PATENT SPECIFICATION (11) 1 490 306

1 490 306

(21) Application No. 44299/75 (22) Filed 28 Oct. 1975
(31) Convention Application No. 2 458 965
(32) Filed 13 Dec. 1974 in
(33) Fed. Rep. of Germany (DT)
(44) Complete Specification published 2 Nov. 1977
(51) INT CL² C07D 231/56; A61K 31/415
(52) Index at acceptance
C2C 1403 213 220 227 22Y 247 250 252 25Y 271 280 281 305 30Y 311 313 314 31Y 321 322 323 326 32Y 332 337 338 339 340 342 34Y 364 366 368 36Y 43X 440 443 451 452 453 456 45Y 491 579 57Y 584 601 611 616 617 619 620 621 627 628 62X 62Y 630 634 637 65X 666 670 671 672 676 678 68Y 694 698 69Y 72Y 73Y 790 79Y KB KJ KK KZ LP LS LW LY NB NF NR

(72) Inventors KARL HEINRICH MAYER, SIEGFRIED PETERSEN, ERICH KLAUKE, FRIEDRICH HOFFMEISTER and WOLFGANG WUTTKE

(54) 3-AMINO-INDAZOLECARBOXYLIC ACID DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR USE AS MEDICAMENTS

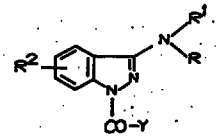
(71) We, BAYER AKTIENGESELLSCHAFT, a body corporate organised under the laws of Germany, of Leverkusen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new 3-amino-indazole-carboxylic acid derivatives, a process for their preparation and their use as compounds which act on the central nervous system, and especially as analgesics.

It has already been disclosed that 3-amino-indazoles have an action on the central nervous system and can be used as analgesics and antipyretics (compare German Auslegeschrift (German Published Specification) 1,280,878). In this published specification, 3 - amino - 5 - trifluoromethyl - indazole, which is chemically the nearest compound of the same type of action, is particularly singled out as a compound having especially advantageous therapeutic properties.

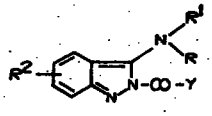
3-Amino-indazoles find their main use in dyestuff chemistry and are known, inter alia, as starting materials for the preparation of dyestuffs (compare German Auslegeschrift (German Published Specification) 1,149,839).

According to the present invention we provide 3-amino-indazolecarboxylic acid derivatives of the isomeric formulae



(I a)

and



(I b)

in which

Y represents alkoxy, alkylamino or dialkylamino,

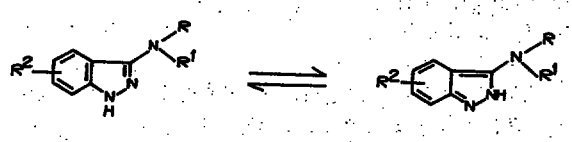
R represents hydrogen or methyl,

R^1 represents hydrogen, methyl or formyl and

R^2 represents 1, 2 or 3 substituents independently selected from hydrogen, alkyl, alkoxy, nitro, amino, alkylamino, dialkylamino, acylamino, alkoxycarbonylamino, halogen, trifluoromethyl, cyano and alkoxycarbonyl, and their salts.

The compounds of the invention (i.e. the compounds of the formulae Ia) and Ib) and their salts have powerful actions on the central nervous system, and especially possess very good analgesic, antipyretic and antiphlogistic properties. Consequently, of those compounds of the invention which are salts, those which are pharmaceutically acceptable are preferred.

The 3-amino-indazolecarboxylic acid derivatives of the formulae (I a) and (I b) may be obtained by reacting a 3-amino-indazole of the tautomeric formulae



(a) II (b)

in which R, R^1 and R^2 have the abovementioned meaning with a carbonic acid derivative of the formula

$$Y—CO—X \qquad (III)$$

in which Y represents the radical OR^3 or the radical



wherein

R^3, R^4 and R^5 each denote alkyl,

X represents halogen, or, if Y represents OR^3, the radical O—$COOR^3$, or

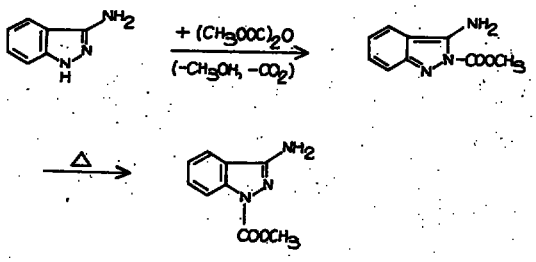
X and Y conjointly denote an imide group of the formula $=NR^6$, wherein R^6 denotes alkyl,

in the presence of an inert organic solubilising agent and, if appropriate, in the presence of an acid-binding agent, usually at a temperature of from −20 to +250°C and thereafter, if appropriate, in a further reaction step the amino group in the 3-position is formylated with formic acid or methylated with formaldehyde in the presence of formic acid. The resulting compounds may be converted to the corresponding salts by conventional techniques, e.g. by reaction with a base in an inert solvent.

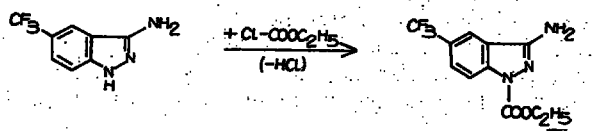
Surprisingly, the new 3-amino-indazolecarboxylic acid derivatives according to the invention show better toleration and a substantially greater analgesic and antipyretic as well as antiphlogistic (anti-oedematous) action than the amino-indazoles known from the state of the art, especially than 3- 3-amino-5-trifluoromethyl-indazole, which is chemically the nearest active compound of the same type of action. The compounds according to the invention thus represent an enrichment of pharmacy.

The reaction scheme which follows shows, by way of example, the reactions of the individual reactants which can be used according to the invention:

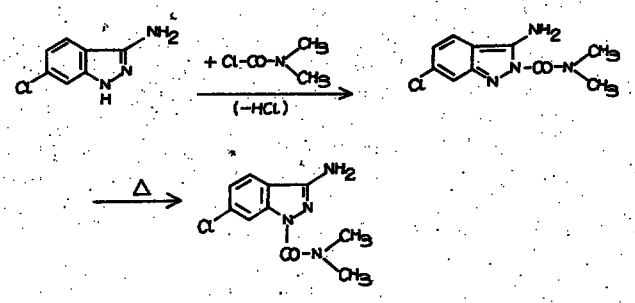
a)



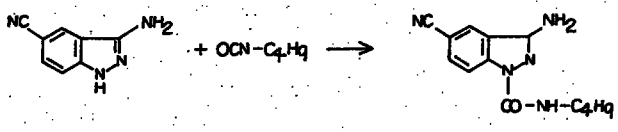
b)



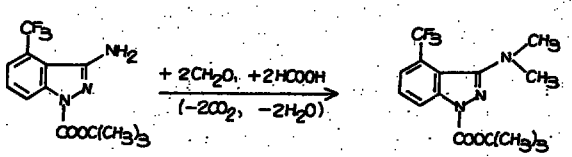
c)



d)



Reaction course of an optional subsequent bis-methylation of the NH_2-group:



The formation of the two isomeric forms (Ia) and (Ib) of the compounds according to the invention can be influenced by the choice of the reaction temperature. At lower temperatures, the isomeric form (Ib), with the substituents in the 2-position, is formed preferentially, whilst at higher temperatures compounds of the isomeric form (Ia), with the substituents in the 1-position, are formed preferentially. Ib-isomers can also be rearranged to the Ia-isomers by subsequent heating (see the equation for reaction a) and c)).

In the formula (II), R^2 preferably represents 1 or 2 substituents independently selected from hydrogen, nitro, amino, cyano, trifluoromethyl, halogen, alkyl, alkoxy, alkylamino, dialkylamino, alkoxycarbonyl, alkoxycarbonylamino and acylamino, halogen being, in particular, chlorine or bromine, and the alkyl, alkoxy and acyl radicals mentioned containing 1 to 4 carbon atoms, especially 1 or 2 carbon atoms.

Compounds of the formula (II) in which R^2 represents hydrogen, nitro, amino, halogen, trifluoromethyl, cyano and alkoxycarbonylamino are particularly important.

The 3-amino-indazoles of the tautomeric formula (II) to be used as starting materials are known or can be prepared according to known processes (compare J. Amer. chem. Soc. *65* (1943), 1804, J. chem. Soc. (London) *1959*, 2363, Liebigs Ann. Chem. *716* (1968), 47).

The following may be mentioned as individual examples: 3 - amino - indazole, 3 - amino - 4 - methyl - indazole, 3 - amino - 5 - isopropyl - indazole, 3 - amino-6 - n - butyl - indazole, 3 - amino - 4,7 - bis - methyl - indazole, 3 - amino - 5,6-bis - ethyl - indazole, 3 - amino - 5 - ethyl - 6 - isopropyl - indazole, 3 - amino-6 - methoxy - indazole, 3 - amino - 5 - ethoxy - indazole, 3 - amino - 5,6 - bis-methoxy - indazole, 3 - amino - 4 - methyl - 7 - n - propoxy - indazole, 3 - amino-5 - nitro - indazole, 3 - amino - 5,7 - dinitro - indazole, 3,5 - diamino - indazole, 3,5,7 - tris - amino - indazole, 3,5 - diamino - 7 - nitro - indazole, 3 - amino - 5-methylamino - indazole, 3 - amino - 5 - t - butylamino - indazole, 3 - amino - 5-dimethylamino - indazole, 3 - amino - 5 - formylamino - indazole, 3 - amino - 5,7-bis - formylamino - indazole, 3 - amino - 5 - acetylamino - indazole, 3 - amino - 5-pivaloylamino - indazole, 3 - amino - 4 - chloro - indazole, 3 - amino - 5 - chloro-indazole, 3 - amino - 6 - chloro-indazole, 3 - amino - 5 - bromo - indazole, 3-amino - 6 - fluoro - indazole, 3 - amino - 4,7 - dichloro - indazole, 3 - amino - 4-methyl - 6 - chloro - indazole, 3 - amino - 4 - ethyl - 5 - bromo - indazole, 3-amino - 4 - ethoxy - 6 - chloro - indazole, 3 - amino - 4 - trifluoromethyl - indazole, 3 - amino - 5 - trifluoromethyl - indazole, 3 - amino - 6 - trifluoromethyl - indazole, 3 - amino - 7 - trifluoromethyl - indazole, 3 - amino - 5 - trifluoromethyl - 6 - ethyl-indazole, 3 - amino - 5 - methoxy - 6 - trifluoromethyl - indazole, 3 - amino - 5-trifluoromethyl - 7 - nitro - indazole, 3,7 - diamino - 5 - trifluoromethyl - indazole,

3 - amino - 5 - trifluoromethyl - 7 - n - butylamino - indazole, 3 - amino - 5 - trifluoromethyl - 7 - i - propionylamino - indazole, 3 - amino - 5 - cyano - indazole, 3 - amino - 5 - cyano - 7 - nitro - indazole, 3 - amino - 5 - cyano - 7 - formylamino - indazole, 3 - amino - 5 - ethoxycarbonyl - indazole, 3 - amino - 5 - n-butoxycarbonyl - indazole, 3 - formylamino - indazole, 3 - methylamino - indazole, 3 - dimethylamino - indazole, 3 - formylamino - 5 - ethyl - indazole, 3 - dimethylamino - 6 - ethoxy - indazole, 3 - dimethylamino - 5,6 - bis - methoxy - indazole, 3 - formyl - 5 - nitro - indazole, 3 - methylamino - 5 - amino - indazole, 3 - dimethylamino - 6 - chloro - indazole and 3 - formylamino - 5 - trifluoro - methyl-indazole.

The carbonic acid derivatives of the formula (III) to be used as starting materials are known or can be prepared by the known method. The following may be listed individually:

a) Pyrocarbonic acid esters: pyrocarbonic acid methyl ester, pyrocarbonic acid ethyl ester, pyrocarbonic acid propyl ester, pyrocarbonic isopropyl ester and pyrocarbonic acid butyl ester (compare Liebigs Ann. Chem. *624*, pages 30—36, (1959)).

b) Chlorocarbonic acid esters: chlorocarbonic acid methyl ester, chlorocarbonic acid ethyl ester, chlorocarbonic acid propyl ester, chlorocarbonic acid isopropyl ester and chlorocarbonic acid butyl ester (compare Beilsteins Handbuch der Organischen Chemie (Beilstein's Handbook of Organic Chemistry), edition IV, 3rd supplement, volume 3, pages 23—26).

c) Carbamic acid halides: dimethylcarbamic acid chloride, dimethylcarbamic acid bromide, diethylcarbamic acid chloride, methyl-ethyl-carbamic acid chloride, methyl-ethylcarbamic acid bromide, dipropylcarbamic acid bromide, diisopropylcarbamic acid chloride and dibutylcarbamic acid bromide (compare Beilsteins Handbuch der Organischen Chemie (Beilstein's Handbook of Organic Chemistry), edition IV, 3rd supplement, volume 4, pages 144, 222 and 301).

d) Carbonic acid imides (isocyanates); methyl isocyanate, ethyl isocyanate, propyl isocyanate, isopropyl isocyanate, n-butyl isocyanate and tert.-butyl isocyanate (compare Beilsteins Handbuch der Organischen Chemie (Beilstein's Handbook of Organic Chemistry), edition IV, 3rd supplement, volume 4, pages 156, 227, 263, 279, 303, 321 and 325).

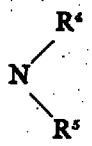
In the formula (III)

Y preferably represents the OR^3 radical,

wherein

R^3 represents alkyl with 1 to 4 C atoms, especially 1 to 2 C atoms, or

Y preferably represents the radical



wherein

R^4 and R^5 preferably denote alkyl with 1 to 4 C atoms and

X preferably represents halogen, especially chlorine or, if Y represents OR^3, the radical $O—COOR^3$,

wherein

R^3 has the abovementioned meaning, or

X+Y conjointly preferably represent the imide group of the formula $=NR^6$

wherein

R^6 denotes alkyl with 1—4 C atoms, especially with 1 to 2 C atoms.

In the formulae I, II and III preferred alkyl groups are straight-chain or branched alkyl groups with 1 to 4, especially with 1 to 2, C atoms. Methyl, ethyl, n- and i-propyl and n-, i- and t-butyl may be mentioned as examples.

Preferred alkoxy groups are straight-chain or branched alkoxy groups with 1 to 4, especially with 1 to 2, C atoms. Methoxy, ethoxy, n- and i-propoxy and n-, i- and t-butoxy may be mentioned as examples.

Preferred alkylamino and dialkylamino groups are straight-chain or branched alkylamino or dialkylamino with 1 to 4, especially 1 to 2, C atoms in the alkyl groups.

Methylamino, dimethylamino, ethylamino, diethylamino, methylethylamino, n- and i-propylamino, n- and i-dipropylamino, n-, i- and t-butylamino, n-, i- and t-dibutylamino and propylbutylamino may be mentioned as examples.

Preferred acylamino groups are straight-chain or branched acylamino with 1 to 6, especially 1 to 4, C atoms in the acyl radical. Formylamino, acetylamino, propionylamino, n- and i-butyrylamino, valeroylamino, isovaleroylamino and pivaloylamino may be mentioned as examples.

Preferred halogen atoms are fluorine, chlorine, bromine and iodine, especially chlorine or bromine.

Preferred alkoxycarbonyl groups are straight-chain or branched alkoxycarbonyl with 1 to 4, especially 1 to 2, C atoms in the alkoxy radical. Methoxycarbonyl, ethoxycarbonyl, n- and i-propoxycarbonyl and n-, i- and t-butoxycarbonyl may be mentioned as examples.

Preferred alkoxycarbonylamino groups are straight-chain or branched alkoxycarbonylamino with 1 to 4, especially 1 to 2, C atoms in the alkoxy radical. Examples which may be mentioned are methoxycarbonylamino, ethoxycarbonylamino, n- and i-propoxycarbonylamino and i-, i- and t-butoxycarbonylamino.

Diluents which can be used are all organic solvents which are inert towards the particular reactants. These preferentially include aliphatic alcohols such as methanol, ethanol, isopropanol or butanol, hydrocarbons such as benzene, toluene and xylene, halogenohydrocarbons such as chloroform, carbon tetrachloride, chlorobenzene and dichlorobenzenes, carboxylic acid esters such as ethyl acetate, nitriles such as acetonitrile and propionitrile, ketones such as acetone and methyl isobutyl ketone, ethers such as tetrahydrofurane or dioxane, carboxylic acid amide such as dimethylformamide or dimethylacetamide, heterocyclic bases such as pyridine, picolines, lutidines, collidines, quinoline or isoquinoline, and also commercially available technical mixtures of these solvents. In the reaction with pyrocarboxylic acid esters it is also possible to use an excess of these pyrocarboxylic acid esters, which at the same time act as solvents.

In carrying out the process according to the invention, suitably 100 to 1,000 ml of the diluent are employed per mol of the 3-amino-indazole of the formula (II).

The reaction can be carried out under normal pressure but also under elevated pressure. In general, it is carried out under normal pressure.

In the course of the reaction according to the invention, the starting materials as a rule dissolve entirely or partially whilst the end products crystallise out. The separating-out of the end products can be accelerated by cooling and/or by adding precipitants such as lower aliphatic ethers, for example diethyl ether and dibutyl ether, or lower aliphatic hydrocarbons, for example petroleum ether, light benzine, ligroin or halogenohydrocarbons, for example carbon tetrachloride.

The reaction temperatures can be varied within a substantial range. In general, temperatures between −20 and +250°C, preferably between −10 and 100°C, especially between 0 and 50°C, are used.

The thermal rearrangement of the I b compounds, which are substituted in the 2-position, to the I a compounds, which are substituted in the 1-position, can be effected by heating the I b compounds, in the absence of solvents, to temperatures above their melting point, or by heating them in the presence of solvents. Suitable solvents for the rearrangement are all inert higher-boiling organic solvents, especially ethers such as diethyl glycol dimethyl ether, diethylene glycol diethyl ether and diethylene glycol dibutyl ether, carboxylic acid amides, such as dimethylformamide and dimethylacetamide, aromatic hydrocarbons or aromatic hydrocarbon derivatives, such as xylene, tetralin, chlorobenzene, dichlorobenzenes, nitrobenzene or anisole. Heterocyclic bases such as pyridine, picolines, lutidines, collidines, quinoline and isoquinoline are particularly suitable as well as mixtures of these bases with other organic solvents.

The reaction temperatures for this rearrangement can be varied within a substantial range. In general, the reaction is carried out at temperatures between 20 and 250°C, preferably between 50 and 200°C, especially between 100 and 170°C.

The formylation or methylation of the NH_2— group in the 3-position in the formula I is carried out by heating with formic acid or a mixture of formaldehyde and formic acid at temperatures around 100°C.

All customary acid-binders can be used as the acid-binding agents. These include inorganic bases such as alkali metal hydroxides, for example calcium hydroxide or barium hydroxide, alkali metal carbonates or alkaline earth metal carbonates such as sodium carbonate, potassium carbonate, calcium carbonate or sodium bicarbonate, as well as amides such as sodamide and organic bases such as tertiary amines, for example triethylamine, N,N-dimethylaniline, pyridines, quinolines and isoquinolines. The use of pyridines, lutidines and collidines or quinoline as acid-binding agents is particularly

appropriate, since these bases at the same time may also be used as especially suitable diluents.

The following may be mentioned individually as new active compounds: 3 - amino-indazole - 1 - carboxylic acid methyl ester, 3 - diamino - indazole - 2 - carboxylic acid ethyl ester, 3 - amino - indazole - 1 - carboxylic acid n - butylamide, 3 - amino-indazole - 2 - carboxylic acid dimethylamide, 3 - dimethylamino - indazole - 1-carboxylic acid ethyl ester, 3 - formylamino - indazole - 1 - carboxylic acid n - butyl ester, 3 - amino - 5 - methyl - indazole - 1 - carboxylic acid diethylamide, 3 - amino-5,6 - bis - methoxy - indazole - 1 - carboxylic acid ethyl ester, 3 - amino - 5,6 - bis-methoxy - indazole - 2 - carboxylic acid ethyl ester, 3 - formylamino - 5 - nitro-indazole - 1 - carboxylic acid i - propylamide, 3 - amino - 5 - ethoxycarbonylamino-indazole - 1 - carboxylic acid ethyl ester, 3 - amino - 5,7 - bis - ethoxycarbonylamino-indazole - 1 - carboxylic acid ethyl ester, 3 - amino - 4 - chloro - indazole - 2 - carb-oxylic acid methyl ester, 3 - amino - 5 - chloro - indazole - 1 - carboxylic acid n-propylamide, 3 - amino - 5 - chloro - indazole - 1 - carboxylic acid dimethylamide, 3 - dimethylamino - 5 - chloro - indazole - 1 - carboxylic acid n-propyl ester, 3-formylamino - indazole - 1 - carboxylic acid ethylamide, 3 - amino - 6 - chloro-indazole - 1 - carboxylic acid methyl ester, 3 - amino - 6 - chloro - indazole - 1-carboxylic acid ethyl ester, 3 - amino - 6 - chloro - indazole - 2 - carboxylic acid ethyl ester, 3 - amino - 6 - chloro - indazole - 1 - carboxylic acid n - butyl ester, 3-amino - 6 - chloro - indazole - 1 - carboxylic acid dimethylamide, 3 - amino - 6-chloro-indazole- 2 - carboxylic acid dimethylamide, 3 - amino - 6 - chloro - indazole-1 - carboxylic acid n - butylamide, 3 - dimethylamino - 6 - chloro - indazole - 1-carboxylic acid ethyl ester, 3 - formylamino - 6 - chloro - indazole - 1 - carboxylic acid di - n - propylamide, 3 - amino - 4,7 - dichloro - indazole - 1 - carboxylic acid ethyl ester, 3 - amino - 5 - bromo - indazole - 1 - carboxylic acid dimethylamide, 3 - amino - 6 - fluoro - indazole - 1 - carboxylic acid t - butyl ester, 3 - amino - 4-trifluoromethyl - indazole - 1 - carboxylic acid methyl ester, 3 - amino - 4 - trifluoro-methyl - indazole - 2 - carboxylic acid dimethyl - amide, 3 - amino - 5 - trifluoro-methyl - indazole - 1 - carboxylic acid methyl ester, 3 - amino - 5 - trifluoromethyl-indazole - 2 - carboxylic acid methyl ester, 3 - amino - 5 - trifluoromethyl - indazole-1 - carboxylic acid ethyl ester, 3 - amino - 5 - trifluoromethyl - indazole - 2 - carb-oxylic acid ethyl ester, 3 - amino - 5 - trifluoromethyl - indazole - 1 - carboxylic acid i - butyl ester, 3 - amino - 5 - trifluoro - methyl - indazole - 1 - carboxylic acid dimethylamide, 3 - amino - 5 - trifluoromethyl - indazole - 1 - carboxylic acid n-butylamide, 3 - methylamino - 5 - trifluoromethyl - indazole - 1 - carboxylic acid ethyl ester, 3 - dimethylamino - 5 - trifluoromethyl - indazole - 1 - carboxylic acid d - n - butylamine, 3 - formylamino - 5 - trifluoromethyl - indazole - 1 - carboxylic acid n - propylamide, 3 - amino - 5 - trifluoromethyl - 7 - ethoxycarbonylamino-indazole - 1 - carboxylic acid ethyl ester, 3 - amino - 5 - cyano - indazole - 2-carboxylic acid methyl ester and 3 - amino - 5 - n - butoxycarbonylamino - indazole-1 - carboxylic acid n - butylamide.

The new active compounds show a strong action on the central nervous system, and in particular show an analgesic action, an antiphlogistic (anti-oedematous) action and an antipyretic action.

The present invention therefore provides a pharmaceutical composition containing as active ingredient a compound of the invention in admixture with a solid or liquefied gaseous diluent, or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 (preferably less than 350) except in the presence of a surface active agent.

The invention further provides a pharmaceutical composition containing as active ingredient a compound of the invention in the form of a sterile or isotonic aqueous solution.

The invention also provides a medicament in dosage unit form comprising a compound of the invention either alone or in admixture with a diluent.

The invention also provides a medicament in the form of tablets (including lozenges and granules), dragees, capsules, pills, ampoules or suppositories comprising a compound of the invention either alone or in admixture with the diluent.

"Medicament" as used in this Specification means physically discrete coherent portions suitable for medical administration. "Medicament in dosage unit form" as used in this Specification means physically discrete coherent portions suitable for medical administration each containing a daily dose or a multiple (up to four times) or sub-multiple (down to a fortieth) of a daily dose of the compound of the invention. Whether the medicament contains a daily dose or, for example, a half, a third, or a quarter of a daily dose will depend on whether the medicament is to be administered

once or, for example, twice, three times or four times a day respectively.

The pharmaceutical compositions according to the invention may, for example, take the form of ointments, gels, pastes, creams, sprays (including aerosols), lotions, suspensions, solutions and emulsions of the active ingredient in aqueous or non-aqueous diluents, syrups, granules or powders.

The diluents to be used in pharmaceutical compositions (e.g. granulates) adapted to be formed into tablets, dragees, capsules and pills include the following:

(a) fillers and extenders, e.g. starch, sugars, mannitol, and silicic acid; (b) binding agents, e.g. carboxymethyl cellulose and other cellulose derivatives, alginates, gelatine and polyvinyl pyrrolidone; (c) moisturizing agents, e.g. glycerol; (d) disintegrating agents, e.g. agar-agar, calcium carbonate and sodium bicarbonate; (e) agents for retarding dissolution e.g. paraffin; (f) resorption accelerators, e.g. quaternary ammonium compounds; (g) surface active agents, e.g. cetyl alcohol, glycerol monostearate; (h) adsorptive carriers, e.g. kaolin and bentonite; (i) lubricants, e.g. talc, calcium and magnesium stearate and solid polyethylene glycols.

The tablets, dragees, capsules and pills formed from the pharmaceutical compositions of the invention can have the customary coatings, envelopes and protective matrices, which may contain opacifiers. They can be so constituted that they release the active ingredient only or preferably in a particular part of the intestinal tract, possibly over a period of time. The coatings, envelopes and protective matrices may be made, for example, of polymeric substances or waxes.

The ingredient can also be made up in microencapsulated form together with one or several of the above-mentioned diluents.

The diluents to be used in pharmaceutical compositions adapted to be formed into suppositories can, for example, be the usual water-soluble or water-insoluble diluents, such as polyethylene glycols and fats (e.g. cocoa oil and high esters [e.g. C_{14}-alcohol with C_{16}-fatty acid]) or mixtures of these diluents.

The pharmaceutical compositions which are ointments, pastes, creams and gels can, for example, contain the usual diluents, e.g. animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide or mixtures of these substances.

The pharmaceutical compositions which are powders and sprays can, for example, contain the usual diluents, e.g. lactose, talc, silicic acid, aluminium hylroxide, calcium silicate, and polyamide powder or mixtures of these substances. Aerosol sprays can, for example, contain the usual propellants, e.g. chlorofluorohydrocarbons.

The pharmaceutical compositions which are solutions and emulsions can, for example, contain the customary diluents (with, of course, the above-mentioned exclusion of solvents having a molecular weight below 200 except in the presence of a surface-active agent), such as solvents, dissolving agents and emulsifiers; specific examples of such diluents are water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils [for example ground nut oil], glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitol or mixtures thereo.

For parenteral administration, the solutions and emulsions should be sterile, and, if appropriate, blood-isotonic.

The pharmaceutical compositions which are suspensions can contain the usual diluents, such as liquid diluents, e.g. water, ethyl alcohol, propylene glycol, surface-active agents (e.g. ethoxylated isostearyl alcohols, polyoxyethylene sorbite and sorbitane esters), microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth or mixtures thereof.

All the pharmaceutical compositions according to the invention can also contain colouring agents and preservatives as well as perfumes and flavouring additions (e.g. peppermint oil and eucalyptus oil) and sweetening agents (e.g. saccharin).

The pharmaceutical compositions according to the invention preferably contain about 0.1 to 99.5, more preferably from 0.5 to 90% of the active ingredient by weight of the total composition.

In addition to a compound of the invention, the pharmaceutical compositions and medicaments according to the invention can also contain other pharmaceutically active compounds. They may also contain a plurality of compounds of the invention.

Any diluent in the medicaments of the present invention may be any of those mentioned above in relation to the pharmaceutical compositions of the present invention. Such medicaments may include solvents of molecular weight less than 200 as sole diluent.

The discrete coherent portions constituting the medicament according to the invention (whether in dosage unit form or not) may be, for example, any of the following: tablets (including lozenges and granules), pills, dragees, capsules, suppositories and ampoules. Some of these forms may be made up for delayed release of the active ingredient. Some, such as capsules, include a protective envelope which renders the portions of the medicament physically discrete and coherent.

The preferred daily dose for administration of the medicaments of the invention is 0.5 mg to 5 g of active ingredient.

The production of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical composition (e.g. a granulate) and then forming the composition into the medicament (e.g. tablets).

This invention further provides a method of combating (including prevention, relief and cure of) the above-mentioned diseases in non-human animals, which comprises administering to the animals a compound of the invention alone or in admixture with a diluent or in the form of a medicament according to the invention.

It is envisaged that these active compounds will be administered perorally, parenterally (for example intramuscularly, intraperitoneally or intravenously), rectally or locally, preferably orally or parenterally. Preferred pharmaceutical compositions and medicaments are therefore those adapted for oral or partenteral administration.

In the case of oral use, tablets can of course also contain, in addition to the excipients mentioned, additives such as sodium citrate, calcium carbonate and calcium phosphate, together with various further substances such as starch, preferably potato starch and gelatine. Furthermore, lubricants such as magnesium stearate, sodium laurylsulphate and talc can be co-used for tablet-making. In the case of aqueous suspensions and/or elixirs which are intended for oral use, the active compounds can be mixed with various flavour-improving agents or dyestuffs in addition to the abovementioned auxiliaries.

In the case of parenteral application, solutions of the active compounds can be employed, using suitable liquid excipients. A fact which has proved particularly advantageous for the case of parenteral application is that the compounds according to the invention can form readily water-soluble salts. These salts are obtained when the compounds according to the invention, in a suitable solvent, are combined with the equimolar amount of a non-toxic inorganic or organic base. As examples there may be mentioned: sodium hydroxide solution, potassium hydroxide solution, ethanolamine, diethanolamine, triethanolamine, amino-tris-hydroxymethylmethane, glucosamine and N-methyl-glucosamine.

Such salts can also be of increased importance for oral application of the compounds according to the invention, in that they accelerate or delay the resorption, as desired. In addition to the salts already mentioned above, examples which may be mentioned are magnesium salts, calcium salts, aluminium salts and iron salts.

In general it has proved advantageous, in the case of parenteral administration, to administer amounts of from 0.01 to 50 mg/kg, preferably about 0.1 to 10 mg/kg of body weight daily to achieve effective results, whilst in the case of oral administration the dosage is about 0.1 to 500 mg/kg, preferably 0.5 to 100 mg/kg of body weight daily.

Nevertheless it can at times be necessary to deviate from the amounts mentioned and in particular to do so as a function of the body weight of the test animal or of the nature of the administration route, but also because of the species of animal and its individual behaviour towards the medicament, or the nature of the formulation of the latter, and the time or interval at which it is administered. Thus, it may in some cases suffice to manage with less than the abovementioned minimum amount whilst in other cases the upper limit mentioned must be exceeded. Where major amounts are administered it can be advisable to divide these into several individual administrations over the course of the day.

These statements apply to the use of the compounds according to the invention both in veterinary medicine and in human medicine.

The analgesic action was determined by the tail flick test on the tails of rats and by the phenylquinone writhing test on rats. In the tail flick, the tail of male rats is irradiated with a focussed heat ray. In this test, untreated animals react, after an average irradiaton time of 5.1 ± 0.8 seconds (reaction time) by drawing away the tail. Under the influence of analgesically active compounds, this reaction time becomes longer. After compounds which, after administration give a reaction time of the animals of at least 20 seconds are considered to be analgesically active. 5 animals are employed per dose. The ED_{50} is the dose which on average lengthens the reaction time of 50% of

the animals employed to at least 20 seconds (literature: Wouff, H.G., J. D. Hardy and H. Goodell: Studies on pain. Measurement of the effect of Morphine, Codeine and other opiates on the pain threshold and an analysis of their relation to the pain experience. J. Clin. Invest., *19*, 659—680 (1940)).

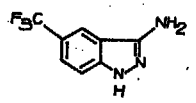
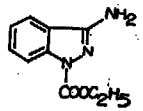
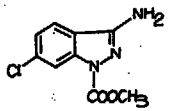
In the phenylquinone writhing test, 100 µg of the substance, dissolved in 0.5 ml of 5% strength alcohol, are injected intraperitoneally into rats. A few minutes after administration, the animals show the characteristic writhing reaction, which consists of the animals showing extreme backward extension of the hind paws, flexing the back and lifting the tail. At the same time, wave-like contractions frequently pass over the abdominal muscles. The inhibition of this writhing syndrone is assessed to be an analgesic effect. The substance to be investigated is administered 30 minutes (in the case of subcutaneous administration) or 60 minutes (in the case of oral administration) before the injection of phenylquinone. 5 animals are employed per substance and per dose. The ED_{50} is the dose at which the number of writhing reactions in the animals employed is on average reduced to half that of the control group (literature: Seigmung, E., R. Cadmus and G. Lu: A method for Evaluation both non-Narcotic and Narcotic Analgesics. Proc. Soc. exp. Biol. Med. *95*, 729—731 (1957)).

The antiphlogistic and anti-oedematous action of the compounds according to the invention was determined by the inhibition of the carrageenin oedema on the paw of rats. In this test, a reference measurement on the normal paws of rats is carried out ½ an hour before and ½ an hour after oral administration of the compound to be tested, using an antiphlogmeter. One hour after administration of the substance, the oedema is started by injecting a carrageenin solution into the planta pedis of one hind paw. 2½ hours and 3 hours after the carrageenin injection, the effect on the oedematously affected paw is measured. The relative paw volume is expressed as a percentage of the reference measurement (=100%). The ED_{50} is the dose at which, in 50% of the animals employed per dose, the difference between the relative paw volume of the treated animals and the relative paw volume of the 10 control groups is 100.

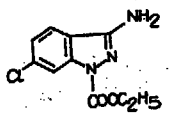
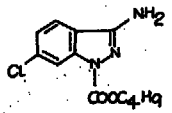
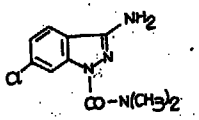
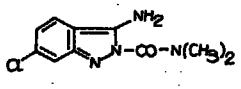
The antipyretic action is determined on rats to which a beer yeast suspension has been administered subcutaneously. The body temperature is measured rectally before, and 16 hours after, administration of the beer yeast. The substance to be tested is administered orally to groups of 5 rats, of which the body temperature has been raised by at least 1°C. Thereafter, the temperature drop is tested rectally. A drop in the body temperature by at least 1°C is assessed as an antipyretic effect. The ED_{50} is the dose at which, in 50% of the animals employed, the raised body temperature is lowered by 1°C by administration of the active substance according to the invention.

The table which follows shows the individual actions of the compounds according to the invention. 3-Amino-trifluoromethyl-indazole, which is chemically the nearest compound known from the state of the art, was employed for comparison.

TABLE

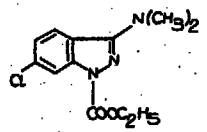
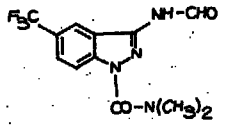
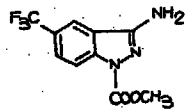
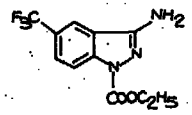
Active compound	Toxicity in mice, LD_{50} mg/kg administered orally	Tail flick test on tails of rats, ED_{50} mg/kg administered orally	Phenylquinone writhing test on rats, ED_{50} mg/kg administered orally	Inhibition of carrageenin oedema on paws of rats, ED_{50} mg/kg administered orally	Antipyretic effect on rats (yeast-induced fever), ED_{50} mg/kg administered orally
 known: DAS (German Published Specification) 1,280,878	228 (199–258)	67 (19–78)	61 (32–79)	>100	48 (32–63)
	≈3,000			≈47	
	>1,000	30 (14–82)	≈10	≈40	≈20

TABLE

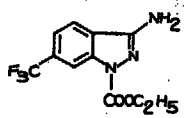
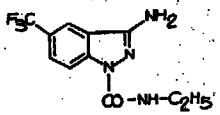
Active compound	Toxicity in mice, LD_{50} mg/kg administered orally	Tail flick test on tails of rats, ED_{50} mg/kg administered orally	Phenylquinone writhing test on rats, ED_{50} mg/kg administered orally	Inhibition of carrageenin oedema on paws of rats, ED_{50} mg/kg administered orally	Antipyretic effect on rats (yeast-induced fever), ED_{50} mg/kg administered orally
	≈2,000			≈77	
	>1,000			67 (38–117)	
	>1,000				41 (26–53)
			17 (11–26)		23 (16–30)

17

TABLE

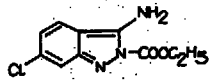
Active compound	Toxicity in mice, LD_{50} mg/kg administered orally	Tail flick test on tails of rats, ED_{50} mg/kg administered orally	Phenylquinone writhing test on rats, ED_{50} mg/kg administered orally	Inhibition of carrageenin oedema on paws of rats, ED_{50} mg/kg administered orally	Antipyretic effect on rats (yeast-induced fever), ED_{50} mg/kg administered orally
	>5,000		17 (12–24)	68 (44–138)	5.2 (1.1–11)
	>1,000			92 (44–216)	14 (12–15)
		41 (26–65)			≥50
	>5,000		1.0 (0.3–23.4)		

TABLE

Active compound	Toxicity in mice, LD_{50} mg/kg administered orally	Tail flick test on tails of rats, ED_{50} mg/kg administered orally	Phenylquinone writhing test on rats, ED_{50} mg/kg administered orally	Inhibition of carrageenin oedema on paws of rats, ED_{50} mg/kg administered orally	Antipyretic effect on rats (yeast-induced fever), ED_{50} mg/kg administered orally
		53 (32–81)			≧ 50
	>1,000	53 (36–85)			51 (28–88)

Preparation examples

Example 1.



0.3 mol of 3-amino-6-chloro-indazole in 250 ml of pyrocarbonic acid diethyl ester are heated, whilst stirring, to 50°C for about 5 hours, until the evolution of CO_2 has ceased. After cooling, 250 ml of diethyl ether are added and 90% of theory

of 3 - amino - 6 - chloro - indazole - 2 - carboxylic acid ethyl ester are isolated, by filtration, in the form of yellow crystals. Melting point: 163—165°C.

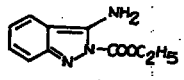
Example 2.

The reaction product of Example 1 is also obtained, in 80% yield, on reacting 0.1 mol of 3 - amino - 6 - chloro - indazole and 0.15 mol of pyrocarbonic acid diethyl ester in 50 ml of ethanol in 2 hours at 50°C.

Example 3.

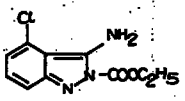
The reaction product of Example 1 is also obtained, in 65% yield, on reacting 0.2 mol of 3 - amino - 6 - chloro - indazole, 0.22 mol of chlorocarbonic acid ethyl ester and 0.22 mol of sodium bicarbonate in 150 ml acetone in 3 hours at 20—30°C.

Example 4.



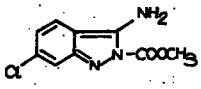
Analogously to Example 1, 0.01 mol of 3 - amino - indazole and 0.01 mol of pyrocarbonic acid diethyl ester in 20 ml of dimethylformamide give 3-amino-indazole-2-carboxylic acid ethyl ester (melting point: 182—183°C; 78% of theory) in 15 minutes aa 5—10°C.

Example 5.



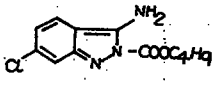
Analogously to Example 1, 0.2 mol of 3 - amino - 4 - chloro - indazole in 100 ml of pyrocarbonic acid diethyl ester gives 3 - amino - 4 - chloro - indazole - 2 - carboxylic acid ethyl ester (melting point: 109—111°C; 63% of theory) in 3 hours at 20—30°C.

Example 6.



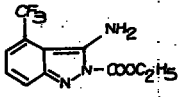
Analogously to Example 1, 0.1 mol of 3 - amino - 6 - chloro - indazole in 50 ml of pyrocarbonic acid dimethyl ester gives 3 - amino - 6 - chloro - indazole - 2-carboxylic acid methyl ester (melting point: 198—200°C; 90% of theory) in 30 minutes at 30—50°C.

Example 7.



Analogously to Example 1, 0.05 mol of 3 - amino - 6 - chloro - indazole and 0.075 mol of pyrocarbonic acid di - n - butyl ester give 3 - amino - 6 - chloro-indazole - 2 - carboxylic acid n -butyl ester (melting point: 169—170°C; 81% of theory) in 5 hours at 50°C.

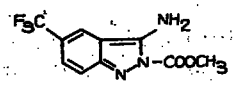
Example 8.



Analogously to Example 1, 0.06 mol of 3 - amino - 4 - trifluoromethyl - indazole

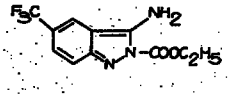
in 50 ml of pyrocarbonic acid diethyl ester gives 3 - amino - 4 - trifluoromethyl-indazole - 2 - carboxylic acid ethyl ester (melting point: 100—101°C; 85% of theory) in 10 minutes at 20°C.

Example 9.



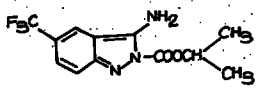
Analogously to Example 1, 0.1 mol of 3 - amino - 5 - trifluoromethyl - indazole in 50 ml of pyrocarbonic acid dimethyl ester gives 3 - amino - 5 - trifluoromethyl-indazole - 2 - carboxylic acid methyl ester (melting point: 164—165°C; 64% of theory) in 2 hours at 50°C.

Example 10.



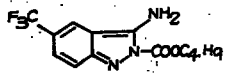
Analogously to Example 1, 0.01 mol of 3 - amino - 5 - trifluoromethyl - indazole and 0.125 mol of pyrocarbonic acid diethyl ester in 100 ml of ethanol give 3 - amino-5 - trifluoromethyl - indazole - 2 - carboxylic acid ethyl ester (melting point: 182—184°C; 82% of theory) in 1 hour at 80°C.

Example 11.



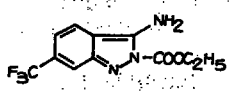
Analogously to Example 1, 0.05 mol of 3 - amino - 5 - trifluoromethyl - indazole and 0.055 mol of pyrocarbonic acid di-isopropyl ester give 3 - amino - 5 - trifluoromethyl - indazole - 2 - carboxylic acid isopropyl ester (melting point: 184—186°C; 82% of theory) in 5 minutes at 20—30°C.

Example 12.



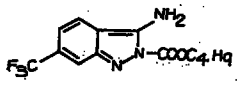
Analogously to Example 1, 0.05 mol of 3 - amino - 5 - trifluoromethyl - indazole and 0.055 mol of pyrocarbonic acid di - n - butyl ester give 3 - amino - 5 - trifluoromethyl - indazole - 2 - carboxylic acid n - butyl ester (melting point: 147—149°C; 73% of theory) in 5 minutes at 20—30°C.

Example 13.



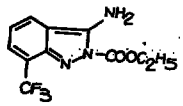
Analogously to Example 1, 0.04 mol of 3 - amino - 6 - trifluoromethyl - indazole and 50 ml of pyrocarbonic acid diethyl ester in 25 ml of ethanol give 3 - amino - 6-trifluoromethyl - indazole - 2 - carboxylic acid ethyl ester (melting point: 153—155°C; 77% of theory) in 1 hour at 20°C.

Example 14.



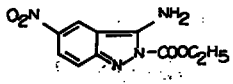
Analogously to Example 1, 0.05 mol of 3 - amino - 6 - trifluoromethyl - indazole and 0.055 mol of pyrocarbonic acid di - n - butyl ester give 3 - amino - 6 - trifluoromethyl - indazole - 2 - carboxylic acid n - butyl ester (melting point: 139—140°C; 93% of theory) in 1 hour at 50°C.

Example 15.



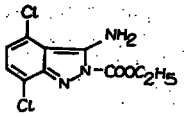
Analogously to Example 1, 0.05 mol of 3 - amino - 7 - trifluoromethyl - indazole and 0.055 mol of pyrocarbonic acid diethyl ester give 3 - amino - 7 - trifluoromethyl-indazole - 2 - carboxylic acid ethyl ester (melting point: 174—175°C; 93% of theory) in 5 minutes at 20—25°C.

Example 16.



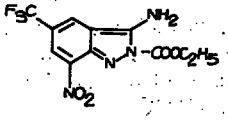
Analogously to Example 1, 0.2 mol of 3 - amino - 5 - nitro - indazole and 0.22 mol of pyrocarbonic acid diethyl ester in 100 ml of dimethylformamide give 3 - amino-5 - nitro - indazole - 2 - carboxylic acid ethyl ester (melting point: 226—227°C; 76% of theory) in 8 hours at 10—20°C.

Example 17.



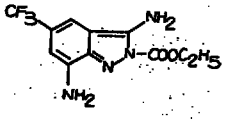
Analogously to Example 1, 0.15 mol of 3 - amino - 4,7 - dichloro - indazole in 100 ml of pyrocarbonic acid diethyl ester gives 3 - amino - 4.7 - dichloro - indazole-2 - carboxylic acid ethyl ester (melting point: 143—145°C; 69% of theory) in 5 hours at 50°C.

Example 18.



Analogously to Example 1, 0.1 mol of 3 - amino - 5 - trifluoromethyl - 7 - nitro-indazole and 150 ml of pyrocarbonic acid diethyl ester in 100 ml of ethanol give 3-amino - 5 - trifluoromethyl - 7 - nitro - indazole - 2 - carboxylic acid ethyl ester (melting point: 186—187°C; 74% of theory) in 30 minutes at 80°C.

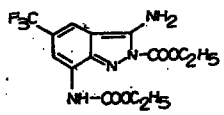
Example 19.



Analogously to Example 1, 0.1 mol of 3,7 - diamino - 5 - trifluoromethyl-

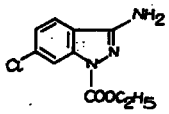
indazole in 70 ml of pyrocarbonic acid diethyl ester gives 3,7 - diamino - 5 - trifluoromethyl - indazole - 2 - carboxylic acid ethyl ester (melting point: 193—194°C; 90% of theory) in 1 hour at 20—30°C.

Example 20.



Analogously to Example 1, 0.1 mol of 3,7 - diamino - 5 - trifluoromethyl-indazole in 70 ml of pyrocarbonic acid diethyl ester gives 3 - amino - 5 - trifluoromethyl - 7 - ethoxycarbonylamino - indazole - 2 - carboxylic acid ethyl ester (melting point: 229—230°C; 89% of theory) in 20 minutes at 70°C.

Example 21.



0.1 mol of 3 - amino - 6 - chloro - indazole in 100 ml of pyrocarbonic acid diethyl ester is heated for 5 hours to 100°C, whilst stirring. After cooling, 100 ml of diethyl ether are added and 3 - amino - 6 - chloro - indazole - 1 - carboxylic acid ethyl ester is isolated, by filtration, in the form of colourless crystals (melting point: 190—192°C; 60% of theory).

Example 22.

The reaction product of Example 21 is also obtained, in 70% yield, on reacting 0.2 mol of 3 - amino - 6 - chloro - indazole and 0.5 mol of pyrocarbonic acid diethyl ester in 500 ml of ethanol in 10 hours at 80°C.

Example 23.

The reaction product of Example 21 is also obtained, in 35% yield, on reacting 0.2 mol of 3 - amino -6 - chloro - indazole and 0.22 mol of chlorocarbonic acid ethyl ester in 150 ml of pyridine in 1 hour at 20—30°C.

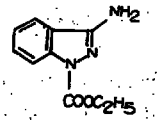
Example 24.

The reaction product of Example 21 is also obtained, in 90% yield, on reacting 0.2 mol of 3 - amino - 6 - chloro - indazole 2 - carboxylic acid ethyl ester in 80 ml of 2,4,6-trimethylpyridine in 15 minutes at 170°C.

Example 25.

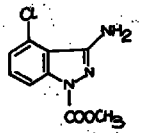
The reaction product of Example 21 is also obtained, in 65% yield, on reacting 0.1 mol of 3 - amino - 6 - chloro - indazole and 0.12 mol of pyrocarbonic acid diethyl ester in 50 ml of quinoline in 1 hour at 20—30°C and subsequently 30 minutes at 160°C.

Example 26.



Analogously to Example 24, 0.07 mol of 3 - amino - indazole - 2 - carboxylic acid ethyl ester in 50 ml of nitrobenzene gives 3 - amino - indazole - 1 - carboxylic acid ethyl ester (melting point: 163—165°C; 83% of theory) in 10 minutes at 210°C.

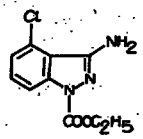
Example 27.



Analogously to Example 23, 0.05 mol of 3 - amino - 4 - chloro - indazole and

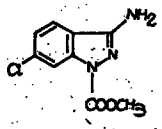
0.055 mol of chlorocarbonic acid methyl ester in 50 ml of pyridine give 3 - amino-4 - chloro - indazole - 1 - carboxylic acid methyl ester (melting point: 190—191°C; 58% of theory) in 1 hour at 20—30°C.

Example 28.



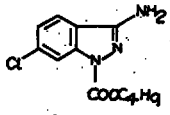
Analogously to Example 23, 0.1 mol of 3 - amino - 4 - chloro - indazole and 0.105 mol of chlorocarbonic acid ethyl ester in 80 ml of pyridine give 3 - amino - 4-chloro - indazole - 1 - carboxylic acid ethyl ester (melting point: 167—169°C; 62% of theory) in 1 hour at 50°C.

Example 29.



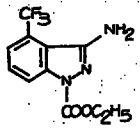
Analogously to Example 24, 0.05 mol of 3 - amino - 6 - chloro - indazole - 2-carboxylic acid methyl ester in 50 ml of 2 - methyl - pyridine gives 3 - amino - 6-chloro - indazole - 1 - carboxylic acid methyl ester (melting point: 210—211°C; 55% of theory) in 15 minutes at 125°C.

Example 30.



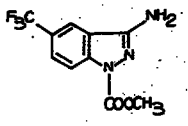
Analogously to Example 24, 0.04 mol of 3 - amino - 6 - chloro - indazole - 2-carboxylic acid n - butyl ester in 25 ml of pyridine gives 3 - amino - 6 - chloro-indazole - 1 - carboxylic acid n - butyl ester (melting point: 139—140°C; 617% of theory) in 15 minutes at 100°C.

Example 31.



Analogously to Example 21, 0.06 mol of 3 - amino - 4 - trifluoromethyl - indazole in 50 ml of pyrocarbonic acid diethyl ester gives 3 - amino - 4 - trifluoromethyl-indazole - 1 - carboxylic acid ethyl ester (melting point: 185—186°C; 68% of theory) in 2 hours at 75°C.

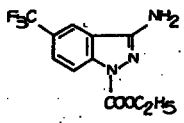
Example 32.



Analogously to Example 24, 0.065 mol of 3 - amino - 5 - trifluoromethyl-indazole - 2 - carboxylic acid methyl ester in 70 ml of 4 - methyl - pyridine gives

3 - amino - 5 - trifluoromethyl - indazole - 1 - carboxylic acid methyl ester (melting point: 177—178°C; 55% of theory) in 5 minutes at 140°C.

Example 33.

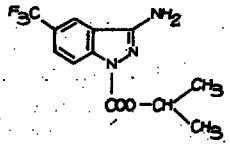


Analogously to Example 24, 0.175 mol of 3 - amino - 5 - trifluoromethyl-indazole - 2 - carboxylic acid ethyl ester in 80 ml of 2,4,6 - trimethyl - pyridine gives 3 - amino - 5 - trifluoromethyl - indazole - 1 - carboxylic acid ethyl ester (melting point: 181—183°C; 87% of theory) in 30 minutes at 170°C.

Example 34.

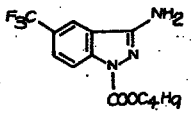
The reaction product of Example 33 may also be obtained in 86% yield by reacting a mixture of 1.6 mol of 3 - amino - 5 - trifluoromethyl - indazole - 2-carboxylic acid ethyl ester, 370 ml of xylene and 20 ml of pyridine for ten minutes at 135—140°C.

Example 35.



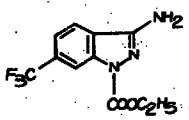
Analogously to Example 24, 0.04 mol of 3 - amino - 5 - trifluoromethyl - indazole-2 - carboxylic acid isopropyl ester in 25 ml of nitrobenzene gives 3 - amino - 5-trifluoromethyl - indazole - 1 - carboxylic acid isopropyl ester (melting point: 162—163°C; 57% of theory) in 15 minutes at 210°C.

Example 36.



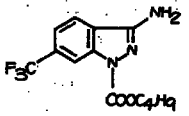
Analogously to Example 24, 0.02 mol of 3 - amino - 5 - trifluoromethyl-indazole - 2 - carboxylic acid n - butyl ester in 15 ml of 1,2 - dichlorobenzene gives 3 - amino - 5 - trifluoromethyl - indazole - 1 - carboxylic acid n - butyl ester (melting point: 125—127°C; 80% of theory) in 15 minutes at 175°C.

Example 37.



Analogously to Example 22, 0.04 mol of 3 - amino - 6 - trifluoromethyl - indazole and 50 ml of pyrocarbonic acid diethyl ester in 25 ml of ethanol give 3 - amino - 6-trifluoromethyl - indazole - 1 - carboxylic acid ethyl ester (melting point: 168—169°C; 64% of theory) in 2 hours at 80°C.

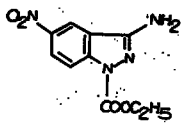
Example 38.



Analogously to Example 24, 0.03 mol of 3 - amino - 6 - trifluoromethyl-

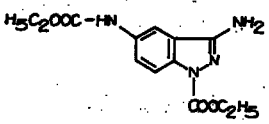
indazole - 2 - carboxylic acid n - butyl ester in 20 ml of nitrobenzene gives 3 - amino-6 - trifluoromethyl - indazole - 1 - carboxylic acid n - butyl (melting point: 133—134°C; 80% of theory) in 10 minutes at 200°C.

Example 39.



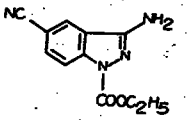
Analogously to Example 24, 0.05 mol of 3 - amino - 5 - nitro - indazole - 2-carboxylic acid ethyl ester in 50 ml of nitrobenzene gives 3 - amino - 5 - nitro-indazole - 1 - carboxylic acid ethyl ester (melting point: 236—237°C; 93% of theory) in 5 minutes at 210°C.

Example 40.



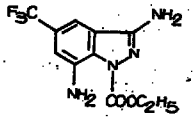
Analogously to Example 21, catalytic hydrogenation of 0.15 mol of 3 - amino-5 - nitro - indazole with Raney nickel in tetrahydrofurane at 75°C, followed by reaction of the solution, which has been freed from the catalyst, with 0.6 mol of pyrocarbonic acid diethyl ester, in 2 hours at 50°C, gives 3 - amino - 5 - ethoxy-carbonylamino - indazole - 1 - carboxylic acid ethyl ester (melting point: 173—174°C; 42% of theory).

Example 41.



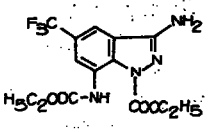
Analogously to Example 24, 0.07 mol of 3 - amino - 5 - cyano - indazole and 0.08 mol of pyrocarbonic acid diethyl ester in 50 ml of 3 - methyl - pyridine give 3 - amino - 5 - cyano - indazole -1- carboxylic acid ethyl ester (melting point: 252°C; 57% of theory) in 15 minutes at 20°C followed by 10 minutes at 100°C.

Example 42.



Analogously to Example 24, 0.1 mol of 3,7 - diamino - 5 - trifluoromethyl-indazole - 2 - carboxylic acid ethyl ester in 30 ml of nitrobenzene gives 3,7 - diamino-5 - trifluoromethyl - indazole - 1 - carboxylic acid ethyl ester (melting point: 217—218°C; 60 %of theory) in 1 hour at 210°C.

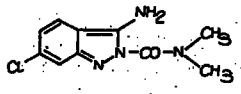
Example 43.



Analogously to Example 24, 0.025 mol of 3 - amino - 5 - trifluoromethyl - 7-

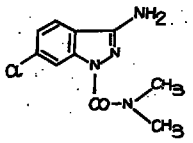
ethoxycarbonylamino - indazole - 2 - carboxylic acid ethyl ester in 30 ml of dimethylformamide gives 3 - amino - 5 - trifluoromethyl - 7 - ethoxycarbonylamino - indazole-1 - carboxylic acid ethyl ester (melting point: 236—237°C; 65% of theory) in 1 hour at 155°C.

Example 44.



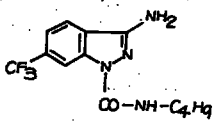
0.15 mol of dimethylcarbamic acid chloride is added dropwise, whilst stirring, to 0.1 mol of 3 - amino - 6 - chloro - indazole in 50 ml of pyridine, in the course of which the temperature rises to 45°C. After 1½ hours, 250 ml of water are allowed to run in and the reaction product is isolated by filtration. After dissolving the product in chloroform, filtering off a by-product of melting point 237—238°C and evaporating the solution, 3 - amino - 6 - chloro - indazole - 2 - carboxylic acid dimethylamide (melting point: 178—180°C; 58% of theory) is obtained.

Example 45.



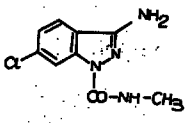
0.06 mol of 3 - amino - 6 - chloro - indazole - 2 - carboxylic acid dimethylamide in 25 ml of nitrobenzene is heated to 210°C for 15 minutes under N_2. Evaporation in vacuo and recrystallisation of the residue from ethanol gives 3 - amino - 6 - chloro-indazole - 1 - carboxylic acid - dimethylamide (melting point: 170—172°C; 68% of theory).

Example 46.



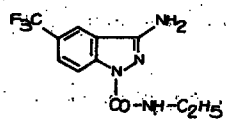
0.0275 mol of n-butyl isocyanate is added dropwise to 0.025 mol of 3 - amino-6 - trifluoromethyl - indazole in 25 ml of chloroform, in the course of which the temperature rises to 30°C. The mixture is stirred for 3 hours at 20°C and finally for 15 minutes at 60°C, and after evaporation 3 - amino - 6 - trifluoromethyl-indazole - 2 - carboxylic acid n - butylamide (melting point: 81—83°C) is obtained; this is rearranged, by brief heating to 200°C in nitrobenzene, to 3 - amino - 6 - trifluoromethyl - indazole - 1 - carboxylic acid n - butylamide (melting point 140—142°C; 86% of theory).

Example 47.



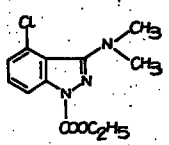
Analogously to Example 46, 0.1 mol of 3 - amino - 6 - chloro - indazole and 0.1 mol of methyl isocyanate in 100 ml of pyridine give 3 - amino - 6 - chloro-indazole - 1 - carboxylic acid methylamide (melting point: 148—150°C; 50% of theory) in 30 minutes at 10—15°C.

Example 48.



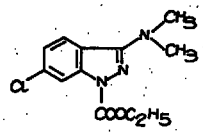
Analogously to Example 46, 0.05 mol of 3 - amino - 5 - trifluoromethyl - indazole and 0.05 mol of ethyl isocyanate in 100 ml of pyridine give 3 - amino - 5 - trifluoromethyl - indazole - 1 - carboxylic acid ethylamide (melting point: 131—132°C; 47% of theory) in 1 hour at 10—15°C.

Example 49.



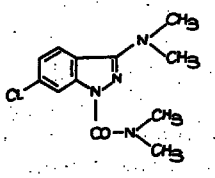
0.05 mol of 3 - amino - 4 - chloro - indazole - 1 - carboxylic acid ethyl ester and 0.125 mol of 40% strength formaldehyde solution in 50 ml of formic acid are heated to 100°C for 5 hours. After evaporation in vacuo and distillation of the residue, 3 - dimethylamino - 4 - chloro - indazole - 1 - carboxylic acid ethyl ester (boiling point$_{0.4}$ 160°C; melting point: 60—62°C; 70% of theory) is obtained.

Example 50.



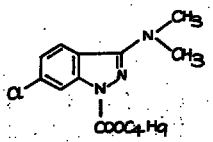
Analogously to Example 49, 0.1 mol of 3 - amino - 6 - chloro - indazole - 1-carboxylic acid ethyl ester and 0.25 mol of 40% strength formaldehyde solution in 150 ml of formic acid give 3 - dimethylamino - 6 - chloro - indazole - 1 - carboxylic acid ethyl ester (melting point: 98—100°C; 69% of theory) in 5 hours at 1000°C.

Example 51.



0.04 mol of 3 - dimethylamino - 6 - chloro - indazole and 0.04 mol of sodium amide in 50 ml of toluene are heated to the boil for 1 hour. 0.04 mol of dimethylcarbamic acid chloride is added dropwise at 60°C and this temperature is maintained for 7 hours, whilst stirring. After cooling, the solution is filtered and evaporated in vacuo. Distillation of the residue gives 3 - dimethylamino - 6 - chloro - indazole - 1-carboxylic acid dimethylamide (boiling point$_{0.35}$ 170°C, melting point: 65—66°C; 75% of theory).

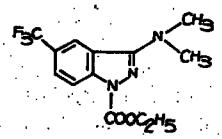
Example 52.



Analogously to Example 21, 0.01 mol of 3 - dimethylamino - 6 - chloro - indazole

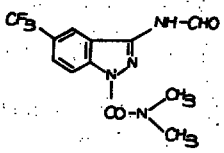
and 0.0125 mol of pyrocarbonic acid di - n - butyl ester give 3 - dimethylamino - 6-chloro - indazole - 1 - carboxylic acid n - butyl ester (melting point: 80—81°C; 71% of theory) in 5 hours at 20°C.

Example 53.



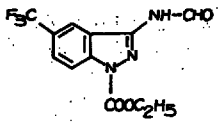
Analogously to Example 21, 0.025 mol of 3 - dimethylamino - 5 - trifluoromethyl - indazole and 0.0275 mol of pyrocarbonic acid diethyl ester give 3 - dimethylamino - 5 - trifluoromethyl - indazole - 1 - carboxylic acid ethyl ester (boiling point$_{0.1}$ 110°C, melting point: 84—86°C; 93% of theory) in 1½ hours at 70—80°C.

Example 54.



0.2 mol of 3 - formylamino - 5 - trifluoromethyl - indazole and 0.05 mol of dimethylcarbamic acid chloride in 20 ml of pyridine are heated for 4 hours to 50°C. After cooling, 150 ml of water are allowed to run in and the reaction product which has crystallised out is isolated by filtration. Recrystallisation from ethanol gives 3-formylamino - 5 - trifluoromethyl - indazole - 1 - carboxylic acid dimethylamide (melting point: 198—200°C; 57% of theory).

Example 55.

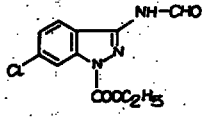


Analogously to Example 54, 0.05 mol of 3 - formylamino - 5 - trifluoromethyl-indazole and 0.1 mol of chlorocarbonic acid ethyl ester in 100 ml of pyridine give 3 - formylamino - 5 - trifluoromethyl - indazole - 1 - carboxylic acid ethyl ester (melting point: 185—187°C; 65% of theory) in 3 hours at 30°C.

Example 56.

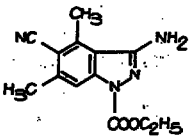
The reaction product of Example 55 is also obtained, in 78% yield, on reacting 0.1 mol of 3 - amino - 5 - trifluoromethyl - indazole - 1 - carboxylic acid ethyl ester and 50 ml of formic acid in 5 hours at 100°C.

Example 57.



Analogously to Example 56, 0.085 mol of 3 - amino - 6 - chloro - indazole - 1-carboxylic acid ethyl ester and 100 ml of formic acid produce 3 - formylamino - 6-chloro - indazole - 1 - carboxylic acid ethyl ester in 3.5 hours at 100°C (melting point 227—230° (decomposition), yield: 71% of theory).

Example 58.



0.86 mol of 3 - amino - 4,6 - dimethyl - 3 - cyano - indazole are stirred together with 0.13 mol of pyrocarbonic acid diethyl ester and 75 mol ethanol. The mixture is allowed to stand for two hours at room temperature and, after the addition of diethyl ether 3 - amino - 4,6 - dimethyl - 5 - cyano - indazole - 2 - carboxylic acid ethyl ester is isolated (melting point: 235—237°C, 90% of theory). After refluxing for 20 minutes in 250 ml of 1,2 - dichloro - benzene, 3 - amino - 4,6 - dimethyl - 5-cyano - indazole - 1 - carbonic acid ethyl ester is obtained (melting point 240—241°C; 95% of theory).

The structure of the reaction products was confirmed by elementary analysis and in part also by mass-spectrometric molecular weight determination. In the case of isomeric compounds, the consistency and position of the substituents was above all confirmed by physico-chemical methods of investigation, especially H^1— and F^{19}— nuclear resonance, IR-spectroscopy and UV-spectroscopy.

Examples of the preparation of starting materials not hitherto described in the literature:

3 - Amino - 4 - trifluoromethyl - indazole (melting point: 129—130°C) from 2,6-dimethylbenzonitrile by chlorination to give 2 - chloro - 6 - trichloromethyl-benzonitrile (melting point: 121—122°C) and subsequent fluorination to give 2-chloro - 6 - trifluoromethyl - benzonitrile (melting point: 45—47°C), and reaction with hydrazine hydrate in dioxane at 150°C in an autoclave.

3 - Amino - 7 - trifluoromethyl - indazole (melting point: 101—102°C) from 2,3 - dimethyl - benzonitrile by chlorination to give 2 - chloro - 3 - trichloromethyl-benzonitrile (melting point: 106—107°C) and fluorination to give 2 - chloro - 3-trifluoromethyl - benzonitrile (melting point: 37—39°C), and reaction with hydrazine hydrate in dioxane at 150°C in an autoclave. The 3 - Amino - 5 - trifluoromethyl-7 - nitro - indazole (melting point: 227—228°C) was prepared from 2 - methoxy - 3-nitro - 5 - trifluoromethyl - benzonitrile and hydrazine hydrate, analogously to J. chem. Soc. [London] *1959*, 2363.

3,7 - Diamino - 5 - trifluoromethyl - indazole (melting point: 198—199°C) from 3 - amino - 5 - trifluoromethyl - 7 - nitro - indazole by catalytic hydrogenation with Raney nickel in dimethylformamide at 50°C.

3 - Amino - 5 - cyano - indazole (melting point: 224—225°C) from 4 - chloro-isophthalic acid dinitrile and hydrazine hydrate analogously to J. chem. Soc. [London] *1959*, 2363.

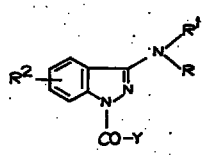
3 - Dimethylamino - 6 - chloro - indazole (melting point: 131—132°C) from 3 - dimethylamino - 6 - chloro - indazole - 1 - carboxylic acid ethyl ester and 10% strength sodium hydroxide solution in methanol at pH 10 and 20°C.

3 - Dimethylamino - 3 - trifluoromethyl - indazole (melting point: 193—196°C) from 3 - dimethylamino - 5 - trifluoromethyl - indazole - 1 - carboxylic acid ethyl ester and 10% strength sodium hydroxide solution in methanol at pH 10 and 20°C.

3 - Amino - 4,6 - dimethyl - 5 - cyano - indazole (melting point: 260—262°C) from 2 - amino - 4,6 - dimethyl - 5 -cyano - benzonitrile by diazotization and subsequent reduction with sulphurous acid.

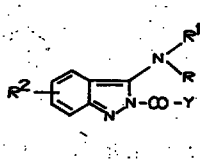
WHAT WE CLAIM IS:—

1. A 3-Amino-indazolecarboxylic acid derivative of the formula



(I a)

or

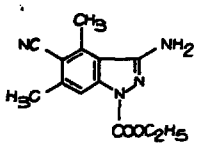


(I b)

in which

Y represents alkoxy, alkylamino or dialkylamino,

Example 58.



0.86 mol of 3 - amino - 4,6 - dimethyl - 3 - cyano - indazole are stirred together with 0.13 mol of pyrocarbonic acid diethyl ester and 75 mol ethanol. The mixture is allowed to stand for two hours at room temperature and, after the addition of diethyl ether 3 - amino - 4,6 - dimethyl - 5 - cyano - indazole - 2 - carboxylic acid ethyl ester is isolated (melting point: 235—237°C, 90% of theory). After refluxing for 20 minutes in 250 ml of 1,2 - dichloro - benzene, 3 - amino - 4,6 - dimethyl - 5-cyano - indazole - 1 - carbonic acid ethyl ester is obtained (melting point 240—241°C; 95% of theory).

The structure of the reaction products was confirmed by elementary analysis and in part also by mass-spectrometric molecular weight determination. In the case of isomeric compounds, the consistency and position of the substituents was above all confirmed by physico-chemical methods of investigation, especially H^1— and F^{19}— nuclear resonance, IR-spectroscopy and UV-spectroscopy.

Examples of the preparation of starting materials not hitherto described in the literature:

3 - Amino - 4 - trifluoromethyl - indazole (melting point: 129—130°C) from 2,6-dimethylbenzonitrile by chlorination to give 2 - chloro - 6 - trichloromethyl-benzonitrile (melting point: 121—122°C) and subsequent fluorination to give 2-chloro - 6 - trifluoromethyl - benzonitrile (melting point: 45—47°C), and reaction with hydrazine hydrate in dioxane at 150°C in an autoclave.

3 - Amino - 7 - trifluoromethyl - indazole (melting point: 101—102°C) from 2,3 - dimethyl - benzonitrile by chlorination to give 2 - chloro - 3 - trichloromethyl-benzonitrile (melting point: 106—107°C) and fluorination to give 2 - chloro - 3-trifluoromethyl - benzonitrile (melting point: 37—39°C), and reaction with hydrazine hydrate in dioxane at 150°C in an autoclave. The 3 - Amino - 5 - trifluoromethyl-7 - nitro - indazole (melting point: 227—228°C) was prepared from 2 - methoxy - 3-nitro - 5 - trifluoromethyl - benzonitrile and hydrazine hydrate, analogously to J. chem. Soc. [London] *1959*, 2363.

3,7 - Diamino - 5 - trifluoromethyl - indazole (melting point: 198—199°C) from 3 - amino - 5 - trifluoromethyl - 7 - nitro - indazole by catalytic hydrogenation with Raney nickel in dimethylformamide at 50°C.

3 - Amino - 5 - cyano - indazole (melting point: 224—225°C) from 4 - chloro-isophthalic acid dinitrile and hydrazine hydrate analogously to J. chem. Soc. [London] *1959*, 2363.

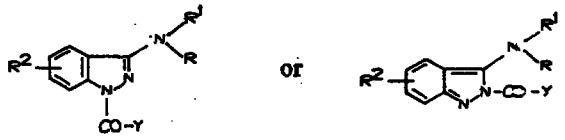
3 - Dimethylamino - 6 - chloro - indazole (melting point: 131—132°C) from 3 - dimethylamino - 6 - chloro - indazole - 1 - carboxylic acid ethyl ester and 10% strength sodium hydroxide solution in methanol at pH 10 and 20°C.

3 - Dimethylamino - 3 - trifluoromethyl - indazole (melting point: 193—196°C) from 3 - dimethylamino - 5 - trifluoromethyl - indazole - 1 - carboxylic acid ethyl ester and 10% strength sodium hydroxide solution in methanol at pH 10 and 20°C.

3 - Amino - 4,6 - dimethyl - 5 - cyano - indazole (melting point: 260—262°C) from 2 - amino - 4,6 - dimethyl - 5 -cyano - benzonitrile by diazotization and subsequent reduction with sulphurous acid.

WHAT WE CLAIM IS:—

1. A 3-Amino-indazolecarboxylic acid derivative of the formula



(I a) (I b)

in which

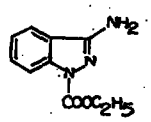
Y represents alkoxy, alkylamino or dialkylamino,

R represents hydrogen or methyl,
R^1 represents hydrogen, methyl or formyl and
R^2 represents 1, 2 or 3 substituents independently selected from hydrogen, alkyl, alkoxy, nitro, amino, alkylamino, dialkylamino, acylamino, alkoxycarbonylamino, halogen, trifluoromethyl, cyano and alkoxycarbonyl,
or a salt thereof.

2. A compound according to claim 1 wherein Y is an alkoxy group containing from 1 to 4 carbon atoms or an alkyl- or dialkyl amino group in which the or each alkyl group contains from 1 to 4 carbon atoms and R^2 represents 1, 2, or 3 substituents independently selected from hydrogen, alkyl groups of from 1 to 4 carbon atoms, alkoxy groups of from 1 to 4 carbon atoms, nitro, amino, alkyl- and dialkyl amino groups in which the or each alkyl group contains from 1 to 4 carbon atoms, acylamino groups containing from 1 to 6 carbon atoms in their acyl parts, alkoxycarbonylamino groups containing from 1 to 4 carbon atoms in their alkoxy part, chlorine, bromine, trifluoromethyl, cyano and alkoxycarbonyl groups containing from 1 to 4 carbon atoms in their alkoxy parts.

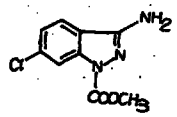
3. A compound according to claim 1 or claim 2 wherein R^2 represents one or two substituents independently selected from hydrogen, nitro, amino, halogen, trifluoromethyl and alkoxycarbonylamino.

4. A compound of the formula



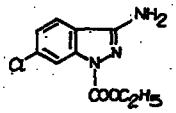
or a salt thereof.

5. A compound of the formula



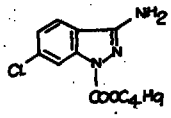
or a salt thereof.

6. A compound of the formula



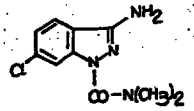
or a salt thereof.

7. A compound of the formula



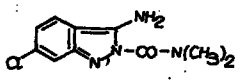
or a salt thereof.

8. A compound of the formula



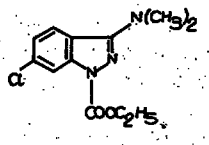
or a salt thereof.

9. A compound of the formula



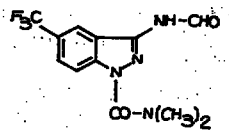
or a salt thereof.

10. A compound of the formula



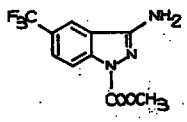
or a salt thereof.

11. A compound of the formula



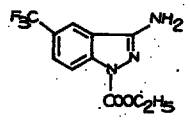
or a salt thereof.

12. A compound of the formula



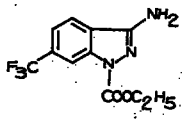
or a salt thereof.

13. A compound of the formula



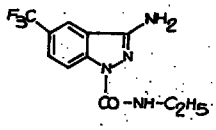
or a salt thereof.

14. A compound of the formula



or a salt thereof.

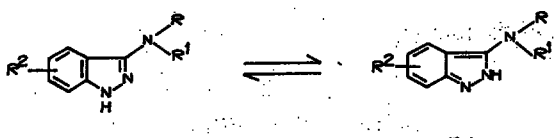
15. A compound of the formula



or a salt thereof.

16. Any compound according to claim 1 specifically described herein other than in Examples 57 and 58, or salts thereof.

17. A process for preparing a compound according to any one of claims 1 to 16 comprising reacting a 3-amino-indazole of the tautomeric formula



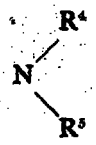
(a) (II) (b)

in which R, R^1 and R^2 are as defined in claim 1 with a carbonic acid derivative of the formula

$$Y—CO—X \qquad (III)$$

in which

Y represents the radical OR^3 or the radical



wherein R^3, R^4 and R^5 each denote alkyl,

X represents halogen, or, if Y represents OR^3, the radical O—$COOR^3$, wherein R^3 has the meaning indicated under Y, or

X and Y conjointly denote an imide group of the formula $=NR^6$, wherein R^6 denotes alkyl,

in the presence of inert organic solubilising agents and, if appropriate, in the presence of an acid-binding agent and thereafter, if appropriate, in a further reaction step the amino group in the 3-position is formylated with formic acid or methylated with formaldehyde in the presence of formic acid.

18. A process according to claim 17 wherein the reaction is effected at a temperature of from −20 to +250°C.

19. A process for the production of a compound according to Claim 1 substantially as hereinbefore described in any of Examples 1 to 33 and 35 to 56.

20. Compounds according to claim 1 whenever prepared by a process according to any one of claims 17 to 19.

21. A pharmaceutical composition containing as an active ingredient a compound according to any one of claims 1 to 16 and 20 in admixture with a solid or liquefied gaseous diluent or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 except in the presence of a surface-active agent.

22. A pharmaceutical composition containing as an active ingredient a compound according to any one of claims 1 to 16 and 20 in the form of a sterile or isotonic aqueous solution.

23. A composition according to claim 21 or 22 containing from 0.5 to 90% by weight of the said active ingredient.

24. A medicament in dosage unit form comprising a compound according to any one of claims 1 to 16 and 20 either alone or in admixture with a diluent.

25. A medicament in the form of tablets, pills, dragees, capsules, ampoules, or suppositories comprising a compound according to any one of claims 1 to 16 and 20, either alone or in admixture with a diluent.

26. A method of combating pain, inflammation or fever in non-human animals which comprises administering to the animals an active compound according to any one of claims 1 to 16 and 20 either alone or in admixture with a diluent or in the form of a medicament according to claim 24or 25.

27. A method according to claim 26 in which the active compound is administered in an amount of 0.01 to 50 mg per kg body weight per day.

28. A method according to claim 26 or claim 27 in which the active compound is administered orally.

29. A compound according to claim 1 as described in Example 57 or 58.

30. A process for preparing a compound according to claim 1 substantially as hereinbefore described in Example 34, 57 or 58.

31. A compound according to claim 1 prepared by a method according to claim 34, 57 or 58.

32. A composition according to any one of claims 21 to 23 wherein the active ingredient is a compound according to claim 29 or 31.

33. A medicament according to claim 24 or 25 wherein the said compound is a compound according to claim 29 or 31.

34. A method according to any one of claims 26 to 28 wherein the active compound is a compound according to claim 29 or 31.

For the Applicants,
CARPMAELS & RANSFORD,
Chartered Patent Agents,
43 Bloomsbury Square,
London, WC1A 2RA.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1977.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.