixture is stirred for 6 hours at room temperature. The clear reaction solution is concentrated in vacuo; the residue is dissolved in 200 ml of water, and 2N hydrochloric acid solution is slowly added until the pH value of 5 is reached. After 16 hours' standing at 0-5°, the precipitated aminic acid is filtered off and well washed with water and then with ether. Upon drying, there is obtained 1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxylic acid, m.p. 222-225° with decomposition.

In an analogous manner there is obtained:

N-propyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxamide, m.p. 110-113° (from ether).

WHAT WE CLAIM IS:

1. Triazole derivatives of the formula I



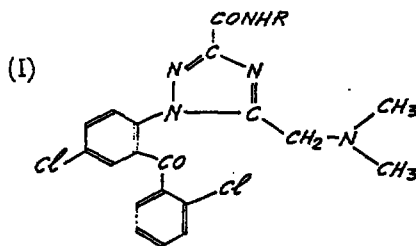
wherein

R represents a straight-chain alkyl having 2 or 3 carbon atoms, and their addition salts with inorganic and organic acids.

2. N-Ethyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxamide and its addition salts with inorganic and organic acids.

3. N-Propyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxamide and its addition salts with inorganic and organic acids.

4. Process for the production of novel triazole derivatives of the formula I





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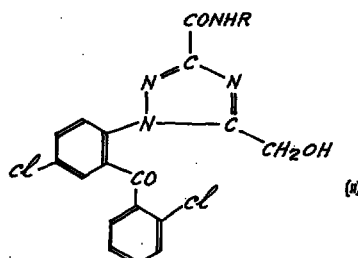
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wherein

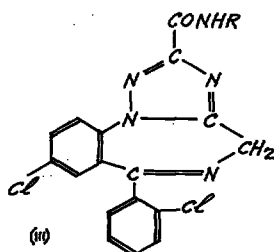
R represents straight-chain alkyl having 2 or 3 carbon atoms, and their addition salts with inorganic and organic acids, in which process

a) a reactive ester of a compound of the formula II



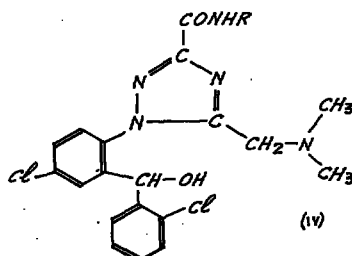
wherein R has the meaning given under formula I, is reacted with dimethylamine or with an alkali metal derivative thereof; or

b) a compound of the formula III



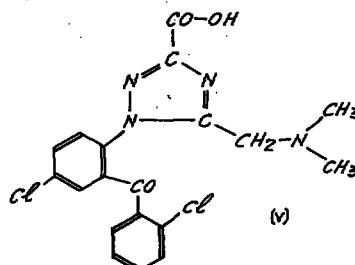
wherein R has the meaning given under the formula I is reacted with formaldehyde and formic acid; or

c) a compound of the formula IV



wherein R has the meaning given under the formula I, is oxidised; or

d) the carboxylic acid of the formula V



or a reactive functional derivative thereof, is reacted with a compound of the formula VI

NH_2R

(VI),

wherein R has the meaning given under the formula I, or with a reactive functional derivative of such a compound; or

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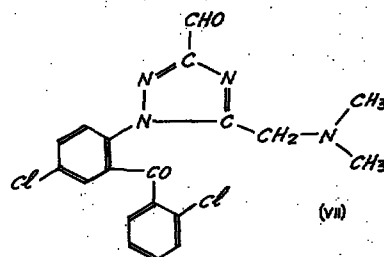
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e) the compound of the formula VII



is reacted with a compound of the formula VI given in the foregoing, wherein R has the meaning given under the formula I, in the presence of an alkali metal cyanide and of a selective oxidising agent; and, optionally a triazole derivative of the formula I obtained by any one of the given processes is converted into an addition salt with an inorganic or organic acid.

5. Process according to Claim 4, wherein a starting material is used in the form of a salt.

6. Process according to Claim 4, wherein there are produced the compounds of the general formula I which are described in the Examples and their addition salts with inorganic and organic acids.

7. Process according to Claim 4, wherein there are produced N-ethyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxamide and its addition salts with inorganic and organic acids.

8. Process according to Claim 4, wherein there are produced N-propyl-1-[2-(o-chlorobenzoyl)-4-chlorophenyl]-5-[(dimethylamino)-methyl]-1H-1,2,4-triazole-3-carboxamide and its addition salts with inorganic and organic acids.

9. A process for the manufacture of triazole derivatives of the formula I set out in Claim 1, substantially as herein described with reference to the examples.

10. Triazole derivatives prepared by the process claimed in any one of Claims 4 and 5.

11. Triazole derivatives of the general formula I set out in Claim 1 substantially as herein described with reference to the examples.

12. Pharmaceutical compositions for the treatment of epilepsy and of conditions of tension and agitation, which compositions contain a triazole derivative according to Claim 1 to 3, or a pharmaceutically acceptable addition salt of such a triazole derivative with an inorganic or organic acid, together with pharmaceutical carrier substances.

13. A pharmaceutical composition according to claim 12 substantially as herein described.

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