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(54) NEW 1-SUBSTITUTED PYRAZOL-5-ONES, THEIR PRODUCTION AND THEIR MEDICINAL USE

(71) We, BAYER AKTIENGESELLSCHAFT, a body corporate, organised under the laws of Germany, of 509 Leverkusen-Bayerwerk, Germany, (Fed Rep) 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:—

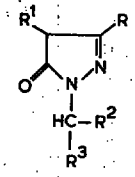
The present invention relates to new 1-substituted pyrazol-5-ones, several processes for their preparation and their medicinal use, especially as diuretics and antihypertensives.

3-Aminopyrazolones have already been used as colour coupling agents for colour photography (A. Weissberger et al, J. Amer. Chem. Soc. *64*, 2183 (1942)) and as intermediate products for the preparation of colour coupling agents (British Patent 599,919; U.S. Patent 2,267,523; U.S. Patent 2,376,380; U.S. Patent 2,511,231; U.S. Patent 2,600,788; U.S. Patent 2,619,419; U.S. Patent 2,672,417).

Certain pyrazol-5-one derivatives are also used as antipyretics, analgesics and antiphlogistics (compare G. Ehrhart and H. Ruschig, "Arzneimittel" ("Medicines"), Volume 1, page 148 (1972).

We have now discovered a new group of 1-substituted pyrazol-5-ones which have strong diuretic, saluretic, antihypertensive and antithrombotic properties.

This invention now provides compounds which are 1-substituted pyrazol-5-ones of the following general formula and their salts:



I

in which

R is a hydrogen, amino, alkyl, alkenyl, phenyl or trifluoromethyl radical;

R^1 is a hydrogen, alkyl, alkenyl, or optionally substituted aryl or aralkyl radicals;

R^2 is an alkyl group; and

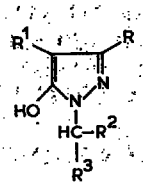
R^3 is a pyridyl radical, or an aryl radical carrying 1 or 2 identical or different substituents, which are selected from halogen, trifluoromethyl, alkyl, alkenyl, and alkoxy radicals or carrying one mono- or dialkylamino, trifluoromethoxy, nitro, nitrile, carbamoyl, alkyl or dialkylcarbamoyl, sulphamyl, or alkyl- or dialkyl-,

sulphamyl radical or a group —B, —COB, or —SO_2B (in which B is a saturated ring containing a nitrogen atom in the 1-position) or an —SO_nAlkyl group (in which n=0, 1 or 2), optionally together with one or two substituents selected from alkyl, alkenyl, alkoxy, halogen and trifluoromethyl radical or carrying none or one only of these substituents and a fused branched or unbranched, saturated or unsaturated, 5-,6- or 7-membered ring optionally containing 1 or 2 oxygen or sulphur atoms.

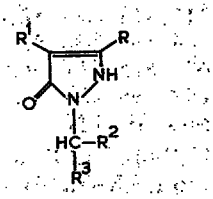
The above-defined compounds are referred to hereinafter as "the compounds of the invention".

The compounds of the invention contain an asymmetric carbon atom which gives rise to optical isomerism. The invention applies equally to all optical forms of the compounds of the invention, whether optically pure or racemic.

In addition to the structure which is represented by the general formula I, the compounds of the invention can also be in one of the following tautomeric forms or in the form of a mixture of such tautomeric forms:

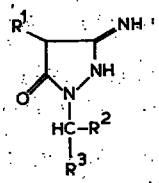


II

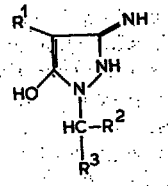


III

The 3-aminopyrazol-5-ones, in particular, can in addition also be present in the following imino-forms:



IV

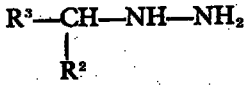


V

The invention applies equally to all tautomeric forms of the new compounds defined above with reference to general formula I and to all mixtures of two or more such tautomeric forms.

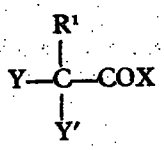
The invention also provides a process for the production of the compounds of the invention, in which either:

A) a hydrazine of the formula



VI

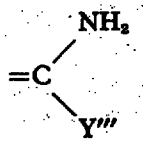
[in which R^2 and R^3 are as defined above]
is reacted with an acetic acid derivative of the general formula:—



VII

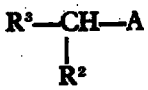
[in which
R^1 is as defined above;
X is a hydroxyl, alkoxy, aralkoxy, amino or alkylamino radical; and either
Y is a hydrogen atom; and

Y′ is a nitrile or —CO . Y″ group (in which Y″ denotes a hydrogen, alkyl, phenyl, or trifluoromethyl radical);
or
Y and Y′ together are a



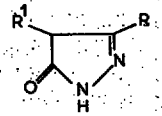
group (in which Y‴ is an alkoxy, aryloxy, aralkoxy, alkylmercapto, aralkylmercapto or amino group);
optionally in the presence of an inert solvent and a basic or acidic catalyst (such as alkali metal hydroxides and carbonates and alkaline earth metal hydroxides and carbonates, or such as hydrogen halide acids, sulphuric acid or sulphonic acids) at temperatures of from 10 to 200°C; or

B) a compound of the general formula:—



VIII

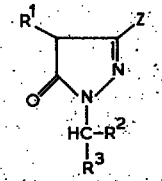
[in which
R^2 and R^3 are as defined above; and
A is a leaving radical
(preferably a halogen, dialkyloxonium, dialkylsulphonium, trialkylammonium, arylsulphonic acid or trifluoromethylsulphonic acid radical)]
is reacted with a pyrazol-5-one derivative of the general formula:—



IX

[in which R and R^1 are as defined above]
optionally in the presence of an inert solvent and an inorganic or organic base (such as alkali metal hydroxides, carbonates, alcoholates, hydrides or amides), at temperatures of from 10 to 200°C; or

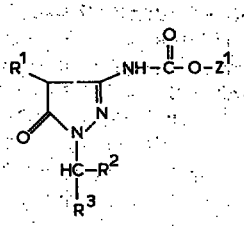
C) (applicable only when R is an amino group) a pyrazol-5-one derivative of the formula:—



X

[in which
R^1, R^2 and R^3 are as defined above; and
Z is a halogen, alkoxy, aralkoxy, alkylmercapto or aralkylmercapto radical]
is reacted with ammonia, optionally in the presence of inert solvents, at temperatures of from 20 to 220°C; or

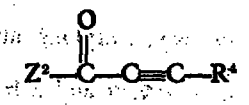
D) (applicable only when R is an amino group) a pyrazol-5-one derivative of the formula:—



XI

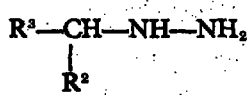
[in which
R^1, R^2 and R^3 are as defined above; and
Z^1 is an alkyl, aryl or aralkyl radical]
is hydrolysed with an acid or base, optionally in the presence of an inert solvent, at temperatures of from 20° to 200°C; or

E) (applicable only when R is a hydrogen, alkyl or phenyl radical and R^1 is a hydrogen atom) an acetylenecarboxylic acid derivative of the general formula



XII

[in which
R^4 is a hydrogen, alkyl or phenyl radical; and
Z^2 is a hydroxyl, alkoxy, aralkoxy, amino or alkylamino radical]
is reacted with a hydrazine of the general formula:—



VI

[in which R^2 and R^3 are as defined above]
optionally in the presence of inert solvents and an inorganic or organic base, at temperatures of from 50° to 200°C.

The five different forms A—E of the method according to the invention are hereinafter referred to as "Process Variants" A—E.

The enantiomers of the compounds according to the invention can be separately prepared according to methods known from the literature (compare, for example, Houben Weyl "Methoden der organischen Chemie", IV/2, pages 509 et seq.), by interaction of the racemic forms of the compounds of the invention with a chiral medium, preferably by reaction of the racemate with the derivative of an optically active acid (for example, camphorsulphonic acid, bromocamphorsulphonic acid or quinic acid) or an optically active base (for example, brucine, morphine or strychnine). A mixture of diastereomeric reaction products is thus obtained, which can be separated and prepared in a pure form with the aid of physico-chemical methods such as, for example, fractionation, and can subsequently be resolved into optically pure components.

Alternatively, the compounds of the invention can be prepared in optically active form by producing them, by one of the methods described above, using optically active precursors. Thus:

(a) an optically pure hydrazine of general formula VI (which can be prepared by known methods) can be reacted with an acetic acid derivative of general formula VII according to Process Variant A; or

(b) an optically pure pyrazol-5-one derivative of the general formula X (which can also be obtained by known methods) can be reacted with ammonia according to Process Variant C; or

(c) an optically pure pyrazol-5-one derivative of the general formula XI can be hydrolysed according to Process Variant D; or

(d) an optically pure hydrazine of general formula VI can be reacted with an acetylene-carboxylic acid derivative of general formula XII according to Process Variant E.

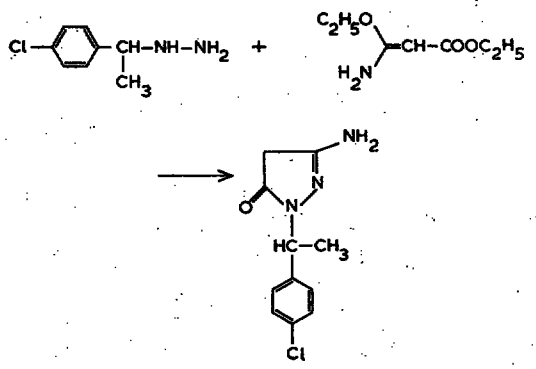
The new free pyrazol-5-one derivatives of general formula I and their salts according to the invention can be interconverted in any suitable manner; methods for such interconversion are known in the art.

Surprisingly, the new compounds of the invention display strong diuretic, saluretic, antithrombotic and anti-hypertensive actions. Hitherto, diuretic, saluretic, antithrombotic and anti-hypertensive actions have not been disclosed for the related pyrazol-5-one derivatives known from the prior art, so that the compounds according to the invention both represent a novel class of compounds and in respect of these specific pharmaceutical actions can be regarded as an enrichment of pharmacy.

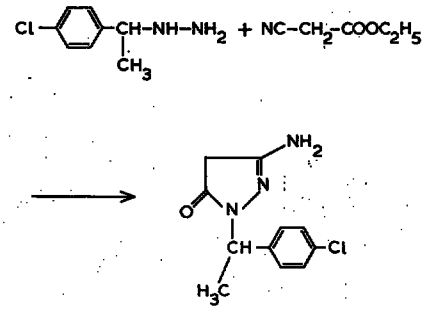
Depending on the nature of the starting compounds used, the synthesis of the compounds of the invention can be illustrated by the following equations, wherein 3 - amino - 1 - (α - methyl - 4 - chlorobenzyl) - pyrazol - 5 - one, 3 - methyl - 1- (α - ethylbenzyl) - pyrazol - 5 - one, 3,4 - dimethyl - 1 - (α - methyl - 3 - chloro-

benzyl) - pyrazol - 5 - one, 3 - amino - 4 - methyl - 1 - (α - ethylbenzyl) - pyrazol-5 - one, 3 - amino - 1 - (α - methyl - 4 - fluorobenzyl) - pyrazol - 5 - one and 3 - methyl - 1 - (α - methyl - 4 - chlorobenzyl) - pyrazol - 5 - one have been chosen as examples and the possible intermediate stages of the reaction sequence, the products of which can at times be isolated, have not been shown.

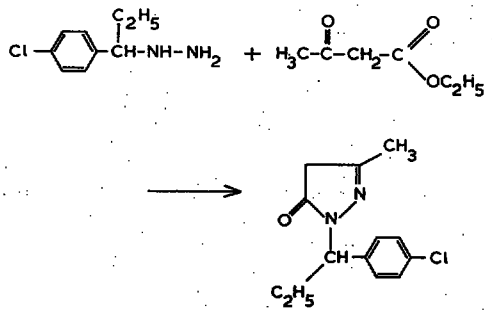
A) 1.)



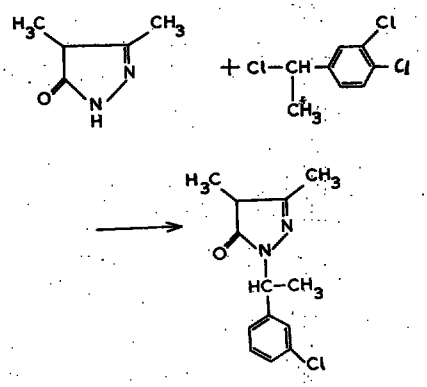
2.)



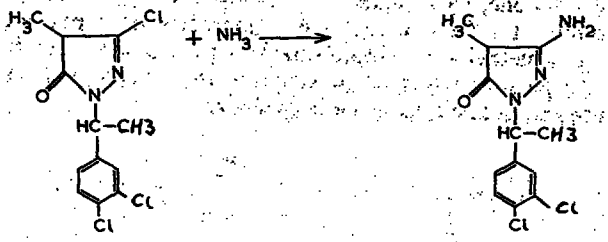
3.)



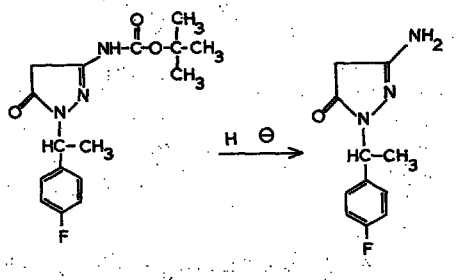
B)



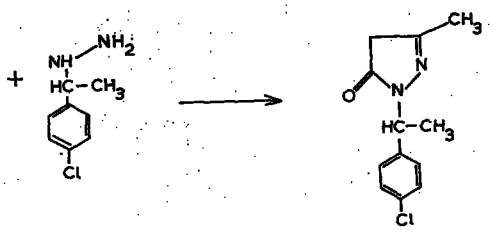
C)



D)

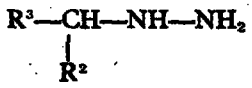


E) $H_5C_2OO-C\equiv C-CH_3$



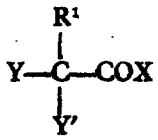
Process Variant A

A hydrazine of the general formula:—



VI

is reacted with an acetic acid derivative of the general formula:—



VII

in accordance with Process A.

In the general formula I and VI, R^2 and R^3 are as defined above, but:
R^2 is preferably an alkyl radical with 1 to 4 carbon atoms; and
R^3 is preferably an unsubstituted naphthyl or pyridyl radical, or a phenyl radical carrying as substituents either:—

(1) 1 or 2 straight-chain or branched alkyl or alkenyl radicals with up to 8 carbon atoms each, especially 1 or 2 alkyl radicals with up to 4 carbon atoms each;
(2) 1 or 2 alkoxy radicals with up to 6 carbon atoms, especially up to 4 carbon atoms each;
(3) a cycloakyl or cycloalkenyl radical with 5, 6 or 7 carbon atoms;
(4) 1 or 2 halogen (eg. fluorine, chlorine and bromine), atoms;
(5) 1 or 2 trifluoromethyl radicals; or
(6) a trifluoromethoxy, nitro or nitrile or dialkylamino group; or
(7) a carbamoyl or sulphamyl group; the nitrogen atom of which can carry 1

or 2 straight-chain or branched alkyl groups with up to 4 carbon atoms each as substituent(s); or

(8) a group —B, —CO . B or —SO_2 . B, in which B is a 5-, 6- or 7-membered ring containing a nitrogen atom in the 1-position and optionally also an oxygen atom but no other heteroatom; or

(9) an SO_n Alkyl group, in which n is 0 or 2 and "Alkyl" is a straight-chain or branched alkyl radical containing up to 4 carbon atoms; or

(10) a fused branched or unbranched saturated or unsaturated 5-, 6- or 7-membered ring containing as sole heteroatoms one sulphur atom or 1 to 2 oxygen atoms.

The hydrazines of the general formula VI used as starting compounds are known from the literature or can be prepared by methods known from the literature (compare, for example, Houben-Weyl's "Methoden der organischen Chemie" ("Methods of organic Chemistry"), volume X, 2, page 6).

As Examples of hydrazines of general formula VI there may be mentioned:
α-methyl-3-chlorobenzylhydrazine,
α-methyl-3-bromobenzylhydrazine,
α-methyl-4-chlorobenzylhydrazine,
α-methyl-4-bromobenzylhydrazine,
α-methyl-3,4-dichlorobenzylhydrazine,
α-methyl-3,4-dibromobenzylhydrazine,
α-methyl-3-bromo-4-chlorobenzylhydrazine,
α-methyl-4-bromo-3-chlorobenzylhydrazine,
α-methyl-4-methylbenzylhydrazine,
α-methyl-3-methylbenzylhydrazine,
α-methyl-3-ethylbenzylhydrazine,
α-methyl-4-trifluoromethylbenzylhydrazine,
α-methyl-4-chloro-3-methylbenzylhydrazine,
α-methyl-4-methyl-3-trifluoromethylbenzylhydrazine,
α-methyl-3-chloro-4-trifluoromethylbenzylhydrazine,
α-methyl-4-chloro-3-trifluoromethylbenzylhydrazine,
α-methyl-4-sulphonamidobenzylhydrazine,
α-methyl-4-chloro-3-sulphonamidobenzylhydrazine,
α-methyl-4-methoxybenzylhydrazine,
α-(naphthyl-(2))-ethylhydrazine,
α-methyl-3,4-tetramethylenebenzylhydrazine,
α-methyl-3,4-methylenedioxybenzylhydrazine,
α-ethyl-4-chlorobenzylhydrazine,
α-ethyl-3-chlorobenzylhydrazine,
α-ethyl-1,4-dichlorobenzylhydrazine,
α-ethyl-4-bromo-3-chlorobenzylhydrazine and
α-ethyl-3-chloro-4-methylbenzylhydrazine.

In the general formulae I and VII:—

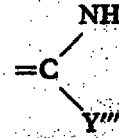
R^1 is preferably a hydrogen atom or an alkyl or alkenyl radical with up to 4 carbon atoms or a phenyl or benzyl group optionally carrying as substituent an alkoxy group with 1 to 2 carbon atoms;

X is preferably a hydroxyl group, an optionally branched alkoxy group with 1 to 6 carbon atoms (especially a methoxy or ethoxy group), a benzyloxy or amino group, or an alkylamino or dialkylamino group, each with 1 to 4 carbon atoms per alkyl group; and preferably either:

Y is a hydrogen atom; and

Y′ is a nitrile or —CO . Y″ group in which Y″ is a hydrogen atom or an alkyl group with 1 to 4 carbon atoms or a phenyl or trifluoromethyl group); or

Y and Y′ together are a group

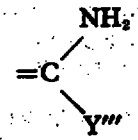


(in which Y‴ is an alkoxy or alkylmercapto radical having 1 to 6 carbon atoms or a benzyloxy, phenoxy, benzylmercapto or amino group).

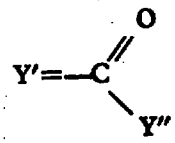
The acetic acid derivatives used as starting compounds, according to the general formula VII, are known from the literature or can be prepared by processes known from the literature (compare Org. Synth., Coll. *I*, 249; Org. Synth. *41*, 50; Cope,

J. Amer. chem. Soc. *67*, 1047 (1945); C.C. Steele, J. Amer. chem. Soc. *53*, 286 (1931); A.H. Cook, J. chem. Soc. (London) *1949*, 3224).

Although referred to in this specification as acetic acid derivatives, the compounds of general formula VII could more accurately be designated as β-aminoacrylic acid derivatives (when Y and Y′ together are a



group, see equation A1 above), cyanoacetic acid derivatives (when Y=H, Y′=CN, see equation A2 above), or β-ketoacid derivatives (Y=H,



see equation A3 above).

As examples of acetic acid derivatives VII there may be mentioned:
cyanoacetic acid methyl ester,
cyanoacetic acid ethyl ester,
cyanoacetic acid propyl ester,
cyanoacetic acid isopropyl ester,
cyanoacetic acid n.-butyl ester (compare Org. Synth. 41, page 5),
cyanoacetic acid isobutyl ester,
cyanoacetic acid t.-butyl ester,
cyanoacetic acid hexyl ester,
cyanoacetic acid benzyl ester,
cyanoacetic acid amide,
cyanoacetic acid methylamide,
cyanoacetic acid diethylamide,
cyanoacetic acid butylamide,
α-cyanopropionic acid methyl ester,
α-cyanopropionic acid n.-butyl ester,
α-cyanopropionic acid ethyl ester,
α-cyanopropionic acid propyl ester,
α-cyanopropionic acid isopropyl ester,
α-cyanopropionic acid isobutyl ester,
α-cyanopropionic acid t.-butyl ester,
α-cyanopropionic acid hexyl ester,
α-cyanopropionic acid benzyl ester,
α-cyanopropionic acid amide,
α-cyanopropionic acid methylamide,
α-cyanopropionic acid diethylamide,
α-cyanopropionic acid butylamide,
α-cyanobutyric acid ethyl ester,
α-cyanobutyric acid t.-butyl ester,
α-cyanobutyric acid diethylamide,
β-amino-β-methoxyacrylic acid ethyl ester,
β-amino-β-ethoxyacrylic acid ethyl ester,
β-amino-β-butoxyacrylic acid butyl ester,
β-amino-β-phenoxyacrylic acid ethyl ester,
β-amino-β-benzyloxyacrylic acid benzyl ester,
β-amino-β-ethoxyacrylic acid amide,
β-amino-β-ethoxyacrylic acid diethylamide,
β-amino-β-methylmercaptoacrylic acid ethyl ester,
β-amino-β-benzylmercaptoacrylic acid ethyl ester,
β-amino-β-methylmercaptoacrylic acid amide,
β,β-diaminoacrylic acid ethyl ester,
β,β-diaminoacrylic acid amide,

β-amino-β-methoxymethacrylic acid ethyl ester,
β-amino-β-ethoxymethacrylic acid ethyl ester,
β-amino-β-butoxymethacrylic acid butyl ester,
β-amino-β-phenoxymethacrylic acid ethyl ester,
β-amino-β-benzyloxymethacrylic acid ethyl ester,
β-amino-β-methylmercaptomethacrylic acid ethyl ester,
β-amino-β-benzylmercaptomethacrylic acid ethyl ester,
β-amino-β-ethoxymethacrylic acid amide,
β-amino-β-ethoxymethacrylic acid diethylamide,
β-amino-β-methylmercaptomethacrylic acid amide,
β,β-diaminomethacrylic acid ethyl ester,
β,β-diaminomethacrylic acid amide,
β-amino-β-ethoxy-α-ethylacrylic acid ethyl ester,
β-amino-β-methylmercapto-α-ethylacrylic acid ethyl ester,
β-amino-β-ethoxy-α-ethylacrylic acid amide,
β-amino-β-ethoxy-α-phenylacrylic acid ethyl ester,
β-amino-β-ethoxy-α-benzylacrylic acid ethyl ester,
α-formylacetic acid ethyl ester,
α-formylpropionic acid ethyl ester,
acetoacetic acid ethyl ester,
acetoacetic acid n.-butyl ester,
acetoacetic acid isopropyl ester,
acetoacetic acid t.-butyl ester,
acetoacetic acid diethylamide,
propionylacetic acid ethyl ester,
propionylacetic acid isopropyl ester,
propionylacetic acid n.-butyl ester,
benzoylacetic acid ethyl ester,
α-acetylpropionic acid ethyl ester,
α-acetylpropionic acid n.-butyl ester,
α-acetylpropionic acid t.-butyl ester,
α-propionylpropionic acid ethyl ester,
α-propionylpropionic acid isopropyl ester,
α-acetylbutyric acid ethyl ester,
α-propionylbutyric acid ethyl ester,
α-propionylbutyric acid isopropyl ester,
α-benzoylacetoacetic acid ethyl ester and
ω,ω,ω-trifluoroacetoacetic acid ethyl ester.

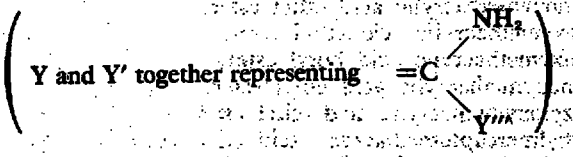
Possible diluents for use in Process Variant A are all inert organic solvents, which—where they are miscible with water—can optionally be diluted with water. Preferred organic solvents include hydrocarbons (such as benzene, toluene and xylene), halogenated hydrocarbons (such as methylene chloride, chloroform, carbon tetrachloride and chlorobenzene), alcohols (such as methanol, ethanol, propanol, butanol, benzyl alcohol, and glycol monomethyl ether), ethers (such as tetrahydrofuran, dioxane and glycol dimethyl ether), amides (such as dimethylformamide, dimethylacetamide, N-methylpyrrolidone and hexamethylphosphoric acid triamide), sulphoxides (such as dimethylsulphoxide), sulphones (such as sulpholane) and bases (such as pyridine, picoline, collidine, lutidine and quinoline).

As basic condensation agents in Process Variant A there may be used inorganic and organic bases. Preferred bases for this purpose include alkali metal hydroxides (such as sodium hydroxide and potassium carbonate) and alcoholates (such as sodium alcoholate and potassium alcoholate).

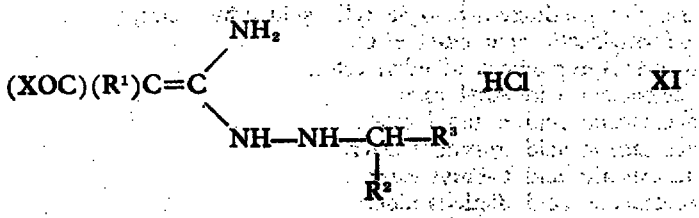
Alternatively there may be used as an acid catalyst, inorganic or organic acid. Preferred acids include hydrogen halide acids, sulphuric acid and sulphonic acids (such as toluenesulphonic acid and trifluoromethylsulphonic acid).

The reaction temperatures in Process Variant A can be varied over a substantial range. In general, the reaction is carried out at a temperature of from 10 to 200°C, preferably from 20 to 100°C. It can be carried out under normal pressure but also in closed vessels at a higher pressure.

In carrying out the process according to the invention, as illustrated by equation A 1), 1 mol of the hydrazine VI and 1 mol of β-aminoacrylic acid derivative VII



are reacted. It is possible to start either from the β-aminoacrylic acid derivative in the free form or from its acid addition salts. In the latter case it is desirable to add 1 mol of a base in order to liberate the β-aminoacrylic acid derivative. If the hydrazine derivative and the β-aminoacrylic acid derivative are employed in the free form, the addition of 1 to 10% of an acid catalyst is desirable. Another possible procedure is to add a correspondingly smaller amount of a base to the reaction mixture for the purpose of neutralising the salt of the β-aminoacrylic acid derivative. When using the acid addition salt, the reaction can also be carried out by isolating the intermediate amidrazone of the general formula:—

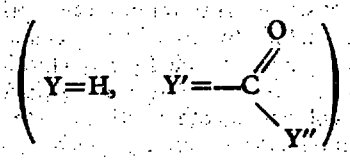


XI

which are first produced, and then cyclising these in a second reaction step, thermally or by the action of a basic condensation agent, to give the compounds of the invention. However, the one-stage synthesis is particularly advantageous.

In carrying out the process according to the invention as illustrated in equation A 2), 1 mol of the cyanoacetic acid derivative VII (Y=H, Y'=nitrile), and 1—3 mols, preferably 2 mols, of the basic condensation agent are employed per 1 mol of the hydrazine VI. With this procedure, the compounds of the invention are obtained in the form of their salts and can be liberated by treatment with equivalent amounts of a dilute acid. They can easily be purified by recrystallisation from a suitable solvent or by dissolving them with dilute sodium hydroxide solution, filtering the solution in the presence of animal charcoal and precipitating the product by means of dilute acids.

If the process according to the invention is carried out as illustrated in reaction scheme A 3), 1 mol of the hydrazine derivative VI is reacted with 1 mol of the β-ketoacid derivative VII



in a suitable diluent, the reaction mixture preferably being stirred for two hours at an elevated temperature after completion of the exothermic initial reaction. The compounds of the invention, which in most cases are obtained in a crystalline form can easily be purified by recrystallisation from a suitable solvent.

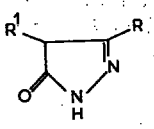
Process Variant B

According to Process Variant B, a compound of the general formula



VIII

is reacted with a pyrazol-5-one derivative of the general formula



IX

In the general formulae I and VIII:

A is a leaving radical which is eliminated, such as a halogen, dialkyloxonium, dialkylsulphonium, trialkylammonium, arylsulphonic acid, or trifluoromethylsulphonic acid radical, but is preferably a chlorine or bromine atom; and

R^2 and R^3 are as defined above.

The halogen compounds of the general formula VIII used in Process Variant B as starting substances are known from the literature or can be prepared by methods known from the literature (compare, for example, Houben-Weyl, "Methoden der organischen Chemie" ("Methods of organic Chemistry"), volume V, 3 (1962) and volume V, 4 (1960)). The following in particular may be mentioned as examples of the halogen compounds VIII which are used:

α-methyl-3-chlorobenzyl chloride,
α-methyl-3-bromobenzyl chloride,
α-methyl-4-chlorobenzyl chloride,
α-methyl-4-bromobenzyl chloride,
α-methyl-3,4-dichlorobenzyl chloride,
α-methyl-4-bromo-3-chlorobenzyl chloride,
α-methyl-4-methylbenzyl chloride,
α-methyl-4-trifluoromethylbenzyl chlorides,
α-methyl-3-chloro-4-methylbenzyl chloride,
α-methyl-4-chlorobenzyl bromide,
α-methyl-3,4-dichlorobenzyl bromide,
α-methyl-3-chloro-4-methylbenzyl bromide,
α-ethyl-3,4-dichlorobenzyl chloride and
α-ethyl-3-chloro-4-methylbenzyl chloride.

In the general formulae I and IX:

R is preferably a hydrogen or trifluoromethyl radical, or an alkyl group with 1 to 4 carbon atoms, especially a methyl or ethyl group or a phenyl or amino group; and

R^1 is as defined above.

The pyrazol-5-one derivatives of general formula IX used as starting compounds in Process Variant B are known from the literature or can be prepared by methods known from the literature (compare, for example, B. Graham et al, J. Amer. chem. Soc. *71*, 983 (1949); R. Jones et al, Tetrahedron *19*, 1947 (1963)).

As examples of pyrazol-5-one derivatives IX there may be mentioned:

3-methyl-pyrazol-5-one,
3-ethylpyrazol-5-one,
3-trifluoromethylpyrazol-5-one,
3,4-dimethylpyrazol-5-one,
3-methyl-4-phenylpyrazol-5-one,
3-methyl-4-benzylpyrazol-5-one,
3-amino-pyrazol-5-one,
3-amino-4-methylpyrazol-5-one and
3-amino-4-phenylpyrazol-5-one.

Possible diluents for use in Process Variant B are all inert solvents. Preferred solvents include hydrocarbons (such as benzene, toluene and xylene), alcohols (such as methanol, ethanol, propanol, butanol benzyl alcohol and glycol monomethyl ether), ethers (such as tetrahydrofuran, dioxane and glycol dimethyl ether) amides (such as dimethylformamide and dimethylacetamide, N-methylpyrrolidone, and hexamethylphosphoric acid triamide), sulphoxides (such as dimethylsulphoxide) and sulphones (such as sulpholane).

Bases which can be used in Process Variant B include in principle, all inorganic and organic ides, carbonates, alcoholates, hydrides and amides.

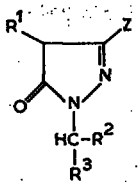
The reaction temperatures in Process Variant B can be varied over a substantial range. Preferably, the reaction is carried out at a temperature of from 20 to 120°C. It is generally carried out under normal pressure but one can also carry it out in a closed vessel at a higher pressure.

In carrying out Process Variant B, a salt is generally first prepared from one mol of the pyrazolone derivative IX in a suitable solvent by means of an equimolar amount of a base. One mol of the halogen compound is added to a solution of this salt and the entire reaction mixture is stirred, preferably at an elevated temperature.

The compounds of the invention are preferably isolated by distilling off the solvent *in vacuo*, taking up the residue in water and rendering the aqueous mixture weakly acid. The compounds of the invention obtained using this procedure can easily be purified by recrystallisation from a suitable solvent.

Process Variant C

According to Process Variant C, a pyrazol-5-one derivative of the general formula:—



X

is reacted with ammonia.

In the general formula, Z is preferably a halogen atom, or a straight-chain or branched alkoxy radical with 1 to 4 carbon atoms, or a benzyloxy or straight-chain or branched alkylmercapto radical, but it most preferably a chlorine or bromine atom, and R^1, R^2 and R^3 are as defined above.

The pyrazol-5-one derivatives of general formula X used as starting compounds in Process Variant C can be prepared in a simple manner by methods known from the literature (compare, for example, Japanese Patent 2872 ('64) (1961) and G. Barnikow, Chem. Ber. *100*, 1661 (1967)).

The following may be mentioned as examples of the preferentially used halogen compounds of general formula X (Z=chlorine or bromine):

3 - chloro - 1 - (α - methyl - 4 - chlorobenzyl) - pyrazol - 5 - one,
3 - chloro - 1 - (α - methyl - 4 - bromobenzyl) - pyrazol - 5 - one,
3 - chloro - 1 - (α - methyl - 3,4 - dichlorobenzyl) - pyrazol - 5 - one,
3 - chloro - 1 - (α - methyl - 4 - bromo - 3 - chlorobenzyl) - pyrazol - 5 - one,
3 - chloro - 1 - (α - methyl - 3 - chloro - 4 - methylbenzyl) - pyrazol - 5 - one,
3 - bromo - 1 - (α - methyl - 4 bromo - 3 - chlorobenzyl) - pyrazol - 5 - one,
3 - bromo - 1 - (α - methyl - 3 - chloro - 4 - methylbenzyl) - pyrazol - 5 - one,
3 - chloro - 1 - (α - ethyl - 3,4 - dichlorobenzyl) - pyrazol - 5 - one,
3 - chloro - 1 - (α - ethyl - 3 - chloro - 4 - methylbenzyl) - pyrazol - 5 - one,
3 - chloro - 4 - methyl - 1 - (α - methyl - 3,4 - dichlorobenzyl) - pyrazol - 5 - one,
3 - chloro - 4 - methyl - 1 - (α - methyl - 4 - bromo - 3 - chlorobenzyl) - pyrazol-5-one, and
3 - chloro - 4 - phenyl - 1 - (α - methyl - 3,4 - dichlorobenzyl) - pyrazol - 5 - one.

Possible diluents for use in Process Variant C are water and all inert organic solvents which—where they are water-miscible—can be diluted with water. Preferred organic solvents include hydrocarbons (such as benzene, toluene and xylene), alcohols (such as methanol, ethanol, propanol, butanol, benzyl alcohol and glycol monomethyl ether), and ethers (such as tetrahydrofuran, dioxane and glycol dimethyl ether).

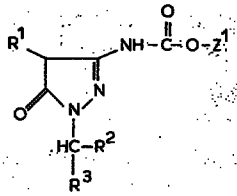
The reaction temperatures in Process Variant C can be varied over a substantial range. The reaction is generally carried out at a temperature of from 20 to 220°C, but preferably from 50 to 150°C. It can be carried out either under normal pressure or in closed vessels at higher pressures.

In carrying out Process Variant C, one mol of the pyrazolone derivative X is generally reacted with a 2-fold to 20-fold, preferably 10-fold, excess of ammonia.

The procedure followed is preferably that the reactants, optionally in an inert solvent, are reacted in a closed vessel at an elevated temperature. The compounds of the invention, thus obtained, can easily be purified by recrystallisation from a suitable solvent.

Process Variant D

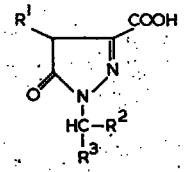
According to Process Variant D, a pyrazol-5-one derivative of the general formula:—



XI

[in which R^1, R^2, R^3 and Z are as defined above and Z^1 is preferably a straight-chain or branched alkyl group with 1 to 6 carbon atoms (especially the t.-butyl group) or a phenyl or benzyl radical] is hydrolysed with an inorganic or organic acid (such as a hydrogen halide acid, sulphuric acid, phosphoric acid, acetic acid, trifluoroacetic acid or a mixture of two or more thereof), or with a base (such as an alkali metal hydroxide or alkaline earth metal hydroxide) optionally in the presence of an inert solvent, at temperatures of from 50° to 200°C.

The pyrazol-5-one derivatives of general formula XI used as starting compounds have not hitherto been disclosed but can be prepared by methods known from the literature, for example by reacting the carboxylic acid of the general formula XIII (R^1, R^2 and R^3 having the abovementioned meaning



XIII

which in turn can be obtained by hydrolysis of the corresponding esters which can be prepared from optionally substituted oxalacetic acid esters and hydrazines of the general formula VI according to a modified Curtius reaction with diphenylphosphoryl azide (T. Shioiri et al, J. Amer. chem. Soc. *94*, 6203 (1972)) or by Weinstock's method (J. Org. Chem. *26*, 3511 (1961)).

The following may be mentioned as examples of pyrazol-5-one derivatives XI:

3 - carboethoxyamino - 1 - (α - methyl - 4 - chlorobenzyl) - pyrazol - 5 - one,
3 - carboethoxyamino - 1 - (α - methyl - 4 - bromobenzyl) - pyrazol - 5 - one,
3 - carboethoxyamino - 1 - (α - methyl - 3,4 - dichlorobenzyl) - pyrazol - 5 - one,
3 - carbo - t. - butoxyamino - 1 - (α - methyl - 3,4 - dichlorobenzyl) - pyrazol - 5-one,
3 - carboethoxyamino - 1 - (α - methyl - 4 - bromo - 3 - chlorobenzyl) - pyrazol-5 - one,
3 - carboethoxyamino - 1 - (α - methyl - 3 - chloro - 4 - methylbenzyl) - pyrazol-5 - one,
3 - carbopropoxyamino - 1 - (α - ethyl - 3,4 - dichlorobenzyl) - pyrazol - 5 - one,
3 - carbo - t. - butoxyamino - 1 - (α - methyl - 4 - bromo - 3 - chlorobenzyl)-pyrazol - 5 - one,
3 - carbo - t. - butoxyamino - 1 - (α - methyl - 3 - chloro - 4 - methylbenzyl)-pyrazol - 5 -one,
3 - carbophenoxyamino - 1 - (α - methyl - 3,4 - dichlorobenzyl) - pyrazol - 5 - one, and
3 - carbobenzyloxyamino - 1 - (α - methyl - 3,4 - dihclorobenzyl) - pyrazol - 5-one.

Possible diluents for use in Process Variant D are water and water-miscible inert organic solvents. Preferred solvents include alcohols (such as methanol, ethanol, propanol, ethylene glycol and glycol monomethyl ether), and ethers (such as tetrahydrofuran or dioxane).

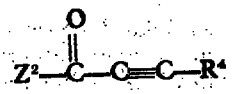
The reaction temperatures in Process Variant D can be varied over a substantial range. Preferably, the reaction is carried out at a temperature of from 70° to 150°C. Normally, the reaction is carried out under normal pressure, but it can also be carried out in closed vessels at a higher pressure.

In carrying out Process Variant D, an aliquot part of the pyrazolone derivative XI, optionally in an inert solvent, is generally stirred with, preferably, a five-fold to twenty-five-fold excess of an aqueous solution of an acid or a base at an elevated

temperature. The compounds of the invention precipitate after neutralisation of the reaction solution and can easily be purified by recrystallisation from a suitable solvent.

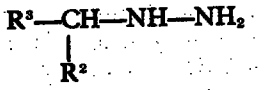
Process Variant E

According to Process Variant E, an acetylenecarboxylic acid derivative of the general formula:—



XII

is reacted with a hydrazine of the general formula:—



VI

In the general formula XII:—

R^4 is preferably a hydrogen atom, or an alkyl group with 1 to 4 carbon atoms or a phenyl group; and

Z^2 is preferably a hydroxyl group, or an optionally branched alkoxy group with 1 to 6 carbon atoms, (especially a methoxy or ethoxy group), a benzyloxy or amino group, or an alkylamino or dialkylamino group, with 1 to 4 carbon atoms per alkyl group.

The reaction is preferably carried out in an inert organic solvent and/or water as a diluent at 70°—150°C in the presence of a basic condensation agent.

The acetylenecarboxylic acid derivatives of the general formula XII used as starting compounds in Process Variant E are known from the literature or can be prepared by methods known from the literature (compare, for example, Beilstein's "Handbuch der organischen Chemie" (Beilstein's Handbook of Organic Chemistry), 2, III, 1,447 et seq (1961) and 9, III, 3,061 et seq (1971)).

As examples of acetlyenecarboxylic acids XII there may be mentioned:

propiolic acid ethyl ester,
propiolic acid n-butyl ester,
propiolic acid iso-propyl ester,
propiolic acid benzyl ester,
propiolic acid amide,
propiolic acid dimethylamide,
propiolic acid ethylamide,
tetrolic acid ethyl ester,
tetrolic acid n-propyl ester,
tetrolic acid isopropyl ester,
phenylpropiolic acid ethyl ester,
phenylpropiolic acid n-butyl ester,
phenylpropiolic acid iso-propyl ester,
phenylpropiolic acid benzyl ester,
phenylpropiolic acid amide,
phenylpropiolic acid ethylamide and
phenylpropiolic acid dimethylamide.

The hydrazines VI used in Process Variant E are the same as those used in Process Variant A, q.v.

Possible diluents for use in Process Variant E are all inert organic solvents which—where they are water-miscible—can be diluted with water. Preferred organic solvents include hydrocarbons (such as benzene, toluene and xylene), halogenated hydrocarbons (such as methylene chloride, chloroform, carbon tetrachloride and chlorobenzene), alcohols (such as methanol, ethanol, propanol, butanol, benzyl alcohol and glycol monomethyl ether), ethers (such as tetrahydrofuran, dioxane and glycol dimethyl ether), amides (such as dimethylformamide, dimethylacetamide, N-methyl-pyrrolidone and hexamethylphosphoric acid triamide), sulphoxides (such as dimethylsulphoxide), sulphones (such as sulpholane) and bases (such as pyridine, picoline, collidine, lutidine and quinoline).

Possible basic condensation agents for use in Process Variant E are inorganic and organic bases. Preferred condensation agents include alkali metal hydroxides

and carbonates (such as sodium hydroxide and potassium carbonate) and alcoholates (such as sodium alcoholate and potassium alcoholate).

The reaction temperatures in Process Variant E can be varied within a substantial range. In general, the reaction is carried out at a temperature of from 50° to 200°C, preferably from 70° to 150°C. It is carried out under normal pressure but can also be carried out in closed vessels at a higher pressure.

In carrying out Process Variant E, 1 mol of the acetylenecarboxylic acid derivative XII, optionally in a suitable diluent, is generally reacted with 1 mol of the hydrazine VI. The compounds of the invention, which in most cases are obtained in a crystalline form, if necessary after evaporating off the diluent, can easily be purified by recrystallisation from a suitable solvent.

The quantities mentioned in Process Variants A to E can of course be varied slightly.

In addition to those mentioned in the Preparative Examples given below, the following compounds of the invention may be mentioned by way of illustration only:

3 - amino - 4 - methyl - 1 - (α - methyl - 3 - chlorobenzyl) - pyrazol - 5 - one,
3 - amino - 4 - methyl - 1 - (α - methyl - 3,4 - dichlorobenzyl) - pyrazol - 5 - one,
3 - amino - 4 - methyl - 1 - (α - methyl - 3 - chloro - 4 - methylbenzyl) - pyrazol-5-one,
3 - amino - 4 - methyl - 1 - (α - methyl - 4 - trifluoromethylbenzyl) - pyrazol-5-one,
3 - amino - 4 - methyl - 1 - (α - methyl - 3 - chloro - 4 - bromobenzyl) - pyrazol-5-one,
3 - amino - 4 - methyl - 1 - (α - (naphthyl - (2)) - ethyl) - pyrazol - 5 - one,
3 - amino - 4 - methyl - 1 - (α - methyl - 3 - fluorobenzyl) - pyrazol - 5 - one*,
3 - amino - 4 - methyl - 1 - (α - methyl - 4 - fluorobenzyl) - pyrazol - 5 - one*,
3 - amino - 4 - methyl - 1 - (α - methyl - 3,4 - difluorobenzyl) - pyrazol - 5 - one*,
3 - amino - 4 - methyl - 1 - (α - methyl - 3 - chloro - 4 - fluorobenzyl) - pyrazol-5-one*,
3 - amino - 4 - methyl - 1 - (α - methyl - 3,4 - di - (fluoromethyl) - benzyl)-pyrazol - 5 - one*,
3 - amino - 4 - methyl - 1 - (α - methyl - 3,4 - tetramethylenebenzyl) - pyrazol-5-one*,
3 - amino - 4 - methyl - 1 - (α - methyl - 2,3 - tetramethylenebenzyl) - pyrazol-5-one*,
3 - amino - 4 - methyl - 1 - (α - (4 - pyridyl) - ethyl) - pyrazol - 5 - one*,
3 - amino - 4 - methyl - 1 - (α - (3 - pyridyl) - ethyl) - pyrazol - 5 - one*,
3,4 - dimethyl - 1 - (α - methyl - 4 - chlorobenzyl) - pyrazol - 5 - one,
3,4 - dimethyl - 1 - (α - methyl - 3 - chloro - 4 - methylbenzyl) - pyrazol - 5 - one,
3,4 - dimethyl - 1 - (α - methyl - 4 - bromo - 3 - chlorobenzyl) - pyrazol - 5 - one,
3,4 - dimethyl - 1 - (α - methyl - 4 - trifluoromethylbenzyl) - pyrazol - 5 - one,
3,4 - dimethyl - 1 - (α - (naphthyl - (2)) - ethyl) - pyrazol - 5 - one,
1 - (α - methyl - 3,4 - dichlorobenzyl) - pyrazol - 5 - one,
3 - amino - 1 (α - methyl - 3 - chlorobenzyl) - pyrazol - 5 - one,
3 - amino - 1 - (α - methyl - 3 - bromobenzyl) - pyrazol - 5 - one,
3 - amino - 1 - (α - methyl - 3 - fluorobenzyl) - pyrazol - 5 - one,
3 - amino - 1 - (α - methyl - 4 - fluorobenzyl) - pyrazol - 5 - one,
3 - amino - 1 - (α - methyl - 4 - chlorobenzyl) - pyrazol - 5 - one,
3 - amino - 1 - (α - methyl - 4 - iodobenzyl) - pyrazol - 5 - one,
3 - amino - 1 - (α - methyl - 4 - trifluoromethylbenzyl) - pyrazol - 5 - one,
3 - amino - 1 - (α - methyl - 4 - trifluoromethoxybenzyl) - pyrazol - 5 - one,
3 - amino - 1 - (α - methyl - 3 - trifluoromethyl - 4 - methoxybenzyl) - pyrazol-5-one,
3 - amino - 1 - (α - methyl - 3 - chloro - 4 - bromobenzyl) - pyrazol - 5 - one,
3 - amino - 1 - (α - methyl - 4 - chloro - 3 - sulphamoylbenzyl) - pyrazol - 5 - one,
3 - amino - 1 - (α - (naphthyl - (2)) - ethyl) - pyrazol - 5 - one,
3 - amino - 1 - (α - ethyl - 4 - nitrobenzyl) pyrazol - 5 - one,
3 - amino - 1 - (α - ethyl - 4 - cyanobenzyl) - pyrazol - 5 - one,
3 - amino - 1 (α - n - propyl - 2 - chloro - 4 - fluorobenzyl) - pyrazol - 5 - one,
3 - amino - 1 - (α - methyl - 3,4 - difluorobenzyl) - pyrazol - 5 - one*,
3 - amino - 1 - (α - methyl - 3,4 - di - (trifluoromethyl) - benzyl) - pyrazol - 5-one*,
3 - amino - 1 - (α - (4 - pyridyl) - ethyl) - pyrazol - 5 - one*,
3 - amino - 1 (α - (3 - pyridyl) - ethyl) - pyrazol - 5 - one*,

3 - amino - 1 - (α - methyl - 3,4 - tetramethylenebenzyl) - pyrazol - 5 - one*,
3 - amino - 1 - (α - methyl - 2,3 - tetramethylenebenzyl) - pyrazol - 5 - one*,
3 - methyl - 1 - (α - methyl - 4 - butylbenzyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 3 - trifluoromethyl - 4 - chlorobenzyl) - pyrazol - 5-one,
3 - methyl - 1 - (α - methyl - 4 - sulphamoylbenzyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 4 - dimethylaminobenzyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 3,4 - tetramethylenebenzyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 3 - chlorobenzyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 2 - chlorobenzyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 3,5 - dichlorobenzyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 3 - fluorobenzyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 4 - chloro - 3 - bromobenzyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 4 - fluoro - 3 - chlorobenzyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 3 - methylbenzyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 4 - ethylbenzyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 4 - chloro - 3 - methyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 4 - fluoro - 3 - methyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 3 - methyl - 5 - chlorobenzyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 3,5 - dimethylbenzyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 3 - chloro - 4 - trifluoromethylbenzyl) - pyrazol - 5-one,
3 - methyl - 1 - (α - methyl - 3 - methyl - 4 - trifluoromethylbenzyl) - pyrazol - 5-one,
3 - methyl - 1 - (α - methyl - 3 - methoxybenzyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 4 - ethoxybenzyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 3 - ethylbenzyl) - pyrazol - 5 - one,
3 - methyl - 1 - (α - methyl - 3,4 - difluorobenzyl) - pyrazol - 5 - one*,
3 - methyl - 1 - (α - (3 - pyridyl) - ethyl) - pyrazol - 5 - one*,
3 - methyl - 1 - (α - methyl - 3,4 - tetramethylenebenzyl) - pyrazol - 5 - one*,
3 - methyl - 1 - (α - methyl - 2,3 - tetramethylenebenzyl) - pyrazol - 5 - one*,
3 - ethyl - 1 - (α - methyl - 3 - methyl - 4 - chlorobenzyl) - pyrazol - 5 - one,
3 - ethyl - 1 - (α - methyl - 3 - chloro - 4 - methylbenzyl) - pyrazol - 5 - one,
3 - ethyl - 1 - (α - methyl - 3,4 - dichlorobenzyl) - pyrazol - 5 - one,
3 - ethyl - 1 - (α - methyl - 4 - trifluoromethoxybenzyl) - pyrazol - 5 - one,
3 - ethyl - 1 - (α - methyl - 4 - methyl - 3 - trifluoromethylbenzyl) - pyrazol - 5-one,
3 - ethyl - 1 - (α - methyl - 4 - bromo - 3 - chlorobenzyl) - pyrazol - 5 - one,
3 - iospropyl - 1 - (α - methyl - 3,4 - dichlorobenzyl) - pyrazol - 5 - one,
3 - trifluoromethyl - 1 - (α - methyl - 4 - chlorobenzyl) - pyrazol - 5 - one*,
3 - trifluoromethyl - 1 - (α - methyl - 3 - chlorobenzyl) - pyrazol - 5 - one*,
3 - trifluoromethyl - 1 - (α - methyl - 4 - bromobenzyl) - pyrazol - 5 - one*,
3 - trifluoromethyl - 1 - (α - methyl - 4 - fluorobenzyl) - pyrazol - 5 - one*,
3 - trifluoromethyl - 1 - (α - methyl - 3 - chloro - 4 - methyl) - pyrazol - 5 - one*,
3 - trifluoromethyl - 1 - (α - (naphthyl - (2)) - ethyl) - pyrazol - 5 - one*,
3 - trifluoromethyl - 1 - (α - methyl - 3 - bromo - 4 - chlorobenzyl) - pyrazol - 5-one*,
3 - phenyl - 1 - (α - methyl - 3,4 - dichlorobenzyl) - pyrazol - 5 - one,
3 - phenyl - 1 - (α - methyl - 3 - chloro - 4 - methylbenzyl) - pyrazol - 5 - one,
3 - phenyl - 1 - (α - methyl - 3 - methyl - 4 - chlorobenzyl) - pyrazol - 5 - one,
3 - phenyl - 1 - (α - ethyl - 3,4 - dichlorobenzyl) - pyrazol - 5 - one,
3 - phenyl - 4 - methyl - 1 - (α - methyl - 4 - trifluoromethylbenzyl) - pyrazol - 5-one,
3 - phenyl - 4 - methyl - 1 - (α - methyl - 3,4 - dichlorobenzyl) - pyrazol - 5 - one,
3 - phenyl - 4 - ethyl - 1 - (α - methyl - 3 - chloro - 4 - methoxybenzyl) - pyrazol-5-one, and
3 - phenyl - 4 - ethyl - 1 - (α - ethyl - 3,4 - dimethylbenzyl) - pyrazol - 5 - one.

The new compounds of the invention can be used as medicines. On oral or parenteral use, they increase the elimination of water and salt and can therefore be used for the treatment of oedematous and hypertonic conditions and for flushing out toxic substances. In addition, the compounds can be employed in the case of acute renal failure.

To demonstrate the diuretic and saluretic action of the compounds of the invention, as a function of time, 3 - methyl - 1 - (α - methyl - 3,4 - dichlorobenzyl)-

pyrazol - 5 - one, described in Example 6, was administered to dogs. The remaining compounds show comparable properties. The activities of some compounds are shown in Table II.

Diuresis experiment with dogs

a) Method

Beagle bitches were used. On the day of the experiment, the animals were given 1 ml/kg of a solution which contained 0.4% of NaCl and 0.2% of KCl every 30 minutes by means of a probang. Thereafter, the test preparation was administered orally and the urine was collected. A change in the excretion of electrolyte was detected through comparison with control groups which were given the solvents used. The amounts of urine were converted to ml/kg. It was then possible to calculate the excretion in μequivalent/kg from the volume of urine and the measured electrolyte concentration. Sodium and potassium were determined by flame photometry and chloride was determined potentiometrically.

b) Results

The results are shown in Table I and II. The renal excretion of sodium and water was increased substantially after oral administration of the test preparation. The effect depended on the dose.

TABLE I

Excretion in ml or μmol/kg/30 minutes

		Minutes after administration						
		1–30	31–60	61–90	91–120	121–150	151–180	Total excretion after administration
Control	Urine	1.1	1.3	1.3	1.4	1.4	0.7	7.2
	Na^+	68	79	45	57	51	36	336
	K^+	88	88	64	45	42	25	352
1 mg/kg	Urine	4.5	11.9	4.6	3.9	1.0	0.6	26.5
p.o.	Na^+	358	1,238	535	428	64	14	2,637
	K^+	170	259	165	212	102	67	975
3 mg/kg	Urine	10.0	16.1	9.8	5.0	2.5	2.0	45.4
p.o.	Na^+	969	1,932	1,251	622	283	218	5,275
	K^+	216	259	216	152	119	103	1,065

Effect of 3-methyl-1-(α-methyl-3,4-dichlorobenzyl)-pyrazol-5-one on the renal excretion of electrolyte and excretion of water of conscious dogs in respect of variation with time and total effect after 3 hours (average values for groups of 4 animals).

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TABLE Ia

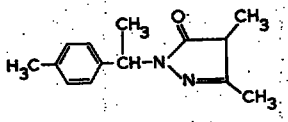
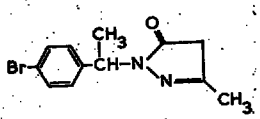
Excretion in ml or μmol/kg/15 minutes

Dose mg/kg i.v.	Control Periods of 15 minutes			Administration Periods of 15 minutes						Total effect
		1	2	3 1st period after administration	4	5	6	7	8 6th period after administration	Total excretion after administration (3rd – 8th period)
0.3	Urine	2.6	3.0	5.4	7.4	6.9	6.0	5.3	4.8	35.8
	Na^+	16	13	266	516	502	469	418	361	2,532
	K^+	12	12	53	74	52	43	38	27	287
1.0	Urine	2.7	3.7	9.5	14.8	14.3	13.9	12.9	11.7	77.1
	Na^+	16	20	885	1,565	1,467	1,363	1,272	1,181	7,733
	K^+	31	24	103	127	113	109	107	98	657

Effect of 3-amino-1-(α-methyl-3,4-dichlorobenzyl)-pyrazol-5-one on the renal excretion of electrolyte and excretion of water of conscious dogs, in respect of variation with time and total effect after 1.5 hours (average values for groups of 4 animals).

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TABLE II

	Excretion in μ equivalent or ml/kg/1 hour			
		Na^+	K^+	H_2O
Control		168	136	2.4
	3 mg/kg	1.158	358	10.5
	3 mg/kg	1.106	334	8.7

As stated above, the invetion also relates to the use in human and veterinary medicine of the compounds of the invention.

The present invention 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 provide 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 descrete coherent portions suitable for medical administration. "Medicament in dosage unit form" as used in this Specification means physical 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 cabonate 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 com-

positions 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 hydroxide, 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, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitol or mixtures thereof.

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 from 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 parenteral administration of the medicaments of the invention is 0.5 mg.—5g., more preferably 5 mg.—1g. of active ingredient, and, for preoral administration, 5 mg—50 g., more preferably 25mg.—10 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 perorally or parenterally. Preferred pharmaceutical compositions and medicaments are therefore those adapted for parenteral and peroral administration, such as powders, suspensions, tablets, capsules, injectable (i.e. sterile and isotonic) solutions and ampoules of such solutions). Administration in the method of the invention is preferably peroral or parenteral.

In general it has proved advantageous to administer parenterally amounts of from 0.01—50 mg/kg., preferably 0.1—10 mg/kg. body-weight, or perorally amounts of 0.1—500 mg/kg., preferably 0.5—100 mg/kg. body weight per day to achieve effective results. Nevertheless, it can at times be necessary to deviate from those dosage rates, and in particular to do so as a function of the nature and body weight of the human or animal subject to be treated, the individual reaction of this subject to the treatment, the type of formulation in which the active ingredient is administered and the mode in which the administration is carried out, and the point in the progress of the disease or interval at which it is to be administered. Thus it may in some case suffice to use less than the above-mentioned minimum dosage rate, whilst other cases the upper limit mentioned must be exceeded to achieve the desired results. Where larger amounts are administered it can be advisable to divide these into several individual administrations over the course of the day.

The above disclosure applies equally to human and to veterinary medicine.

The following Examples A and B describe, by way of illustration only, the preparation of pharmaceutical compositions and medicaments in dosage unit form according to the invention.

Example A.

200 g of 3 - amino - 1 - (α - methyl - 4 - chlorobenzyl) - pyrazol - 5 - one are ground to a powder and mixed with 300 g of lactose and 200 g of potato starch, and after moistening with an aqueous gelatine solution the mixture is granulated through a sieve.

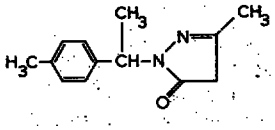
After drying, 60 g of talc and 5 g of sodium laurylsulphate are added. About 10,000 tablets each containing 20 mg of active compound are pressed from this mixture.

Example B.

20 g of the sodium salt of 3 - methyl - 1 - (α - methyl - 3 - chlorobenzyl)-pyrazol - 5 - one are dissolved in 1,000 ml of propylene glycol and the solution is made up to 5,000 ml with water. This solution is filled under aseptic conditions into sterile ampoules each of 5 ml capacity and each containing 20 mg of active compound.

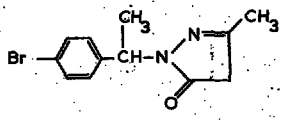
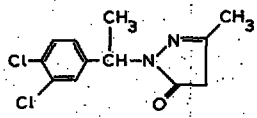
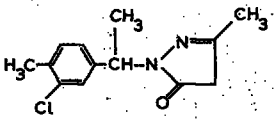
The following Preparative Examples 1—25 describe by way of illustration only the preparation according to the invention of some of the new compounds of the invention.

Example 1.
(3-methyl-1-(α,4-dimethylbenzyl)-pyrazol-5-one)

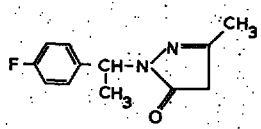


26 g of acetoacetic acid ethyl ester were dissolved in 20 ml of absolute ethanol. 30.0 g of α-methyl-4-methylbenzylhydrazine in a little absolute ethanol were slowly added to this solution under nitrogen. After the exothermic reaction had subsided, the mixture was heated for 2 hours under reflux. On cooling, the crude product crystallised out and was purified by recrystallisation from methanol. Melting point 144—146°C; yield 28 g (65% of theory).

The following compounds were synthesised as described in Example 1:

No.	Structural formula	Recrystallisation from	Yield	Melting point °C
2		Dimethylformamide	63	150 – 152
3		Ethanol	77.7	143 – 145
4		Methanol	80	140 – 142

Example 5.
(3-Methyl-1-(α-methyl-4-fluorobenzyl)-pyrazol-5-one)

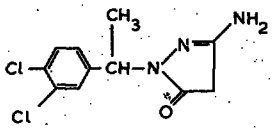


8.3 g (0.074 mol) of tetrolic acid ethyl ester and 11.3 g of α-methyl-4-fluorobenzylhydrazine in 70 ml of n-butanol were heated for 8 hours under reflux.

The solution was concentrated and the solid residue was recrystallised from ethanol.

Melting point 140—142°C; yield 4 g (25% of theory).

Example 6.
(3-Amino-1-(α-methyl-3,4-dichlorobenzyl)-pyrazol-5-one)

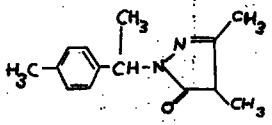


41 g of α-methyl-3,4-dichlorobenzylhydrazine, dissolved in absolute ethanol, were added dropwise to a solution of 31.8 g of β-amino-β-ethoxyacrylic acid ethyl ester and 1.5 g of p-toluenesulphonic acid in 150 ml of ethanol at room temperature under nitrogen gas. After stirring for two hours and standing overnight, the reaction solution was concentrated as far as possible on a rotary evaporator. The residue which remained was dissolved in 2 N sodium hydroxide solution. Any unconverted starting products or by-products were extracted with ether. The aqueous phase was then brought to pH 5 with acetic acid. The oil thereby produced was taken up in methylene

chloride and the organic phase was dried over Na_2SO_4. After evaporating off the solvent, the reaction product crystallised out. It was recrystallised from methanol. Melting point 127—129°C; yield 21 g (38.5% of theory).

Example 7.

(3,4-dimethyl-1-(α,4-dimethylbenzyl)-pyrazol-5-one)

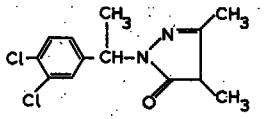
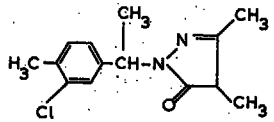
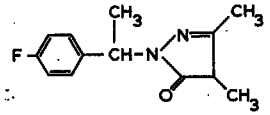


30 g of α-methyl-4-methylbenzylhydrazine in ethanol were added to a solution of 28.8 g (0.2 mol) of α-methylacetoacetic acid ester in 40 ml of ethanol under N_2 gas; during the addition, the temperature rose to 70°C. After completion of the addition, the reaction mixture was heated for 2 hours under reflux.

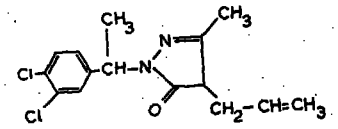
On cooling, the reaction product crystallised out. It was recrystallised from methanol.

Melting point 131—133°C; yield 27 g (59% of theory).

The following compounds were synthesised as described in Example 7:

No.	Structural formula	Recrystallisation from	Yield, % of theory	Melting point °C
8		Ethanol	60	160–162
9		Methanol	65	145–147
10		Ethanol	43	102–104

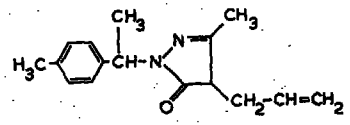
Example 11.
(3-Methyl-4-(prop-2-en-1-yl)-1-(α-methyl-3,4-dichlorobenzyl)-pyrazol-5-one).



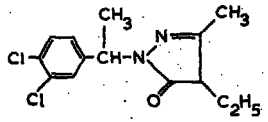
17 g (0.1 mol) of allylacetoacetic acid ester were added to a mixture of 20.5 g of α-methyl-3,4-dichlorobenzylhydrazine and 30 ml of absolute ethanol under nitrogen, whereupon the temperature rose to 55°C. The reaction mixture was heated to the reflux temperature for 2 hours. After cooling, the reaction product crystallised out.

Melting point 124 to 125°C; yield 23.0 g (75% of theory).

The following were obtained analogously to Example 11:

No.	Structural formula	Recrystallisation from	Yield, % of theory	Melting point °C
12		Ethanol	48.5	138–139

Example 13.
(3-Methyl-4-ethyl-1-(α-methyl-3,4-dichlorobenzyl)-pyrazol-5-one)

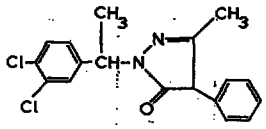


25.2 g of 3-methyl-4-ethylpyrazol-5-one were added in portions to a suspension of 10.0 g (0.22 mol) of sodium hydride in 200 ml of absolute dimethylformamide.

After the evolution of H_2 had ceased, 41.8 g (0.2 mol) of α-methyl-3,4-dichlorobenzyl chloride were added dropwise to the reaction solution. The mixture was then stirred for 2 hours at 60°C, the solvent was distilled off *in vacuo* and the residue was taken up in water and acidified with dilute acetic acid. The crude product thereby obtained was recrystallised from ethanol.

Melting point 153—155°C; yield 16.7 g (28% of theory).

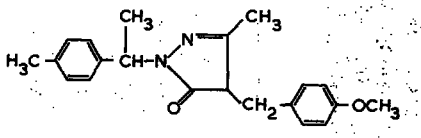
Example 14.
(3-Methyl-4-phenyl-1-(α-methyl-3,4-dichlorobenzyl)-pyrazol-5-one)



20.6 g of α-phenylacetoacetic acid ester were added dropwise under nitrogen to a solution of 20.5 g (0.1 mol) of α-methyl-3,4-dichlorobenzylhydrazine in 20 ml of absolute ethanol, during which the temperature of the reaction mixture rose to 55°C. After heating the reaction solution for two hours under reflux, the reaction product crystallised out on cooling the reaction mixture. The crystals were filtered off, rinsed with ether and recrystallised from an ethanol/dimethylformamide mixture.

Melting point 214—216°C; yield 26 g (75% of theory).

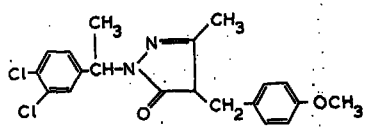
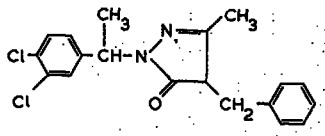
Example 15.
(3-Methyl-4-(4-methoxybenzyl)-1-(α,4-dimethylbenzyl)-pyrazol-5-one)



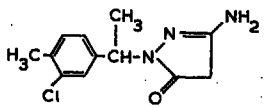
31 g of α-(4-methoxybenzyl)-acetoacetic acid ester were added to a solution of 15 g of α-methyl-4-methylbenzylhydrazine in 30 ml of absolute ethanol in an inert gas atmosphere, during which the temperature of the reaction mixture rose to 60°C. After heating for 2 hours under reflux and standing overnight, the product crystallised out and was recrystallised from a mixture of ethanol and a little dimethylformamide.

Melting point 146—147°C; yield 20 g (60% of theory).

The following were obtained analogously to Example 15:

No.	Structural formula	Recrystallisation from	Yield, % of theory	Melting point °C
16		Ethanol	64	172–174
17		Dimethylformamide/ethanol	73	175–177

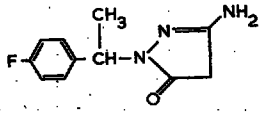
Example 18.
(3-Amino-1-(α,4-dimethyl-3-chlorobenzyl)-pyrazol-5-one)



0.2 mol of 1 - (α - methyl - 3 - chloro - 4 - methylbenzyl) - 3 - chloropyrazol-5-one was dissolved in 100 ml of ethanol, 17 g of ammonia were added and the mixture was heated to 150°C for 2 hours in a stirred autoclave. After concentrating the reaction solution, the crude product was obtained. It was recrystallised twice from ethanol.

Melting point 86—88°C; yield 4.2 g (8.5% of theory).

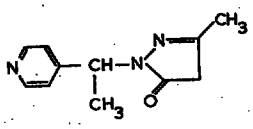
Example 19.
(3-Amino-1-(α-methyl-4-fluorobenzyl)-pyrazol-5-one)



0.1 mol of (1 - (α - methyl - 4 - fluorobenzyl) - 3 - ethoxy - carbonylamino-pyrazol - 5 - one was boiled in 200 ml of aqueous Zn hydrochloric acid for 2 hours under reflux after addition of 40 ml of glacial acetic acid. After cooling, and neutralisation with dilute sodium hydroxide solution, crystalline product could be filtered off. The product was recrystallised from a little ethanol.

Melting point 128—130°C; yield 17.5 g (79% of theory).

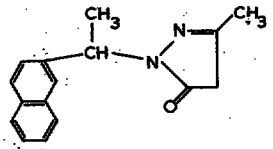
Example 20.
(3-Methyl-1-(2-[α-pyrid-4-yl]-ethyl)-pyrazol-5-one)



This compound is obtained from acetoacetic acid ester and α-pyridyl-(4)-ethyl-hydrazine. It is recrystallised from ethanol.

Melting point 146—148°C; yield 42% of theory.

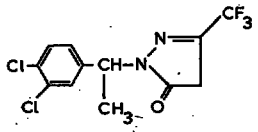
Example 21.
(3-Methyl-1-(α-[β-naphthyl]-ethyl)-pyrazol-5-one)



This compound was obtained from α-naphthyl-(2)-ethylhydrazine and acetoacetic acid ester. It was recrystallised from ethanol.

Melting point 145—147°C; yield 35% of theory.

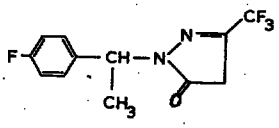
Example 22.
(3-Trifluoromethyl-1-(α-methyl-3,4-dichlorobenzyl)-pyrazol-5-one)



This compound was obtained from trifluoroacetoacetic acid ethyl ester and α-methyl-3,4-dichlorobenzylhydrazine. It was recrystallised from ether/ethanol.

Melting point 203—205°C; yield 23% of theory.

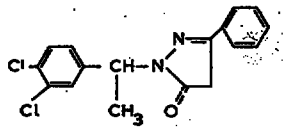
Example 23.
(3-Trifluoromethyl-1-(α-methyl-4-fluorobenzyl)-pyrazol-5-one)



This compound was obtained from trifluoroacetoacetic acid ethyl ester and α-methyl-4-fluorobenzylhydrazine. It was purified by precipitation from ether with petroleum ether.

Melting point 168—170°C; yield 32% of theory.

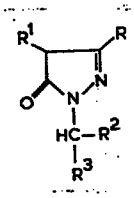
Example 24.
(3-Phenyl-1-(α-methyl-3,4-dichlorobenzyl)-pyrazol-5-one)



This compound was obtained from benzoylacetic acid ester and α-methyl-3,4-dichlorobenzylhydrazine. It was recrystallised from dimethylformamide.
Melting point 155—157°C; yield 86% of theory.

WHAT WE CLAIM IS:—

1. Compounds which are 1-substituted pyrazol-5-ones of the following general formula and their salts:



I

in which:

R is a hydrogen, amino, alkyl, alkenyl, trifluoromethyl, or phenyl radical;
R^1 is a hydrogen, alkyl, alkenyl or optionally substituted aryl or aralkyl radical;
R^2 is an alkyl group; and
R^3 is a pyridyl radical or an aryl radical carrying 1 or 2 identical or different substituents which are selected from halogen, trifluoromethyl, alkyl, alkenyl, and alkoxy radicals, or carrying one mono- or dialkylamino, trifluoromethoxy, nitro, nitrile, carbamoyl, alkyl- or dialkylcarbamoyl, sulphamyl, or alkyl- or dialkylsulphamyl radical, or a group —B, —CO . B or —SO_2B (in which B is a saturated ring containing a nitrogen atom in the 1-position) or a —SO_n Alkyl group (in which n=0, 1 or 2), optionally together with one or two substituents selected from alkyl, alkoxy, alkenyl, halogen and trifluoromethyl radicals or carrying none or 1 only of these substituents and a fused branched or unbranched, saturated or unsaturated 5-, 6- or 7-membered ring optionally containing 1 or 2 oxygen or sulphur atoms.

2. Compounds according to claim 1 in which R is a hydrogen atom, an alkyl group with up to 4 carbon atoms, a phenyl group, or an amino group.

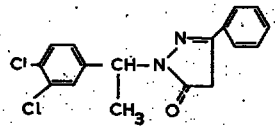
3. Compounds according to claim 1 or 2 in which R^1 is a hydrogen atom or an alkyl or alkenyl radical with up to 4 carbon atoms, or a phenyl or benzyl group optionally carrying as a substituent a methoxy or ethoxy group.

4. Compounds according to claim 1, 2 or 3 in which R^2 has up to 4 carbon atoms.

5. Compounds according to any preceding claim in which R^3 is a phenyl radical and carries as substituents either:—

(1) 1 or 2 straight-chain or branched alkyl or alkenyl radicals with up to 8 carbon atoms each; or
(2) 1 or 2 alkoxy radicals with up to 6 carbon atoms each; or
(3) a cycloalkyl or cycloalkenyl radical with 5, 6 or 7 carbon atoms; or
(4) 1 or 2 halogen atoms; or
(5) 1 or 2 trifluoromethyl radicals; or
(6) a trifluoromethoxy, nitro, nitrile or dialkylamino group; or
(7) a carbamoyl or sulphamyl group, the nitrogen atoms of which can carry 1 or 2 straight-chain or branched alkyl groups with up to 4 carbon atoms each as substituents; or
(8) a group —B, —CO . B or —SO_2B, in which B is a 5-, 6- or 7-membered ring containing a nitrogen atom in the 1-position, and also optionally an oxygen atom, but no other hetero-atoms; or
(9) an —SO_nAlkyl group in which n=0 or 2, and Alkyl is straight-chain or branched and containing 1 to 4 carbon atoms; or
(10) a fused, branched or unbranched, saturated or unsaturated 5-, 6- or 7-membered ring containing as sole hetero-atoms 1 sulphur atom or 1 or 2 oxygen atoms.

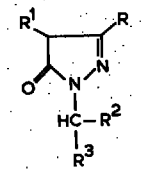
Example 24.
(3-Phenyl-1-(α-methyl-3,4-dichlorobenzyl)-pyrazol-5-one)



This compound was obtained from benzoylacetic acid ester and α-methyl-3,4-dichlorobenzylhydrazine. It was recrystallised from dimethylformamide.
Melting point 155—157°C; yield 86% of theory.

WHAT WE CLAIM IS:—

1. Compounds which are 1-substituted pyrazol-5-ones of the following general formula and their salts:



I

in which:

R is a hydrogen, amino, alkyl, alkenyl, trifluoromethyl, or phenyl radical;
R^1 is a hydrogen, alkyl, alkenyl or optionally substituted aryl or aralkyl radical;
R^2 is an alkyl group; and
R^3 is a pyridyl radical or an aryl radical carrying 1 or 2 identical or different substituents which are selected from halogen, trifluoromethyl, alkyl, alkenyl, and alkoxy radicals, or carrying one mono- or dialkylamino, trifluoromethoxy, nitro, nitrile, carbamoyl, alkyl- or dialkylcarbamoyl, sulphamyl, or alkyl- or dialkylsulphamyl radical, or a group —B, —CO . B or —SO_2B (in which B is a saturated ring containing a nitrogen atom in the 1-position) or a —SO_n Alkyl group (in which n=0, 1 or 2), optionally together with one or two substituents selected from alkyl, alkoxy, alkenyl, halogen and trifluoromethyl radicals or carrying none or 1 only of these substituents and a fused branched or unbranched, saturated or unsaturated 5-, 6- or 7-membered ring optionally containing 1 or 2 oxygen or sulphur atoms.

2. Compounds according to claim 1 in which R is a hydrogen atom, an alkyl group with up to 4 carbon atoms, a phenyl group, or an amino group.

3. Compounds according to claim 1 or 2 in which R^1 is a hydrogen atom or an alkyl or alkenyl radical with up to 4 carbon atoms, or a phenyl or benzyl group optionally carrying as a substituent a methoxy or ethoxy group.

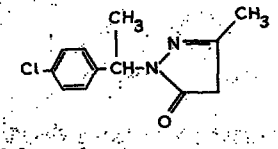
4. Compounds according to claim 1, 2 or 3 in which R^2 has up to 4 carbon atoms.

5. Compounds according to any preceding claim in which R^3 is a phenyl radical and carries as substituents either:—

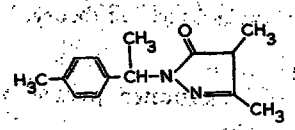
(1) 1 or 2 straight-chain or branched alkyl or alkenyl radicals with up to 8 carbon atoms each; or
(2) 1 or 2 alkoxy radicals with up to 6 carbon atoms each; or
(3) a cycloalkyl or cycloalkenyl radical with 5, 6 or 7 carbon atoms; or
(4) 1 or 2 halogen atoms; or
(5) 1 or 2 trifluoromethyl radicals; or
(6) a trifluoromethoxy, nitro, nitrile or dialkylamino group; or
(7) a carbamoyl or sulphamyl group, the nitrogen atoms of which can carry 1 or 2 straight-chain or branched alkyl groups with up to 4 carbon atoms each as substituents; or
(8) a group —B, —CO . B or —SO_2B, in which B is a 5-, 6- or 7-membered ring containing a nitrogen atom in the 1-position, and also optionally an oxygen atom, but no other hetero-atoms; or
(9) an —SO_nAlkyl group in which n=0 or 2, and Alkyl is straight-chain or branched and containing 1 to 4 carbon atoms; or
(10) a fused, branched or unbranched, saturated or unsaturated 5-, 6- or 7-membered ring containing as sole hetero-atoms 1 sulphur atom or 1 or 2 oxygen atoms.

6. Compounds according to claim 5 in which R^3 is an unsubstituted naphthyl radical.

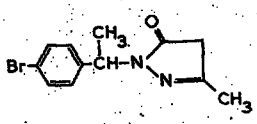
7. The compound of the formula:—



8. The compound of the formula:—



9. The compound of the formula:—



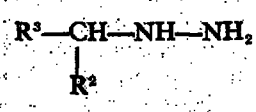
10. Compounds according to claim 1 which are hereinbefore specifically mentioned other than those according to claims 7, 8 and 9, those marked *, and those mentioned in Examples 8, 10, and 18—25.

11. Compounds which are 1-substituted pyrazol-5-ones of the general formula I given in claim 1 and their salts, in which general formula R, R^1, R^2 and R^3 can have any of the meanings given in claims 1 to 6 but in addition R can be a trifluoromethyl group.

12. Compounds according to claim 1 which are hereinbefore marked * or mentioned in Examples 5, 10, and 18—25.

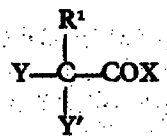
13. A process for the production of a compound according to any of claims 1 to 10 in which either:

(A) a hydrazine of the general formula:—



VI

[in which R^2 and R^3 are as defined in claim 1, 3, 5 or 6]
is reacted with an acetic acid derivative of the general formula:—



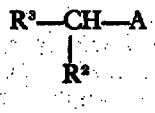
VII

[in which
R^1 is as defined in claim 1 or 3;
X is a hydroxyl, alkoxy, aralkoxy, amino or alkylamino group;
and either:
Y is a hydrogen atom; and
Y′ is a nitrile or —CO . Y″ group (in which Y″ is a hydrogen, alkyl or phenyl radical); or
Y and Y′ together are a group:



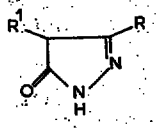
(in which Y‴ is an alkoxy, aryloxy, aralkoxy, alkylmercapto, aralkylmercapto or amino group)];
at 10—200°C; or

(B) a compound of the general formula:—



VIII

[in which
R^2 and R^3 are as defined in any of claims 1, 4, 5 and 6, and A is a leaving radical]
is reacted with a pyrazol-5-one derivative of the general formula:—

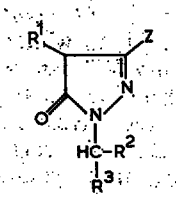


IX

[in which R and R^4 are as defined in any of claims 1, 2 and 3] at 10—200°C.

14. A process for the production of a compound according to claim 11 or 12, in which either:—

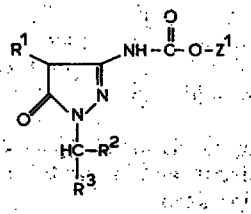
(C) (applicable only to compounds in which R is an amino group) a pyrazol-5-one derivative of the general formula:—



X

[in which
R^1, R^2 and R^3 are as defined in any of claims 1, 3—6 and 11; and
Z is a halogen, alkoxy, aralkoxy, alkylmercapto, or aralkylmercapto radical]
is reacted with ammonia at 20—220°C; or

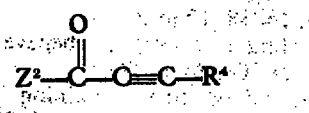
(D) (applicable only to compounds in which R is an amino group) a pyrazol-5-one of the general formula:—



XI

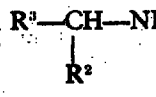
[in which
R^1, R^2 and R^3 are as defined in any of claims 1, 3—6 and 11; and
Z′ is an alkyl, aryl, or aralkyl radical]
is hydrolysed with an acid or base at 20—200°C; or

(E) (applicable only to compounds in which R is a hydrogen, alkyl or phenyl radical and R^1 is a hydrogen atom) an acetylenecarboxylic acid derivative of the general formula:—



XII

[in which
R^4 is a hydrogen, alkyl or phenyl radical; and
Z^2 is a hydroxyl, alkoxy, aralkoxy, amino or alkylamino radical]
is reacted with a hydrazine of the general formula:—



VI

[in which R^2 and R^3 are as defined in any of claims 1, 4—6 and 11]: at 50—200°C.

15. A process according to claim 13 (part A) in which the reaction is carried out at 20—100°C, in the presence of an acid catalyst or a basic condensation agent and an inert organic solvent optionally mixed with water.

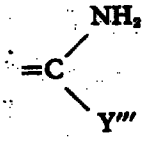
16. A process according to claim 13 (part A) or 15 in which:

X is a hydroxyl group, an optionally branched alkoxy group with up to 6 carbon atoms, a benzyloxy or amino group, or an alkylamino or dialkylgroup; the alkyl groups of which have up to 4 carbon atoms each; and either

Y is a hydrogen atom; and

Y′ is a nitrile or —CO . Y″ group (in which Y″ is a hydrogen atom or an alkyl group with up to 4 carbon atoms or a phenyl group); or

Y and Y′ together are a group



(in which Y‴ is an alkoxy or alkylmercapto group having up to 6 carbon atoms or a benzyloxy, phenoxy, benzylmercapto or amino group).

17. A process according to claim 13 (part A), 15 or 16 for the production of a compound according to claim 11, in which R, R^1, R^2 and R^3 can have any of the meanings given in claim 11, and Y‴ can be a trifluoromethyl group.

18. A process according to claim 13 (part B) in which the reaction is carried out at 20—120°C in an inert organic solvent in the presence of a base.

19. A process according to claim 13 (part B) or 18 in which A is a halogen, dialkyloxonium, dialkylsulphonium, trialkylammonium, arylsulphonic acid or trifluoromethylsulphonic acid radical.

20. A process according to claim 13 (part B), 18 or 19 for the production of a compound according to claim 11, in which R, R^1, R^2 and R^3 can have any of the meanings given in claim 11.

21. A process according to claim 14 (part C) in which the reaction is carried out in water and/or an inert organic solvent as a diluent at 50—150°C.

22. A process according to claim 14 (part C) or 21 in which Z is a chlorine or bromine atom.

23. A process according to claim 14 (part D) in which the hydrolysis is carried out in the presence of water as diluent at 70—150°C.

24. A process according to claim 14 (part D) or 23 in which Z^1 is a straight-chain branched alkyl group with up to 6 carbon atoms or a phenyl or benzyl radical.

25. A process according to claim 14 (part E) in which the reaction is carried out in an inert organic solvent and/or water as a diluent at 70—150°C in the presence of a basic condensation agent.

26. A process according to claim 25 in which Z^2 is a hydroxyl radical, or a methoxy or ethoxy group, or a benzyloxy or amino group, or an alkylamino or dialkylamino group with up to 4 carbon atoms in each alkyl group.

27. A process for the production of a compound according to claim 1 substantially as hereinbefore described in Example 1 or 6.

28. A process for the production of a compound according to claim 11 substantially as hereinbefore described in any of Examples 2—5 and 7—25.

29. Compounds according to claim 1 whenever produced by a process according to any of claims 13, 15, 16, 18, 19 or 27.

30. Compounds according to claim 11 whenever produced by a process according to any of claims 14, 17, or 20—26 or 28.

31. A pharmaceutical composition containing as an active ingredient a compound according to any of claims 1 to 10, and 29 in admixture with a solid or liquefied gaseous diluent or in admixture with a liquid diluent other than a solvent of molecular weight less than 200 except in the presence of a surface-active agent.

32. A pharmaceutical composition containing as an active ingredient a compound according to any of claims 1 to 10 and 29 in the form of a sterile or isotonic aqueous solution.

33. A composition according to claim 21 or 32 containing from 0.5 to 90% of the said active ingredient by weight.

34. A composition according to claim 31, 32 or 33 (insofar as they are dependent upon claim 1) in which the said active ingredient is a compound according to claim 11, 12 or 30.

35. A pharmaceutical composition substantially as hereinbefore described in Example A or B.

36. A medicament in dosage unit form comprising a compound according to any of claims 1 to 10 and 29 either alone or in admixture with a diluent.

37. A medicament in the form of tablets, pills, dragees, capsules, ampoules or suppositories comprising a compound according to any of claims 1 to 10 and 29 either alone or in admixture with a diluent.

38. A medicament in dosage unit form substantially as hereinbefore described in Example A or B.

39. A medicament according to claim 36 or 37 (insofar as they are dependent upon claim 1) in which the said active compound is a compound according to any of claims 11, 12 and 30.

40. A method of combatting disorders of fluid and salt metabolism and of the circulatory and blood-clotting systems in non-human animals comprising administering to the animals an active compound according to any of claims 1 to 10 and 29 either alone or in admixture with a diluent or in the form of a medicament according to claim 36, 37 or 38.

41. A method according to claim 40 in which the said active compound is administered perorally.

42. A method according to claim 40 or 41 in which the said compound is administered in an amount of 0.5 to 100 mg/kg body weight/day.

43. A method according to claim 40 in which the said active compound is administered parenterally.

44. A method according to claim 43 in which the said active compound is administered in an amount of 0.1 to 10 mg/kg body weight/day.

45. A method according to claim 40, substantially as hereinbefore described.

46. A method according to any of claims 40—44 in which the said active compound is a compound according to any of claims 11, 12 and 30.

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