

PATENT SPECIFICATION

NO DRAWINGS

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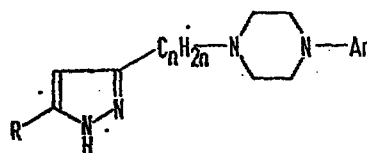
COMPLETE SPECIFICATION

3-(Piperazinoalkyl)-Pyrazoles and their preparation

We, E. MERCK AKTIENGESellschaft, a German Body Corporate of 250 Frankfurterstrasse, Darmstadt, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with certain novel 3-(piperazinoalkyl)-pyrazoles, with processes for their preparation and with compositions containing them.

We have found that 3-(piperazinoalkyl)-pyrazoles of the formula:



in which R is H or alkyl having from 1 to 4 C atoms; Ar is a phenyl group which may, if desired, be mono- or poly-substituted by alkyl and/or alkoxy groups having in each case 1—4 C atoms, trifluoromethyl and/or halogen, and n is an integer from 1 to 4, and their acid addition salts, have valuable pharmacological properties. As well as being well tolerated by human beings, these compounds have appreciable centrally depressive effects, such as narcosis - prolonging, narcosis - potentiating, tranquilising and/or neuroleptic effects. Hypotensive, noradrenaline- and adrenaline-potentiating or stimulating, e.g. thymo-analeptic and tetrabenazine-antagonistic, and antihistaminic and bronchospasmodic properties have also been observed. For instance, in a narcosis-potentiating test based on the method of Janssen *et al* [*J. Med. Pharm. Chem.*, 1, 281—297 (1959)] on rats which were treated with doses of 7.5 mg/kg of sodium hexobarbital (intravenously), this dose being below the threshold of narcosis, the following ED₅₀ values were obtained:

Substance	Time taken to act (mins.)	ED ₅₀ (subcutaneous, mg/kg)-95% limits of confidence in parentheses.
3-[2-(N'- <i>m</i> -chloro-phenyl-piperazino)-ethyl]-5-methyl-pyrazole	30	1.5 (1.2 — 1.9)
3-[2-(N'- <i>m</i> -tolyl-piperazine)-ethyl]-5-methyl-pyrazole	30	3.4 (2.7 — 4.2)
Chlorpromazine (control)	30	6.1 (5.3 — 7.1)
	60	7.0 (6.2 — 7.9)

[Price 4s. 6d.]

30

or *p*-fluorophenyl, *o*-, *m*- or *p*-chlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,4,6-trichlorophenyl, *o*-, *m*- or *p*-bromophenyl, 2,4-dibromophenyl, or *o*-, *m*- or *p*-iodophenyl group.

The group $-C_nH_{2n}-$ is preferably a $-(CH_2)_n-$ group, such as $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH_2CH_2CH_2-$; it can also, for example, be $-CH(CH_3)-$, $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$, $-CH(C_2H_5)-$, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH_2CH(CH_3)-$, $-CH(C_2H_5)CH_2-$, $-CH_2CH(C_2H_5)-$, $-CH(n-C_3H_7)-$ or $-CH(iso-C_3H_7)-$.

When X is a reactive esterified hydroxy group, it must be one that can be replaced in the reaction with an amine by an amino group; preferred acyloxy groups of this kind are acetoxy, methane sulfonyloxy and *p*-toluenesulfonyloxy. When reducing conditions are used, it is possible to use starting compounds which correspond to formulae II, V, VI or X but which contain instead of one or two CH_2X radicals, aldehyde or ester groups or other higher oxidation stage groups which are reduced under the reaction conditions to CH_2OH groups.

By "hydrogen-replaceable groups" are to be understood halogen atoms, preferably chlorine or bromine atoms, and carbonyl, hydroxy and benzyl groups.

The formula I compounds are preferably obtained by reaction of 3-(halogenalkyl)-pyrazoles or their formula II analogues with formula III 1-substituted piperazines.

As formula II starting compounds there can be considered more particularly the following pyrazoles: 3-chloromethyl-, 3-bromomethyl-, 3-iodomethyl-, 3-hydroxymethyl-, 3-(1-chloroethyl)-, 3-(1-bromoethyl)-, 3-(1-iodoethyl)-, 3-(1-hydroxyethyl)-, 3-(2-chloroethyl)-, 3-(2-bromoethyl)-, 3-(2-iodoethyl)-, 3-(2-hydroxyethyl)-, 3-(3-chloropropyl)-, 3-(3-bromopropyl)-, 3-(3-iodopropyl)-, 3-(3-hydroxypropyl)-, 3-(4-chlorobutyl)-, 3-(4-bromobutyl)-, 3-(4-iodobutyl)- and 3-(4-hydroxybutyl)-pyrazoles, and the 5-methyl-, 5-ethyl-, 5-*n*-propyl-, 5-iso-propyl- and 5-*n*-butyl derivatives of these compounds and the esters, more particularly the methanesulfonates and *p*-toluenesulfonates, of the hydroxy compounds mentioned.

As formula III compounds, the following piperazines are preferred: N-phenyl, N-*o*-tolyl-, N-*m*-tolyl-, N-*p*-tolyl-, N-*p*-ethylphenyl-, N-*o*-methoxyphenyl-, N-*m*-methoxyphenyl-, N-*p*-methoxyphenyl-, N-*o*-trifluoromethylphenyl-, N-*m*-trifluoromethylphenyl-, N-*p*-trifluoromethylphenyl-, N-*o*-fluorophenyl-, N-*m*-fluorophenyl-, N-*p*-fluorophenyl-, N-*o*-chlorophenyl-, N-*m*-chlorophenyl-, N-*p*-chlorophenyl-, N-*o*-bromophenyl-, N-*m*-bromophenyl-, N-*p*-bromophenyl-, N-*o*-iodo-

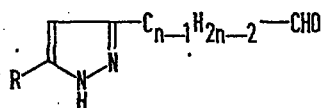
phenyl-, N-*m*-iodophenyl and N-*p*-iodophenyl-piperazine.

The formula II and III compounds are either known or can readily be prepared by syntheses similar to those of known compounds. For instance, pyrazole-3-carboxylic acid esters can be reduced catalytically or with lithium aluminium hydride to 3-hydroxymethyl pyrazoles. 2-Hydroxy-4-pyrones can be reacted with hydrazine to form pyrazole-3-acetic acid hydrazides which are converted by alcoholysis to the corresponding esters and reduction thereof gives 3-(2-hydroxyethyl)-pyrazoles. 3-(3-Hydroxypropyl)- and 3-(4-hydroxybutyl)-pyrazoles (II, X=OH, *n*=3 or 4) can be obtained by condensation of $R-CO-CH_2$ carbonyl compounds with γ -butyrolactone or δ -valerolactone to form 2-hydroxy-2-acylmethyltetrahydrofurans or -pyrans and by a subsequent reaction with hydrazine.

The corresponding halogen compounds (II, X=Cl, Br or I) can be obtained from the corresponding alcohols by reaction with, for example, thionyl chloride or hydrobromic or hydriodic acid, and the corresponding acylates and sulphonc acid esters can be obtained by conventional esterification, for example with acid anhydrides or acid halides, such as acetic anhydride, methane- or *p*-toluene-sulfonyl chloride. The formula III piperazines can be obtained by reaction of formula VII amines with diethanolamine or morpholine or bis-(2-chloroethyl)-amine or from piperazine and halides, preferably bromides, of the formula ArX .

The formulae II and III compounds are reacted together by methods described in the literature for the alkylation of amines. The reaction can be carried out without solvent by fusing the starting materials together, if desired in a closed tube or autoclave, or in the presence of an inert solvent, such as benzene, toluene, xylene, ketones such as acetone or butanone, alcohols such as methanol, ethanol, tetrahydrofuran or dioxane, or a mixture of these solvents with one another or with water. It is advantageous to add an acid binding agent, such as a hydroxide, carbonate, bicarbonate or some other weak acid salt of an alkali or alkaline earth metal, preferably sodium, potassium or calcium, or an organic base, such as triethylamine, dimethylaniline, pyridine or quinoline, or an excess of the formula III piperazine derivative can be used. Depending upon the conditions used, the reaction time can be from a few minutes to 14 days and the reaction temperature is suitably from 0 to 200° C., preferably from 100 to 130° C. If the reaction is carried out without solvent at about 120° C., the reaction is complete within from $\frac{1}{2}$ to 2 hours. When a solvent is used, heating for from 12 to 24 hours is usually necessary to obtain good yields.

In a variant of the method described above, an aldehyde of the formula



XI

is reacted with a formula III piperazine under catalytic hydrogenation conditions; suitable conditions are those described in the literature for reductive alkylations. The formula XI aldehydes can be obtained by oxidation of the corresponding primary alcohols of formula II (X=OH).

The formula I compounds can also be obtained by reaction of a formula IV 3-(aminoalkyl)-pyrazole with a formula V nitrogen mustard compound.

The 3-(aminoalkyl)-pyrazoles can be obtained from the foregoing formula II 3-(haloalkyl)-pyrazoles by reaction with ammonia or potassium phthalimide; more particularly, the following can be used: 3-aminomethylpyrazole, 3-(2-aminoethyl)-pyrazole, 3-(3-aminopropyl)-pyrazole and 3-(4-aminobutyl)-pyrazole, and the 5-methyl-, 5-ethyl-, 5-*n*-propyl-, 5-iso-propyl- and 5-*n*-butyl- derivatives of these compounds.

As formula V starting compounds, there can be mentioned, more particularly: bis-(2-chloroethyl)-aniline, bis-(2-bromoethyl)-aniline and *N*-phenyl-morpholine and their derivatives which are substituted in the aromatic nucleus similarly to the formula III piperazines mentioned above.

The formula VI nitrogen mustard compounds (prepared, for example, by reaction of the formula II (X=Cl, Br or I) 3-haloalkyl-pyrazoles with diethanolamine or by reaction of the formula IV with amines with ethylene chlorhydrin or with ethylene oxide and subsequent conversion of the hydroxy groups into halogen atoms, for example with thionyl chloride) can be reacted under similar conditions with formula VII amines. Suitable formula VI compounds are, for example: 3-[bis - 2(- chloroethyl) - aminomethyl] pyrazole, 3 - [2 - (bis - (2 - chloroethyl)-amino)ethyl] - pyrazole, 3 - [3 - (bis - (2-chloroethyl) - amino) - propyl] - pyrazole and 3 - [4 - (bis - (2 - chloroethyl) - amino)-butyl] pyrazole and their 5-methyl, 5-ethyl, 5-*n*-propyl, 5-isopropyl and 5-*n*-butyl derivatives, the corresponding bis-(2-bromoethyl)- compounds and 3-(morpholinoalkyl)-pyrazoles (readily obtainable from the 3-(halogenalkyl)-pyrazoles and morpholine). Suitable formula VII compounds are, for example: aniline and its derivatives substituted in the aromatic nucleus by methyl, ethyl, methoxy, trifluoromethyl, fluorine, chlorine, bromine and/or iodine.

As another way of obtaining the formula I

compounds, formula VIII *N'*-atom substituted 3-(2-aminoethylaminoalkyl)-pyrazoles can be reacted, advantageously in the presence of an acid binding agent, with formula IX ethylene dihalides, preferably ethylene chloride or ethylene bromide or similar compounds. To obtain the formula VIII compounds, a formula XI aldehyde is reacted with a substituted ethylene diamine derivative having the formula Ar-NHCH₂CH₂NH₂ to form the corresponding Schiff's base and the latter is catalytically hydrogenated. Suitable formula VIII compounds are, for example: 3-(2-anilinoethylaminomethyl)-pyrazole, 3-[2-(2-anilinoethylamino) - ethyl] - pyrazole, 3 - [3 - (2-anilinoethylamino - propyl) - pyrazole and 3 - [4-(2 - anilinoethylamino) - butyl] - pyrazole, and then derivatives substituted in the aromatic nucleus as hereinbefore described, and the 5-methyl, 5-ethyl, 5-*n*-propyl, 5-iso-propyl and 5-*n*-butyl derivatives of such compounds.

In general, formula IV compounds are reacted with formula V compounds, and formula VI compounds are reacted with formula VII compounds, under the conditions described above for the reaction of formula II with formula III compounds. More vigorous conditions are usually used for the reaction of formula VIII compounds with formula IX compounds; for instance, heating is used, possibly in the presence of a higher boiling inert solvent and of a strong base, such as sodium hydroxide or sodium carbonate, with agitation for from 6 to 8 hours at temperatures of from 120 to 160° C.

If an *N*-substituted morpholine is used as starting material, its hydrochloride is advantageously heated at from 230 to 240° C. for some time together with the hydrochloride of 3-(aminoalkyl)-pyrazole, the water which is evolved in the reaction being removed by distillation.

In addition, a formula X 1,3-dicarbonyl compound can be reacted with hydrazine, the process being carried out in the same way as known methods for forming pyrazoles from β -carbonyl compounds and hydrazines. In general the hydrazine is formed *in situ* by an aqueous or alcoholic solution of its sulphate or hydrochloride being mixed with an equivalent quantity of caustic soda or caustic potash solution. The formula X compound is added to the hydrazine solution in drops, if desired in an inert organic solvent, such as methanol, ethanol, tetrahydrofuran or dioxane and with or without cooling, the reaction being completed either by allowing the reaction mixture to stand or with agitation and/or heating. The reaction is normally carried out at a temperature of from 0° C. to the boiling point of the particular solvent used and takes from a few minutes to 10 hours to complete.

The formula X starting compounds can be obtained, for example, by reaction of end-

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2,4-dione
suitable f
5 example:
tane - 2
-heptane
-hexane
-octane
10 -heptane
and -oct
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position-halogenated 1,3-dicarbonyl compounds, such as 1-bromo- or 1-chloro-pentane-2,4-dione with formula III arylpiperazines. As suitable formula X starting compounds are, for example: 1 - (N' - phenylpiperazino) - pentane - 2,4 - dione, -hexane - 2,4 - dione, -heptane - 2,4 - dione, -octane - 2,4 - dione, -hexane - 3,5 - dione, -heptane - 3,5 - dione, -octane - 3,5 - dione, -nonane - 3,5 - dione, -heptane - 4,6 - dione, -octane - 4,6 - dione and -octane - 5,7 - dione, and their derivatives substituted in the aromatic nucleus as hereinbefore described.

Another way of obtaining a formula I compound is to start from an intermediate which has the same basic structure but which also contains one or more hydrogen-replaceable groups and/or C=C double bonds and/or C≡C triple bonds, the intermediate being treated with a hydrogen-evolving agent.

For instance, chlorine or bromine atoms can be replaced by hydrogen in the aromatic nucleus, in the pyrazole nucleus, or in the alkylene chain by catalytic hydrogenation or by treatment with chemical reducing agents. For example, 5-halogen pyrazoles can be converted into the halogen-free pyrazole compounds by treatment with zinc and hydrochloric acid or with phosphorus and hydrogen iodide. For instance, 5-bromo-3-(N'-phenylpiperazinomethyl)-pyrazole- which can be obtained by reaction of γ-(N'-phenylpiperazino)-acetoacetic acid ethyl ester with hydrazine and reaction of the resulting 3-(N' - phenylpiperazinomethyl) - pyrazolone-(5) with phosphoroxo-bromide- can be reduced in this way to 3-(N'-phenylpiperazinomethyl)-pyrazole.

As another example, 1-benzyl-3-formyl-pyrazoles can be converted with malonic acid in pyridine/piperidine into pyrazolyl-(3)-acrylic acids which can, if desired, be hydrogenated to β-(pyrazolyl-3)-propionic acids; the acid chlorides of such acids can be converted by reaction with formula III 1-substituted piperazines into the corresponding acid amides which (after decomposition of the benzyl group, see hereinafter) can be converted, for example with LiAlH₄, into the corresponding formula I compounds; an extra catalytic hydrogenation must be given in the case of the acrylic acid derivative.

In the preparation of formula I compounds, it is often advantageous to use intermediates having protective groups, removable by reduction, in the 1-position of the pyrazole ring (see above). Thus for instance, the reaction of 1-benzyl-3-(3-aminopropyl)-pyrazole with N,N-bis-(2-chloroethyl)-aniline gives 1-benzyl-3-[3 - (N' - phenyl - piperazino) - propyl]-pyrazole which when catalytically hydrogenated yields 3-[3-(N'-phenyl-piperazino)-propyl]-pyrazole. Another way of removing the benzyl group is to dissolve or suspend the

benzyl compound in liquid ammonia and to add a slight excess of sodium.

Suitable catalysts for effecting catalytic hydrogenation and/or hydrogenolysis are, for example: noble metal, nickel and cobalt catalysts and copper-chromium oxide. The noble metal catalysts can be present on supports, for example palladium on carbon, calcium carbonate or strontium carbonate, or be used as oxide catalysts, such as platinum oxide, or as finely divided metal catalysts. Nickel and cobalt catalysts are conveniently used as Raney metals, and nickel can conveniently be supported on diatomaceous earth or pumice stone. Hydrogenation can be carried out at room temperature and normal pressure or at elevated temperature and/or elevated pressure. Pressures of from 1 to 100 atmospheres and temperatures of from -80 to +150° C. are preferably used; the reaction is conveniently carried out in the presence of a solvent, such as water, methanol, ethanol, isopropanol, tert. butanol, ethyl acetate, tetrahydrofuran or acetic acid. The free bases or the corresponding salts, e.g. the hydrochlorides, can be subjected to hydrogenation. The hydrogenation conditions must be such that the other reducible groups or systems present in the molecule, for instance, the pyrazole ring and the aromatic ring, are not attacked as well. Consequently, in the hydrogenation of C=C double bonds and in the hydrogenolysis of benzyl groups, it is preferable to work at normal pressure and to interrupt hydrogenation when the calculated amount of hydrogen has been absorbed.

Reductions with chemical agents such as those mentioned above can be carried out by methods described in the literature. For instance, reduction with lithium aluminium hydride can be carried out in ether or tetrahydrofuran or di-n-butylether, preferably at boiling point; in many cases, it is advantageous to extract difficultly soluble starting materials continuously with the boiling solvent by the Soxhlet method.

Bromine atoms in the pyrazole nucleus are conveniently replaced by hydrogen by dissolving the pyrazole in concentrated hydrochloric acid, adding a large excess of zinc and heating the mixture to about 100° C. for several hours. Chlorine atoms can be split off reductively, for example by mixing the pyrazole compound with the same quantity of phosphorus, adding about 4 parts by volume of 20% hydriodic acid and heating in a sealed tube at from 170 to 180° C. for about 10 hours. In all these processes care must, of course, be taken to ensure that other groups which may be present do not also react undesirably with the particular reagent used; for instance, hydrogen iodide may split off alkoxy groups.

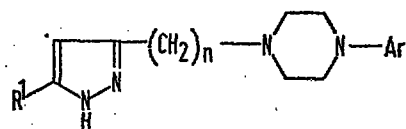
The formula I products obtained by any of the methods described above are isolated from the reaction mixtures by conventional

procedures, such as extraction, and are purified by distillation or crystallisation of the bases or their salts, more particularly the hydrochlorides. Chromatographic methods can also be used for isolation and purification.

Formula I compounds can be salified by conventional procedures to form their acid addition salts; the acids which are used for this reaction are those which yield physiologically acceptable salts. They can be organic and inorganic acids, such as aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or poly-basic carboxylic or sulphonic acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, oxalic acid, malonic acid, lactic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, tartaric acid, malic acid, aminocarboxylic acids, sulfamic acid, benzoic acid, salicylic acid, phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane sulphonic acid, ethane disulphonic acid, β -hydroxyethane sulphonic acid, *p*-toluene sulphonic acid, naphthalene-mono- and -disulphonic acid, sulphuric acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid or phosphoric acids, such as orthophosphoric acid.

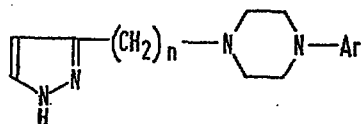
The formula I free bases can, if required, be obtained from their salts by treatment with strong bases, such as sodium or potassium hydroxide or carbonate.

Preferred compounds according to the invention are those of the following formulae and their physiologically acceptable acid addition salts:



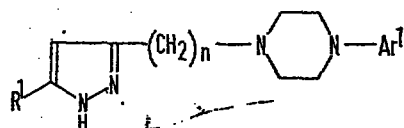
XII

in which *n* and Ar have the above-stated meanings and R¹ is an alkyl group containing 1 to 4 C. atoms;



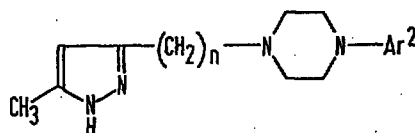
XIII

in which *n* and Ar have the above-stated meanings;



XIV

in which *n* and R¹ have the above-stated meanings and Ar¹ is phenyl, *o*-, *m*- or *p*-tolyl, *o*-, *m*- or *p*-ethylphenyl, *o*-, *m*- or *p*-methoxyphenyl, *o*-, *m*- or *p*-trifluoromethylphenyl, *o*-, *m*- or *p*-fluorophenyl, *o*-, *m*- or *p*-chlorophenyl, *o*-, *m*- or *p*-bromophenyl, or *o*-, *m*- or *p*-iodophenyl;



XV

in which *n* has the above-stated meaning and Ar² is phenyl, *o*-, *m*- or *p*-tolyl, or *o*-, *m*- or *p*-chlorophenyl.

For use in human and veterinary medicine the novel compounds are used in admixture with any suitable inert, physiologically acceptable carrier. Suitable carriers are organic and inorganic substances which are suitable for parenteral or enteral application and which do not react with the novel compounds, such as water, vegetable oils, polyethylene glycols, gelatine, lactose, starch, magnesium stearate, talc, petroleum jelly and cholesterol. For parenteral application, solutions, preferably oily or aqueous solutions, and suspensions, emulsions and implants are used. For enteral application, tablets or dragees which can, if desired, be sterilised or mixed with adjuvants, such as preservatives, stabilisers, wetting agents, osmotic pressure adjusting salts or buffer substances, are suitably used. The compounds according to the invention are preferably formulated in a dosage of from 2 to 100 mg per dosage unit.

In order that the invention may be more fully understood, the following examples are given by way of illustration only:—

EXAMPLE 1

7.2 g of 3-(2-chloroethyl)-5-methyl-pyrazole and 19.6 g of N-(*m*-chlorophenyl)-piperazine were mixed and heated at from 120 to 130° C. for 2 hours. After cooling, the mixture was triturated with cold aqueous ammonia and extracted with benzene. Excess N-(*m*-chlorophenyl)-piperazine is removed from the extraction residue by distillation. The residue is filtered over silica gel (elution agent: acetone: benzene: chloroform: methanol 4:4:2:1) and the crude base thus obtained was converted into the hydrochloride. 8 g of 3-[2-(N'-*m*-chlorophenyl-piperazino)-ethyl]-5-methyl-pyrazole dihydrochloride, m.p. 238—240° C. (from ethanol), were obtained. The trisulphate has m.p. 198—200° C.

The following compounds were obtained similarly: 3-[2 - (N' - phenylpiperazino)-ethyl] - 5 - methyl - pyrazole; dihydrochloride,

m.p. 174—
phenylpiper-
zole; dihyd
3 - [2 - (N'
ethyl] - 5 - m
m.p. 218—
fluoromethyl
methyl - pyr
233° C.; 3
ethyl] - 5 -
dihydrate, 1
p - tolyl -
pyrazole;
226—228°
15 piperazino)
chloride, 1
methoxyph
methyl -
m.p. 250—
20 5 - methyl
chlorophen
methyl-pyr
158—160°
piperazino
25 dihydrochl

14.4
pyrazole
were agi
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the salts
was conc
35 treated i
chloric a
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out and
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40 pyrazole
176° C.

7.2 g
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m.p. 174—176° C; 3-[2 - (N' - o - chlorophenyl)piperazino) - ethyl] - 5 - methyl-pyrazole; dihydrochloride, m.p. 216—218° C.; 3 - [2 - (N' - p - chlorophenyl)piperazino) - ethyl] - 5 - methyl - pyrazole; trihydrochloride, m.p. 218—220° C.; 3 - [2 - (N' - m - trifluoromethylphenyl - piperazino) - ethyl] - 5 - methyl - pyrazole; trihydrochloride, m.p. 231—233° C.; 3 - [2 - (N' - m - tolyl - piperazino) - ethyl] - 5 - methyl - pyrazole; trihydrochloride dihydrate, m.p. 234—236° C.; 3 - [2 - (N' - p - tolyl - piperazino) - ethyl] - 5 - methyl-pyrazole; trihydrochloride dihydrate, m.p. 226—228° C.; 3-[2-(N'-*m*-tert.-butylphenyl-piperazino)-ethyl]-5-methyl-pyrazole; trihydrochloride, m.p. 231—233° C.; 3-[2-(N'-*p*-methoxyphenyl - piperazino) - ethyl] - 5 - methyl - pyrazole; trihydrochloride hydrate, m.p. 250—252° C.; from 3-(3-chloropropyl)-5 - methyl - pyrazole, 3 - [3 - (N' - *m*-chlorophenyl - piperazino) - propyl] - 5 - methyl-pyrazole; trihydrochloride hydrate, m.p. 158—160° C.; 3-[3-N'-*o*-chlorophenyl-piperazino) - propyl] - 5 - methyl - pyrazole; dihydrochloride hydrate, m.p. 152—154° C.

EXAMPLE 2

14.4 g of 3-(2-chloroethyl)-5-methyl-pyrazole and 16.2 g of N-phenyl-piperazine were agitated in 200 ml of butanol in the presence of 15.2 g of anhydrous potassium carbonate at from 100—110° C. for 20 hours. After cooling, the residue was filtered from the salts which separated out and the filtrate was concentrated *in vacuo*. The residue was treated in a little butanol with ethereal hydrochloric acid; after brief heating the solution was filtered from the resins which separated out and was allowed to cool. 10 g of 3-[2-(N'-phenylpiperazino) - ethyl] - 5 - methyl-pyrazole dihydrochloride hydrate, m.p. 174—176° C. (from ethanol), were obtained.

EXAMPLE 3

7.2 g of 3-(2-chloroethyl)-5-methyl pyrazole and 16.2 g of N-phenylpiperazine were boiled in 75 ml of toluene for 12 hours. After cooling, the N-phenyl-piperazine hydrochloride which had crystallised out was removed by suction filtration, the filtrate was concentrated and the residue was purified via the hydrochloride. 9 g of 3-[2-(N'-phenylpiperazino)-ethyl]-5-methyl - pyrazole dihydrochloride hydrate, m.p. 174—176° C. (from ethanol), were obtained.

EXAMPLE 4

25.3 g of *m*-chlorophenyl-bis-(2-chloroethyl)-amine and 42 g of 3-(2-aminoethyl)-5-methyl-pyrazole (obtained by reacting 3-(2-chloroethyl)-5-methyl-pyrazole with potassium phthalimide and then hydrolysing) were boiled in a mixture of 800 ml of acetone and 800 ml of water for 24 hours. The acetone was then removed *in vacuo* and the aqueous mixture was made alkaline with aqueous caustic soda solution and extracted with benzene. The residue from the benzene phase was converted by means of ethereal hydrochloric acid into 3-[2 - (N' - *m* - chlorophenyl - piperazino)-ethyl] - 5 - methyl - pyrazole dihydrochloride, m.p. 238—240° C.

EXAMPLE 5

10 g of [2-(5-methylpyrazolyl-3)-ethyl]-bis-(2-chloroethyl)-amine and 10.6 g of aniline were boiled in a mixture of 300 ml of acetone and 300 ml of water for 24 hours. The mixture was then concentrated, made alkaline with aqueous caustic soda solution and extracted with benzene. After drying and removal of the solvent, 3-[2-(N'-phenylpiperazino)-ethyl]-5-methyl-pyrazole was obtained from the benzene extract; dihydrochloride hydrate, m.p. 174—176° C.

EXAMPLE 6

20.9 g of 3-(3-morpholinopropyl)-5-methyl-pyrazole and 13.7 g of *m*-chloroaniline were dissolved in 20 ml of concentrated hydrochloric acid. The solution was concentrated to dryness *in vacuo* and the residue was heated at 230—240° C. for 4 hours, the water evolved being distilled off. After cooling, the residue was mixed with aqueous caustic soda solution and extracted with benzene. After removal of the solvent, 3 - [3 - (N' - *m* - chlorophenyl-piperazino) - propyl] - 5 - methyl - pyrazole was obtained; trihydrochloride hydrate, m.p. 158—160° C.

EXAMPLE 7

2.2 g of 3-(2-anilinoethylaminomethyl)-pyrazole (obtained by reacting 1-benzyl-3-formyl-pyrazole with N-phenylethylene diamine, hydrogenation of the resulting Schiff's base with platinum oxide in ethanol to form 1 - benzyl - 3 - (2 - anilinoethyl - amino-methyl)-pyrazole and reductive decomposition of the benzyl group with sodium in liquid ammonia) were agitated in 500 ml of boiling xylene in the presence of 2.1 g of ethylene dibromide and 25 g of anhydrous powdered sodium carbonate for 10 hours. After chromatographic working up of the reaction product, 3 - (N' - phenyl - piperazino - methyl)-pyrazole was obtained.

EXAMPLE 8

A solution of 6 g of 1-(N'-phenylpiperazino)-pentane-2,4-dione (obtained by reacting 1-phenylpiperazine with 1-chloropentane-2,4-dione) in 40 ml of ethanol was added dropwise with agitation to a solution of 10 g of hydrazine hydrate in 60 ml of ethanol. The mixture was then heated under reflux for 1 hour, concentrated, aqueous caustic soda solution and benzene were added to the concen-

rated mixture, and the benzene phase was separated. After removal of the benzene by evaporation, 3-(N'-phenylpiperazino-methyl)-5-methyl-pyrazole, m.p. 146—147° C., was obtained. The monohydrochloride hydrate has m.p. 200° C.

EXAMPLE 9

3 g of 3-[2-(N'-p-chlorophenyl-piperazino)-ethyl]-5-methyl-pyrazole were hydrogenated in the presence of 0.5 g of 5% palladium-charcoal catalyst and in 40 ml of methanol at normal pressure and at a temperature of 55° C. until no more hydrogen was absorbed. The mixture was cooled and the catalyst was removed by suction filtration, the solution was concentrated and the residue mixed with ethereal hydrochloric acid. After recrystallisation from ethanol, 2.9 g of 3-[2-(N'-phenyl-piperazino)-ethyl]-5-methyl-pyrazole dihydrochloride hydrate, m.p. 174—176° C., were obtained.

EXAMPLE 10

1 g of sodium was added in small pieces to a fine suspension of 7.1 g of 1-benzyl-3-(N'-phenyl-piperazinomethyl)-pyrazole in 65 ml of liquid ammonia. 3 g of ammonium chloride were added and the ammonia was evaporated. The residue was mixed with water and extracted with chloroform. The chloroform residue was recrystallised from ether. 3-(N'-phenyl-piperazinomethyl)-pyrazole was obtained.

The starting material was prepared as follows:

a) 18.8 g of 1-benzyl-3-hydroxymethyl-pyrazole were dissolved in 50 ml of chloroform and the solution was added portionwise to 15 ml of thionyl chloride. The mixture was boiled for 10 minutes and then concentrated. The residue was mixed with 37 g of N-phenyl-piperazine and heated at 120—130° C. for 1 hour. After cooling, the mixture was triturated with aqueous ammonia and extracted with benzene. Excess N-phenylpiperazine was removed from the extraction residue. The base remaining was purified via the hydrochloride. 1-Benzyl-3-(N'-phenyl-piperazino-methyl)-pyrazole was obtained.

b) 22 g of crude 1-benzyl-pyrazol-3-yl carboxylic acid chloride in 100 ml of absolute ether were added dropwise, with agitation and cooling, to a solution of 16.2 g of N-phenyl-piperazine and 11 g of triethylamine in 500 ml of absolute ether. Upon completion of the reaction mixture was shaken thoroughly with water and, after addition of benzene, the organic phase was separated off, dried and concentrated. The acid amide was dried and dissolved in 200 ml of absolute tetrahydrofuran and the solution was added dropwise to a suspension of 5 g of lithium aluminium hydride in 250 ml of absolute ether with agitation and white pure nitrogen was passed through the reaction flask. The reaction mixture

was boiled for 20 hours. After conventional processing and chromatographic purification, 1-benzyl-3-(N'-phenyl-piperazino-methyl)-pyrazole was obtained.

EXAMPLE 11

In the same manner as in Example 8, 1-benzyl-3-[4-(N'-phenyl-piperazino)-butyl]-5-methyl-pyrazole was decomposed with sodium in liquid ammonia to form 3-[4-(N'-phenyl-piperazino)-butyl]-5-methyl-pyrazole.

The starting material was obtained as follows:

A Grignard compound was prepared in 100 ml of absolute ether from 11.9 g of N-phenyl-N'-(3-chloropropyl)-piperazine and 1.3 g of magnesium. To the Grignard compound there was added, dropwise, a solution of 9.3 g of 1-benzyl-3-formyl-5-methyl-pyrazole in 100 ml of absolute ether. After agitation for 1 hour, the mixture was decomposed by an addition of ice and dilute hydrochloric acid, then made alkaline with aqueous ammonia, and the ethereal solution was separated, dried and concentrated. The crude residue, consisting of (1-benzyl-5-methyl-pyrazolyl-3)-[3-(N'-phenyl-piperazino)-propyl]-carbinol, together with a little 1-(1-benzyl-5-methyl-pyrazolyl-3)-4-(N'-phenyl-piperazino)-butene, was hydrogenated in ethanol in the presence of 5% palladium-charcoal at normal pressure. After conventional working up, 1-benzyl-3-[4-(N'-phenyl-piperazino)-butyl]-5-methyl-pyrazole was obtained.

EXAMPLE 12

7.2 g of 3-(N'-o-chlorophenyl-piperazino-carbonyl)-5-methyl-pyrazole in 75 ml of absolute tetrahydrofuran were added dropwise to a suspension of 4.5 g of lithium aluminium hydride in 150 ml of absolute tetrahydrofuran. The mixture was boiled for 20 hours. After the addition of 70 ml of ethyl acetate, 4.5 ml of water, 45 ml of 15% aqueous caustic soda solution and a further 13.5 ml of water, the inorganic precipitate was removed by suction filtration and washed with ether. The filtrate was concentrated and 6.5 g of oily 3-(N'-o-chlorophenyl-piperazinomethyl)-5-methyl-pyrazole were obtained. The dihydrochloride has m.p. 225—227° C.

The starting material was obtained as follows:

4.2 g of 5-methylpyrazole-3-carboxylic acid-anhydride (prepared from 5-methylpyrazole-3-carboxylic acid by treatment with thionyl chloride) and 8 g of N-(o-chlorophenyl)-piperazine were heated at 90—100° C. for 1 hour. The melt set during heating. The mixture was then mixed with ethanol, the mixture was boiled, then cooled, the residue was separated by suction filtration and washed again in

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90

95

100

105

110

115

120

125

cold ethanol. 7.2 g of 3-(N'-o-chlorophenyl-piperazino-carbonyl)-5-methyl-pyrazole, m.p. 194—197° C., were obtained.

The following compounds were obtained similarly: from 3-(N'-m-chlorophenyl-piperazino-carbonyl)-5-methyl-pyrazole (m.p. 145—147° C.): 3-(N'-m-chlorophenyl-piperazino-methyl)-5-methyl-pyrazole; trihydrochloride ethanol solvate, m.p. 190—194° C. (decomp.);

from 3-(N'-p-chlorophenyl-piperazino-carbonyl)-5-methyl-pyrazole (m.p. 152—154° C.): 3-(N'-p-chlorophenyl-piperazino-methyl)-5-methyl-pyrazole, m.p. 138—140° C.; dihydrochloride, m.p. 193—195° C.;

from 3-(N'-p-tolyl-piperazino-carbonyl)-5-methyl-pyrazole (m.p. 175—176° C.); 3-(N'-p-tolyl-piperazino-methyl)-5-methyl-pyrazole, m.p. 140—142° C.; trihydrochloride, m.p. 195—197° C.;

from 3-(N'-p-methoxyphenyl-piperazino-carbonyl)-5-methyl-pyrazole; 3-(N'-(p-methoxyphenyl)-piperazino-methyl)-5-methyl-pyrazole, m.p. 156—157° C.; trihydrochloride, m.p. 218—219° C.;

from 3-(N'-m-trifluoromethyl-phenyl-piperazino-carbonyl)-5-methyl-pyrazole (m.p. 198—200° C.); 3-(N'-(m-trifluoromethyl-phenyl)-piperazino-methyl)-5-methyl-pyrazole; trihydrochloride hydrate, m.p. 159—162° C.;

from 3-(N'-m-tolyl-piperazino-carbonyl)-5-methyl-pyrazole (m.p. 130—132° C.); 3-(N'-(m-tolyl)-piperazino-methyl)-5-methyl-pyrazole; dihydrochloride, m.p. 214—217° C.

EXAMPLE 13

The following compounds can be obtained by the method described in Example 1 from the corresponding

3-(ω-chloroalkyl)-pyrazoles and N-aryl-piperazines:

3-[2-(N'-phenyl-piperazino)-ethyl]-pyrazole,

3-[3-(N'-phenyl-piperazino)-propyl]-pyrazole,

3-[4-(N'-phenyl-piperazino)-butyl]-pyrazole, and the following 5-methyl-pyrazoles:

3-[2-(N'-o-tolyl-piperazino)-ethyl]-3-[2-(N'-o-tert.butylphenyl-piperazino)-ethyl]-

3-[2-(N'-p-tert.butylphenyl-piperazino)-ethyl]-

3-[2-(N'-o-methoxyphenyl-piperazino)-ethyl]-

3-[2-(N'-m-methoxyphenyl-piperazino)-ethyl]-

3-[2-(N'-o-trifluoromethylphenyl-piperazino)-ethyl]-

3-[2-(N'-p-trifluoromethylphenyl-piperazino)-ethyl]-

3-[2-(N'-o-fluorophenyl-piperazino)-ethyl]-

3-[2-(N'-m-fluorophenyl-piperazino)-ethyl]-

3-[2-(N'-p-fluorophenyl-piperazino)-ethyl]-

3-[2-(N'-o-bromophenyl-piperazino)-ethyl]-

3-[2-(N'-m-bromophenyl-piperazino)-ethyl]-

3-[2-(N'-p-bromophenyl-piperazino)-ethyl]-

3-[2-(N'-o-iodophenyl-piperazino)-ethyl]-

3-[2-(N'-m-iodophenyl-piperazino)-ethyl]-

3-[2-(N'-p-iodophenyl-piperazino)-ethyl]-

3-[3-(N'-phenyl-piperazino)-propyl]-

3-[3-(N'-p-chlorophenyl-piperazino)-propyl]-

3-[4-(N'-phenyl-piperazino)-butyl]-

3-[4-(N'-o-chlorophenyl-piperazino)-butyl]-

3-[4-(N'-m-chlorophenyl-piperazino)-butyl]-

3-[4-(N'-p-chlorophenyl-piperazino)-butyl]- and the following 5-ethyl-pyrazoles:

3-(N'-phenylpiperazino-methyl)-

3-(N'-o-chlorophenyl-piperazino-methyl)-

3-(N'-m-chlorophenyl-piperazino-methyl)-

3-(N'-p-chlorophenyl-piperazino-methyl)-

3-[2-(N'-phenyl-piperazino)-ethyl]-

3-[2-(N'-o-chlorophenyl-piperazino)-ethyl]-

3-[2-(N'-p-chlorophenyl-piperazino)-ethyl]-

3-[3-(N'-phenyl-piperazino)-propyl]-

3-[3-(N'-o-chlorophenyl-piperazino)-propyl]-

3-[3-(N'-m-chlorophenyl-piperazino)-propyl]-

3-[3-(N'-p-chlorophenyl-piperazino)-propyl]-

3-[4-(N'-phenyl-piperazino)-butyl]-

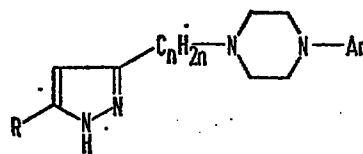
3-[4-(N'-o-chlorophenyl-piperazino)-butyl]-

3-[4-(N'-m-chlorophenyl-piperazino)-butyl]-

3-[4-(N'-p-chlorophenyl-piperazino)-butyl]-

WHAT WE CLAIM IS:—

1. A 3-(piperazinoalkyl)-pyrazole of the formula:



I

cold ethanol. 7.2 g of 3-(N'-*o*-chlorophenyl-piperazino-carbonyl)-5-methyl-pyrazole, m.p. 194—197° C., were obtained.

The following compounds were obtained similarly: from 3-(N'-*m*-chlorophenyl-piperazino-carbonyl)-5-methyl-pyrazole (m.p. 145—147° C.): 3-(N'-*m*-chlorophenyl-piperazino-methyl)-5-methyl-pyrazole; trihydrochloride ethanol solvate, m.p. 190—194° C. (decomp.);

from 3-(N'-*p*-chlorophenyl-piperazino-carbonyl)-5-methyl-pyrazole (m.p. 152—154° C.): 3-(N'-*p*-chlorophenyl-piperazino-methyl)-5-methyl-pyrazole, m.p. 138—140° C.; dihydrochloride, m.p. 193—195° C.;

from 3-(N'-*p*-tolyl-piperazino-carbonyl)-5-methyl-pyrazole (m.p. 175—176° C.): 3-(N'-*p*-tolyl-piperazino-methyl)-5-methyl-pyrazole, m.p. 140—142° C.; trihydrochloride, m.p. 195—197° C.;

from 3-(N'-*p*-methoxyphenyl-piperazino-carbonyl)-5-methyl-pyrazole; 3-(N'-(*p*-methoxyphenyl)-piperazino-methyl)-5-methyl-pyrazole, m.p. 156—157° C.; trihydrochloride, m.p. 218—219° C.;

from 3-(N'-*m*-trifluoromethyl-phenyl-piperazino-carbonyl)-5-methyl-pyrazole (m.p. 198—200° C.); 3-(N'-(*m*-trifluoromethyl-phenyl)-piperazino-methyl)-5-methyl-pyrazole; trihydrochloride hydrate, m.p. 159—162° C.;

from 3-(N'-*m*-tolyl-piperazino-carbonyl)-5-methyl-pyrazole (m.p. 130—132° C.); 3-(N'-(*m*-tolyl)-piperazino-methyl)-5-methyl-pyrazole; dihydrochloride, m.p. 214—217° C.

EXAMPLE 13

The following compounds can be obtained by the method described in Example 1 from the corresponding

3-(ω -chloroalkyl)-pyrazoles and N-aryl-piperazines:

3-[2-(N'-phenyl-piperazino)-ethyl]-pyrazole,

3-[3-(N'-phenyl-piperazino)-propyl]-pyrazole,

3-[4-(N'-phenyl-piperazino)-butyl]-pyrazole, and the following 5-methyl-pyrazoles:

3-[2-(N'-*o*-tolyl-piperazino)-ethyl]-pyrazole, 3-[2-(N'-*o*-tert.butylphenyl-piperazino)-ethyl]-pyrazole,

3-[2-(N'-*p*-tert.butylphenyl-piperazino)-ethyl]-pyrazole,

3-[2-(N'-*o*-methoxyphenyl-piperazino)-ethyl]-pyrazole,

3-[2-(N'-*m*-methoxyphenyl-piperazino)-ethyl]-pyrazole,

3-[2-(N'-*o*-trifluoromethylphenyl-piperazino)-ethyl]-pyrazole,

3-[2-(N'-*p*-trifluoromethylphenyl-piperazino)-ethyl]-pyrazole.

3-[2-(N'-*o*-fluorophenyl-piperazino)-ethyl]-pyrazole,

3-[2-(N'-*m*-fluorophenyl-piperazino)-ethyl]-pyrazole,

3-[2-(N'-*p*-fluorophenyl-piperazino)-ethyl]-pyrazole,

3-[2-(N'-*o*-bromophenyl-piperazino)-ethyl]-pyrazole,

3-[2-(N'-*m*-bromophenyl-piperazino)-ethyl]-pyrazole,

3-[2-(N'-*p*-bromophenyl-piperazino)-ethyl]-pyrazole,

3-[2-(N'-*o*-iodophenyl-piperazino)-ethyl]-pyrazole,

3-[2-(N'-*m*-iodophenyl-piperazino)-ethyl]-pyrazole,

3-[2-(N'-*p*-iodophenyl-piperazino)-ethyl]-pyrazole,

3-[3-(N'-phenyl-piperazino)-propyl]-pyrazole,

3-[3-(N'-*p*-chlorophenyl-piperazino)-propyl]-pyrazole,

3-[4-(N'-phenyl-piperazino)-butyl]-pyrazole,

3-[4-(N'-*o*-chlorophenyl-piperazino)-butyl]-pyrazole,

3-[4-(N'-*m*-chlorophenyl-piperazino)-butyl]-pyrazole,

3-[4-(N'-*p*-chlorophenyl-piperazino)-butyl]-pyrazole,

3-(N'-phenyl-piperazino)-ethylpyrazole, and the following 5-ethyl-pyrazoles:

3-(N'-phenyl-piperazino-methyl)-pyrazole,

3-(N'-*o*-chlorophenyl-piperazino-methyl)-pyrazole,

3-(N'-*m*-chlorophenyl-piperazino-methyl)-pyrazole,

3-(N'-*p*-chlorophenyl-piperazino-methyl)-pyrazole,

3-[2-(N'-phenyl-piperazino)-ethyl]-pyrazole,

3-[2-(N'-*o*-chlorophenyl-piperazino)-ethyl]-pyrazole,

3-[2-(N'-*p*-chlorophenyl-piperazino)-ethyl]-pyrazole,

3-[3-(N'-phenyl-piperazino)-propyl]-pyrazole,

3-[3-(N'-*o*-chlorophenyl-piperazino)-propyl]-pyrazole,

3-[3-(N'-*m*-chlorophenyl-piperazino)-propyl]-pyrazole,

3-[3-(N'-*p*-chlorophenyl-piperazino)-propyl]-pyrazole,

3-[4-(N'-phenyl-piperazino)-butyl]-pyrazole,

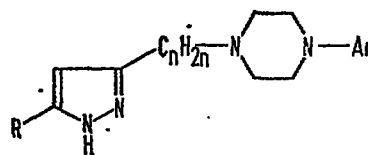
3-[4-(N'-*o*-chlorophenyl-piperazino)-butyl]-pyrazole,

3-[4-(N'-*m*-chlorophenyl-piperazino)-butyl]-pyrazole,

3-[4-(N'-*p*-chlorophenyl-piperazino)-butyl]-pyrazole.

WHAT WE CLAIM IS:—

1. A 3-(piperazinoalkyl)-pyrazole of the formula:



I





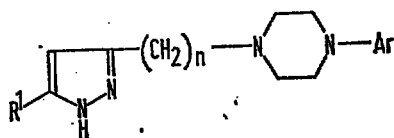
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1,124,710

in which R is H or an alkyl group having from 1 to 4 carbon atoms, Ar is a phenyl group or a phenyl group substituted with one or more alkyl, alkoxy or trifluoromethyl groups or halogen atoms, said alkyl and alkoxy groups having from 1 to 4 carbon atoms, and n is an integer from 1 to 4.

2. A physiologically acceptable acid addition salt of a compound as claimed in claim 1.

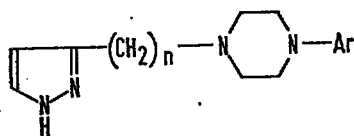
10 3. 3-(Piperazinoalkyl)-pyrazoles of the formula:



XII

15 in which n and Ar have the meanings specified in claim 1 and R^1 is an alkyl group having 1 to 4 carbon atoms.

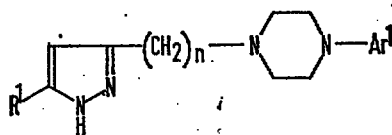
4. 3-(Piperazinoalkyl)-pyrazoles of the formula:



XIII

20 in which n and Ar have the meanings specified in claim 1.

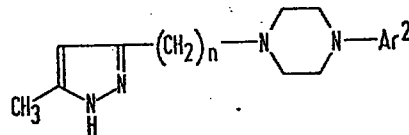
5. 3-(Piperazinoalkyl)-pyrazoles of the formula:



XIV

25 in which n has the meaning specified in claim 1, R^1 has the meaning specified in claim 3, and Ar^1 is phenyl, *o*-, *m*- or *p*-tolyl, *o*-, *m*- or *p*-ethylphenyl, *o*-, *m*- or *p*-methoxyphenyl, *o*-, *m*- or *p*-trifluoromethylphenyl, *o*-, *m*- or *p*-fluorophenyl, *o*-, *m*- or *p*-chlorophenyl, *o*-, *m*- or *p*-bromophenyl, or *o*-, *m*- or *p*-iodophenyl.

30 6. 3-(Piperazinoalkyl)-pyrazoles of the formula:



XV

35 in which n has the meaning specified in claim 1 and Ar^2 is phenyl, *o*-, *m*- or *p*-tolyl, or *o*-, *m*- or *p*-chlorophenyl.

7. 3-[2-(N' -*m*-Tolyl-piperazino)-ethyl]-5-methyl-pyrazole.

8. 3-[2-(N' -*m*-Chlorophenyl-piperazino)-ethyl]-5-methyl-pyrazole.

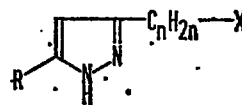
9. A physiologically acceptable acid addition salt of a compound claimed in any of claims 3 to 8.

10. The compounds according to claim 1 or 2 hereinbefore specifically described.

11. A pharmaceutical composition comprising one or more compounds as claimed in any of claims 1 to 10 and an inert, physiologically acceptable carrier.

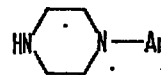
12. A pharmaceutical composition according to claim 1 in dosage unit form, each dosage unit containing from 2 to 100 mg of said compound(s).

13. A process for the preparation of a 3-(piperazinoalkyl)-pyrazole of the formula specified in claim 1, which comprises reacting a compound of the formula



II

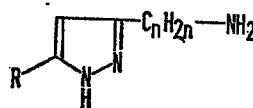
in which R and n have the meanings specified in claim 1 and X is Cl, Br, I, a hydroxy group or a reactive esterified hydroxy group, with a compound of the formula:



III

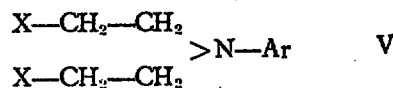
in which Ar has the meaning specified in claim 1.

14. A process for the preparation of a 3-(piperazinoalkyl)-pyrazole of the formula specified in claim 1, which comprises reacting a compound of the formula:



IV

in which R and n have the meanings specified in claim 1, with a compound of the formula:



in which claim 1 or a reactive two X atoms.

15. A (piperazinoalkyl)-pyrazole specified in claim 1.

10

in which claim 1 or a reactive two X oxygen atoms specified in claim 1.

20 A (piperazinoalkyl)-pyrazole specified in claim 1.

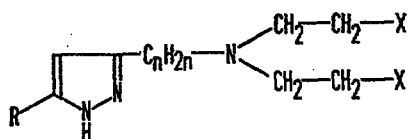
25 in which the formula specified in claim 1.

65

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in which Ar has the meaning specified in claim 1 and X is Cl, Br, I, a hydroxy group or a reactive esterified hydroxy group, or the two X substituents together designate an oxygen atom.

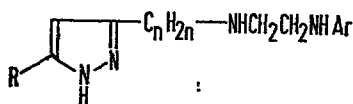
15. A process for the preparation of a 3-(piperazinoalkyl)-pyrazole of the formula specified in claim 1, which comprises reacting a compound of the formula:



VI

in which R and n have the meanings specified in claim 1 and X is Cl, Br, I, a hydroxy group or a reactive esterified hydroxy group, or the two X substituents together designate an oxygen atom, with a compound of the formula H_2N-Ar (VII), in which Ar has the meaning specified in claim 1.

16. A process for the preparation of a 3-(piperazinoalkyl)-pyrazole of the formula specified in claim 1, which comprises reacting a compound of the formula:



VIII

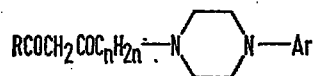
in which R, n and Ar have the meanings specified in claim 1, with a compound of the formula:



IX

in which X is Cl, Br, I, a hydroxy group or a reactive esterified hydroxy group.

17. A process for the preparation of a 3-(piperazinoalkyl)-pyrazole of the formula specified in claim 1, which comprises reacting a compound of the formula:



X

in which R, n and Ar have the meanings specified in claim 1, with hydrazine.

18. A process for the preparation of a 3-(piperazinoalkyl)-pyrazole of the formula specified in claim 1, which comprises reducing a compound of the formula specified in claim 1 but which additionally contains one or more hydrogen-replaceable groups and/or C—C multiple bonds with a hydrogen evolving agent.

19. A process according to any of claims 13 to 18, in which the free base of the formula specified in claim 1 obtained is converted into a physiologically acceptable acid addition salt thereof by treatment with an acid.

20. A process according to any of claims 13 to 18, in which the acid addition salt of a compound of the formula specified in claim 1 obtained is treated to liberate the free base therefrom.

21. A process for the preparation of a 3-(piperazinoalkyl)-pyrazole of the formula specified in claim 1 substantially as herein described in any of the Examples.

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