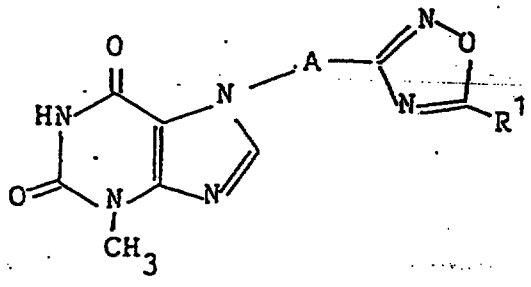
The invention relates to novel oxadiazolylalkylpurine derivatives, processes for their preparation and pharmaceutical agents containing these compounds.

The oxadiazolylalkylpurine derivatives of the invention have the general formula I,



(I),

wherein:
A denotes C_{1-4} alkylene, and
R^1 denotes C_{1-6} alkyl, hydroxyalkyl, haloalkyl, carboxyalkyl, C_{5-6} cycloalkyl, aminoalkyl of the general formula $-(CH_2)_n-NR^2R^3$, wherein
n denotes 1, 2 or 3, and
R^2 and R^3 each denote hydrogen or C_{1-4} alkyl, or, together with the nitrogen atom to which they are bound, form a 5-membered or 6-membered heterocyclic ring optionally containing a second nitrogen atom or an oxygen atom, or
R^1 denotes phenyl, hydroxyphenyl, carboxyphenyl, benzyl or dimethoxybenzyl.

The invention also includes the salts of the compounds of formula I, in particular the pharmaceutically suitable salts.

The alkyl groups may be straight-chain or branched. The dimethoxybenzyl group is advantageously 3,4-dimethoxybenzyl.

The salts of the compounds of the general formula I may be acid addition salts formed using inorganic acids (for example hydrochloric acid, sulphuric acid, phosphoric acid) or organic acids, such as carboxylic acids or sulphonic acids (such as acetic acid, tartaric acid, maleic acid, lactic acid, citric acid, ascorbic acid, benzoic acid, hydroxybenzoylbenzoic acid, nicotinic acid, methanesulphonic acid, toluenesulphonic acid and the like), or salts formed using bases, such as alkali metals or alkaline earth metals (for example sodium, calcium, magnesium and the like), or complex salts (for example salts formed with ethylenediamine).

The compounds of the general formula I are suitable primarily as cough-relieving agents in diseases of the respiratory organs.

Naturally occurring substances and their derivatives have been used for a long time in diseases of the respiratory organs for treatment and particularly for relieving coughing. Compounds having a morphine structure are particularly widely used for this purpose; the most well-known cough-relieving agent is codeine. However, these substances acting non-specifically on the central nervous system have several undesirable side-effects. One dangerous side-effect of codeine is the respiratory-blocking effect. Attempts have therefore been made in recent decades to provide cough-relieving agents of this type which have few side-effects and may not even occur at therapeutic doses.

Certain compounds having a 1,2,4-oxadiazole ring belong to the group of above-mentioned cough-relieving agents (for example oxolamine and prenoxdiazine).

Furthermore, agents containing a 1,2,4-oxadiazole ring, in which the 1,2,4-oxadiazole ring is linked to the nitrogen atom in the 7-position of the theophylline containing a purine structure by means of an alkyl chain, are known from Hungarian patent 186 607 and from European application 89 028. These compounds show significant respiratory-improving and broncholytic effects in addition to the cough-relieving effect, and have advantageous toxicity.

The object of the invention is to indicate novel compounds and their preparation and corresponding pharmaceutical agents, in which the above therapeutically favourable effects are increased further.

For this purpose, preparation and properties of purine derivatives substituted by a 1,2,4-oxadiazole ring have been investigated systematically.

It has thus been found, surprisingly, that the novel compounds of the general formula I have an extremely intense cough-relieving effect.

During the investigation of the relationships between chemical structure and biological effect, the unexpected conclusion was reached that for the compounds of the general formula I the purine ring potentises the cough-relieving effect of the 1,2,4-oxadiazole structure more intensely than is the case for analogous theophyllinyl compounds methyl-substituted in the 1-position, as are known from Hungarian patent 186 607 and European application 89 028.

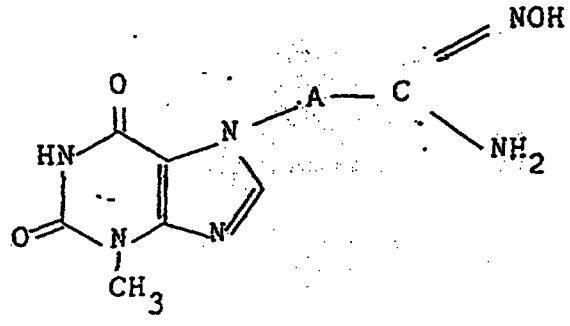
The novel compounds of the invention of the general formula I differ accordingly from the theophyllinyl-oxadiazole derivatives described in Hungarian patent

186 607 and European application 89 028 due to the lack of the methyl group at the nitrogen in the 1-position of the purine structure.

This effect is therefore surprising because it is well known that theophylline is superior to theobromine with regard to its biological activity.

The fact that the 1,2,4-oxadiazole ring plays a fundamental part in the unexpectedly intense and most excellent cough-relieving effect, is proved by the comparative tests carried out using the compounds of the general formula II.

The compounds of the general formula II,



(II),

in which the purine structure is identical to that of the compounds of the general formula I, but the 1,2,4-oxadiazole ring is not closed, namely show virtually no anti-tussive activity.

The cough-relieving effect of the compounds of the invention of formula I is so intense that these compounds are many times superior not only to the known cough-relieving 1,2,4-oxadiazole derivatives mentioned above, but also codeine.

The therapeutic advantage of the compounds of the invention is also accompanied by very favourable toxicity.

Furthermore, it should be emphasised that on the basis of tests carried out on rats and rabbits, the compounds of the general formula I - in contrast to cough-relieving agents having a morphine structure - show no respiratory-blocking effect, indeed they even exert a favourable bronchopulmonary effect.

For the purposes of proof and comparison, results obtained using a test compound of the invention (3,7-dihydro-3-methyl-7-[(5-methyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione (simplest representative of the compounds of the general formula I), two comparative compounds having a 1,2,4-oxadiazole structure, two comparative compounds having morphine structure (codeine and dextromethorphan) and using a starting material of the general formula II (2-(3-methylxanthin-7-yl)-acetamidoxime) are compiled in Table I.

The cough-relieving effect exerted on coughing induced by a 15 % strength citric acid spray was determined 1 hour after peroral administration of the test compound to guinea pigs; the ED_{50} values (mg/kg) obtained are shown in Table I (method: Arzneimittel-Forschung [Medicament Research] 617-621 (1966)).

It can be seen from the results in Table I that for oral administration, the test compound of the general formula I (compound 1) is considerably superior to the test compounds 2-4 and 6 used as comparative compounds as regards the absolute strength of the cough-relieving effect. The xanthinylamidoxime derivative (compound 5) has virtually no cough-relieving activity.

Table I

Compound No.	Chemical notation	Cough-relieving effect (ED_{50}, mg/kg)
1	3,7-dihydro-3-methyl-7-[(5-methyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione	8.5
2 (Comparative compound)	3,7-dihydro-1,3-dimethyl-7-[(5-methyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione	111.2
3 (Comparative compound)	3-(2,2-diphenylethyl)-5-(2-piperidinoethyl)-1,2,4-oxadiazole.HCl (Prenoxdiazine.HCl)	60.5
4 (Comparative compound)	Codeine.HCl	65.7
5	2-(3-methylxanthin-7-yl)-acetamidoxime	no effect at a dose of 50 mg/kg p.o.
6 (Comparative compound)	Dextromethorphan	29.0

As can be seen from Table II, compound 1 of the invention also exerts a long-lasting cough-relieving effect for oral administration (experimental procedure same as for Table I).

Table II

Time between treatment and test (h)	ID_{50} (mg/kg)
0.5	7.5
1.0	8.5
2.0	14.4
4.0	13.8
8.0	32.6

The acute toxicity (i.p.) of compounds 1, 2 and 4 (Table I) determined on rats is shown in Table III.

Table III

Compound No.	Toxicity (LD_{50}, mg/kg)
1	700.0
2 (Comparative compound)	529.7
4 (Comparative compound)	72.4

Compound 1 (3,7-dihydro-3-methyl-7-[(5-methyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione) has a very intense cough-relieving effect not only for oral administration, but also for intravenous administration. It reduces coughing induced by mechanical stimulation of tracheal bifurcation as a function of dose (administered doses from 0.5 to 8.0 mg/kg i.v.) on hares anaesthetised using Nembutal. 2 minutes after intravenous administration, the ED_{50} value is 2.24 (1.85

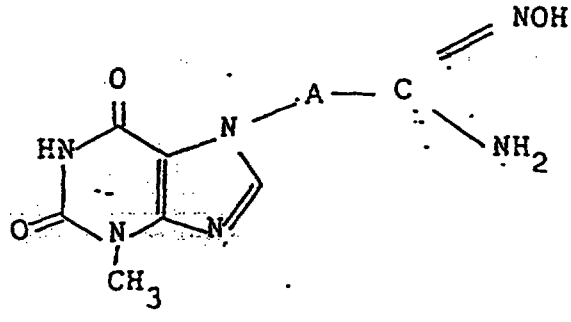
to 2.72) mg/kg, calculated according to Lichfield-Wilcoxon.

In the same test, the comparative compounds codeine and dextromorphan show the same or a somewhat lower effect. Even if the i.p. toxicity data are taken into account, the therapeutic index of compound 1 in this test is ten times more favourable than the therapeutic index of the comparative compounds.

The other compounds falling under the general formula I show a similarly intense cough-relieving effect as for compound 1 in Table I.

The invention also relates to processes for preparing the compounds of the general formula I and their salts, which are characterised in that

a) an amidoxime of the general formula II



(II),

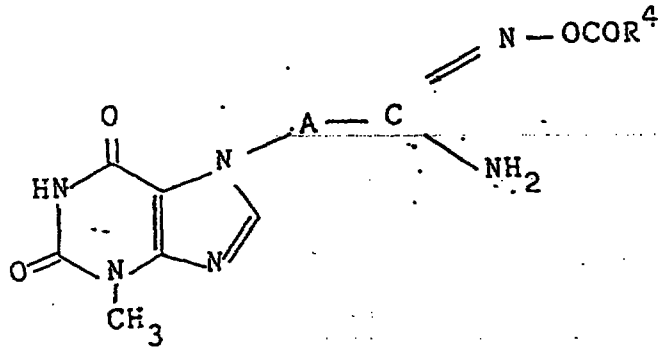
wherein A has the above meaning,

is reacted with a carboxylic acid of the general formula III,

$$R^4\text{-}COOH \qquad (III),$$

wherein R^4 has the meaning of R^1 or denotes a group which can be converted to the group R^1, or a reactive derivative thereof, and if required the group R^4 is converted to a group R^1, or

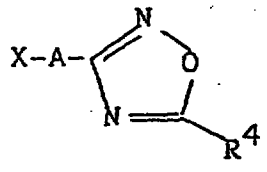
b) an amidoxime of the general formula II, wherein A has the above meaning, is reacted with a carboxylic acid of the general formula III, wherein R^4 has the above meaning, or a reactive derivative thereof, the compound of the general formula IV formed



(IV),

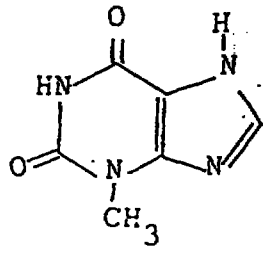
wherein A and R^4 have the above meaning, is cyclised after or without isolation by cleaving water, and if required the group R^4 is converted to a group R^1, or

c) an oxadiazole derivative of the general formula V



(V),

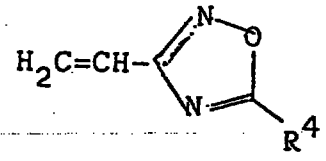
wherein R^4 and A have the above meaning and X denotes halogen or a sulphonate group,
is reacted with 3-methylxanthine of the formula VI



(VI)

or the sodium or potassium salt thereof in the presence of a basic catalyst, and if required the group R^4 is converted to a group R^1.

A process d) of the invention for preparing compounds of the formula I, wherein A denotes the group $-(CH_2)_2-$ and R^1 has the above meaning, is characterised in that an olefin of the general formula VII,



(VII),

wherein R^4 has the above meaning,
is reacted with 3-methylxanthine of the formula VI in the presence of a basic catalyst, and if required the group R^4 is converted to a group R^1,

and if required the compound of the general formula I thus obtained is converted to a particularly therapeutically suitable salt.

According to an advantageous embodiment of process variant a), an amidoxime of the general formula II is reacted with an ester of the general formula VIII,

$$R^4CO_2R^5 \qquad \text{(VIII)},$$

wherein R^4 has the above meaning and R^5 denotes alkyl, preferably methyl or ethyl,

in the presence of a base, preferably an alkali metal or alkaline earth metal hydroxide, carbonate or alcoholate, and in particular of sodium methylate or sodium ethylate, using a polar or apolar organic solvent and/or diluent with heating, preferably at 50 to 150°C, and in particular at the boiling point of the solvent and/or diluent. Suitable organic solvents and/or diluents are in

particular alcohols containing 1 to 4 carbon atoms, N-alkyl acid amides, such as dimethylformamide and aromatic hydrocarbons, such as benzene and chlorobenzene, and advantageously toluene or xylene.

When using apolar solvents it is advantageous to remove the water formed and the alcohol by azeotropic distillation.

According to a further advantageous embodiment of process variant a), an amidoxime of the general formula II is heated with a carboxylic acid of the general formula III

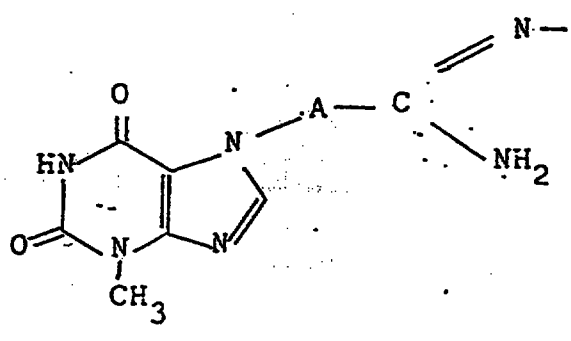
$$R^4\text{-}CO_2H$$

and/or an acid anhydride corresponding to the carboxylic acid of the formula III in the presence of an organic solvent. Aromatic hydrocarbons may preferably be used as organic solvents. It is particularly advantageous to use as solvent the carboxylic acid and/or the corresponding anhydride serving as acylating agent and cyclisation agent. Acylation and ring closure may be carried out at 50 to 150°C and in particular at a temperature of 90 to 110°C.

In process variant a) the reaction time is between half an hour and 24 hours depending on the reactants and solvents used and the reaction temperature.

According to process variant b), acylation is advantageously carried out using an acid anhydride of the general formula $(R^4CO)_2O$ or an acid halide of the general formula R^4COX, wherein R^4 has the above meaning and X denotes halogen, and in particular using the corresponding acid chloride in the presence of an organic solvent and/or diluent. Acetone, pyridine, benzene,

dimethylformamide or - in the case of anhydrides - excess anhydride, dialkyl ethers containing 2 to 4 carbon atoms, dioxane and/or halogenated hydrocarbons, preferably dichloromethane or chloroform, may be advantageously used as reaction medium. If acid halides are used as acylating agents, it is advantageous to employ inorganic or organic acid binders. Inorganic compounds, such as alkali metal carbonates and alkaline earth metal carbonates, for example sodium, potassium and calcium carbonate, hydrogen carbonates, such as sodium hydrogen carbonate, and organic compounds, such as tertiary amines, advantageously pyridine and triethylamine, are suitable for this purpose. If acylating agents are used which contain a basic group R^4, the compound formed of the general formula IV



(IV)

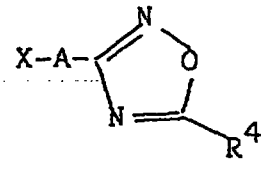
may serve as acid binder.

In process variant b), the formation of the 1,2,4-oxadiazole ring is carried out by pyrolysis in the presence of polar organic solvents and/or water, or apolar solvents as solvents and/or diluents, or in the absence of a solvent.

Ring closure for the compound of the general formula IV is preferably carried out at an optimum pH value of 6 to 8, which is preferably set with the aid of inorganic or organic substances, advantageously using sodium carbonate or triethylamine. The use of a Britton-Robinson buffer has proved to be particularly advantageous. Ring closure

of water-soluble compounds of the general formula IV can be advantageously carried out in water at pH 7.

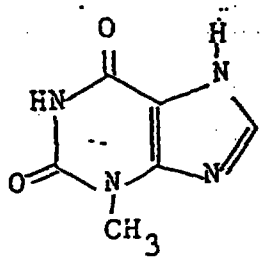
According to process variant c), a compound of the general formula V



(V)

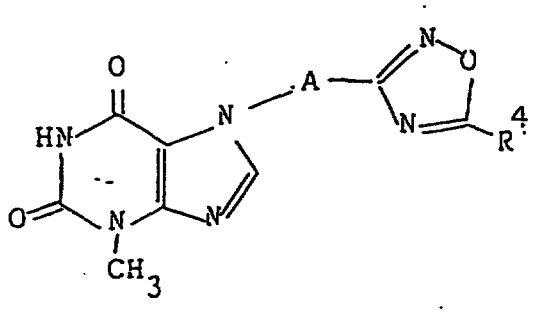
with R^4 and X as defined above

is reacted with 3-methylxanthine of the formula VI



(VI)

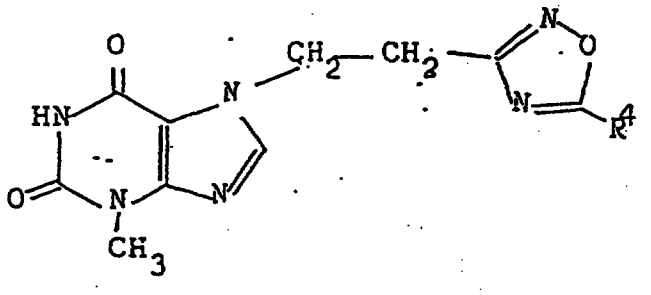
in the presence of an organic solvent and/or diluent, in particular dimethylformamide or one or more alcohols, advantageously n-butanol, in the presence of an inorganic base, for example an alkali metal hydroxide, in particular sodium or potassium hydroxide, or an alkali metal carbonate, for example sodium or potassium carbonate and the like, or an organic base, for example pyridine, triethylamine or piperidine, or the sodium or potassium salt of 3-methylxanthine of formula VI, in solution or suspension, preferably with heating. In the compounds obtained of formula Ia



(Ia)

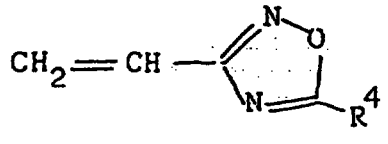
the group R^4 may be converted to a group R^1.

According to process variant d), the compounds of the general formula Ib,



(Ib),

which form a specific sub-group of compounds of the general formula I, wherein A denotes $-(CH_2)_2-$, are prepared such that a compound of the general formula VII



(VII)

is heated with 3-methylxanthine in the presence of a basic catalyst, preferably a quaternary ammonium hydroxide, in particular Triton-B, in the presence of an organic solvent and/or diluent, and then if required the group R^4 is converted to a group R^1.

The 3-methylxanthin-7-yl-alkane carboxylic acid amidoxime of the general formula II used in process variants a) and

b) as starting material, may be prepared in a manner known per se by reacting the corresponding 3-methylxanthin-7-yl carboxylic acid nitriles with hydroxylamine while heating in methanol or ethanol or in aqueous methanol or ethanol.

The oxadiazole derivatives of the general formula V used in process variant c) as starting materials may be prepared in a manner known per se from the corresponding 3-(ω-hydroxyalkyl)-1,2,4-oxadiazolene, by reacting with thionyl chloride, tosyl chloride or mesyl chloride (J. Chem. Res. (M) 1979, 801).

The olefins of the general formula VII used in process variant d) as starting materials can likewise be obtained by known methods (J. Chem. Res. (M) 1979, 801).

Compounds of the general formula Ia and IV, in which R^1 or R^4 denote haloalkyl, may be prepared from the corresponding haloalkane carboxylic acid chlorides and amidoximes of the general formula II in a manner known per se (Hungarian patent 186 607). Compounds of the general formula I, in which R^1 is aminoalkyl, may be prepared, apart from according to process variant a), preferably also from compounds of the general formulae Ia and IV, in which R^4 denotes haloalkyl, by means of substitution carried out using the corresponding amines or substitution and ring closure in a manner known per se.

The invention also relates to pharmaceutical agents which contain a compound of the general formula I or a therapeutically suitable salt, particularly an acid addition salt thereof, as active ingredient. These pharmaceutical agents may be prepared according to conventional pharmaceutical processes. The active ingredient may thus be formulated in the conventional

forms, for example as syrup, tablets, dragees, capsules, suppositories, injection solutions and the like. These pharmaceutical preparations of the invention contain conventional solid or liquid vehicles, diluents, excipients, auxiliaries and the like.

The active ingredient content of the pharmaceutical agents of the invention is between about 0.1 and 100 %, preferably about 1 to 30 %. The daily dose is about 2 to 2,000 mg depending on the type of administration, age and weight of the patient, and the like.

The invention is illustrated in more detail below using examples.

A) Preparation examples

Example 1

35.0 g (0.25 mole) of 3-methylxanthine (Chem. Ber. 83 (1950) 209) are dissolved in 81.4 ml (0.25 mole) of a 10 % strength sodium hydroxide solution; crystallisation takes place within a few minutes. The water is then distilled off under reduced pressure, and the traces of water are removed by azeotropic distillation with toluene. The residue is suspended in 350 ml of dimethylformamide, then a solution of 18.9 g (0.25 mole) of chloroacetonitrile and 80 ml of dimethylformamide is added dropwise with stirring at 100°C. The reaction mixture is stirred for a further hour at 100°C and then filtered while hot; the precipitate (sodium chloride) is washed using hot dimethylformamide; the combined solutions are evaporated to dryness under reduced pressure. The residue is ground with 100 ml of acetone; the crystals are filtered and washed thoroughly with acetone. The 7-cyanomethyl-3-methylxanthine thus obtained may be further processed immediately; melting point 285-287°C.

Example 2

2.5 g of sodium carbonate are added in portions to a solution of 3.2 g of hydroxylamine hydrochloride and 36 ml of water. 10.0 g of 7-cyanomethyl-3-methylxanthine and 30 ml of ethanol are added to the solution thus obtained. The reaction mixture is then stirred for 3 hours at 80°C and subsequently cooled. The 2-(3-methylxanthin-7-yl)-acetamidoxime precipitated is filtered and washed with a small amount of cold water. Yield 11.0 g (86 %). Melting point > 320°C. ^{1}H-NMR(DMSO-d_6): 3.35 (s, 3H, 3-Me); 4.85 (s, 2H, NCH_2-); 8.03 (s, 1H, 8-H); 9.79 (s, 1H, N-OH); 11.21 (bs, 1H, 1-NH).

Example 3

A mixture of sodium methylate solution prepared from 6.76 g of sodium and 290 ml of anhydrous ethanol, 35.0 g of 2-(3-methylxanthin-7-yl)-acetamidoxime and 43.0 ml of ethyl acetate is heated to boiling with stirring for 4 hours. The reaction mixture is then filtered while hot and the filtrate is concentrated under reduced pressure. The residue is dissolved in 200 ml of water. The pH value of the solution is set at 7 using 10 % strength hydrochloric acid. The product precipitated is filtered and crystallised from water twice. 18.0 g of 3,7-dihydro-3-methyl-7-[(5-methyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione are obtained; melting point 262-264°C. ^{1}H-NMR(DMSO-d_6): 2.57 (s, 3H, 5-Me); 3.37 (s, 3H, 3-Me); 5.66 (s, 2H, $-CH_2$); 8.18 (s, 1H, 6-H); 11.19 (bs, 1H, 1-NH).

Example 4

A mixture of 3.76 g (20 mmoles) of sodium 3-methylxanthine, 100 ml of dimethylformamide and 2.60 g

(19.6 mmoles) of 3-chloromethyl-5-methyl-1,2,4-oxadiazole is stirred at 100°C for 1.5 hours. The reaction mixture is then filtered while hot; 5 ml of methanol are added to the filtrate. 3.65 g of 3,7-dihydro-3-methyl-7-[(5-methyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione are obtained; yield 69 %; melting point 262-264°C.

Example 5

A solution of 2-(3-methylxanthin-7-yl)-acetamidoxime and 45.0 ml of acetic acid anhydride is stirred at 140°C for 10 minutes. The cooled solution is diluted with water to 10 times the volume and stirred for 30 minutes. The O-acetyl-2-(3-methylxanthin-7-yl)-acetamidoxime precipitated is filtered and washed with a small amount of methanol. 3.60 g of the product are obtained; melting point 220°C (with decomposition).
^{1}H-NMR(DMSO-d_6): 2.01 (s, 3H, OAc); 3.34 (s, 3H, 3Me); 4.97 (s, 2H, NCH_2-); 6.70 (bs, 2H, NH_2); 8.07 (s, 1H, 6-H); 11.24 (bs, 1H, 1-NH).

Example 6

2.0 g of O-acetyl-2-(3-methylxanthin-7-yl)-acetamidoxime are stirred in a mixture of 160 ml of Britton-Robinson buffer solution (pH = 7) and 200 ml of dimethylformamide at 95°C for 6 hours. The reaction mixture is then concentrated under reduced pressure. After crystallising the residue from water, 1.22 g of 3,7-dihydro-3-methyl-7-[(5-methyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione are obtained; melting point 262 to 264°C.

Example 7

A solution of 2.38 g of 2-(3-methylxanthin-7-yl)-acetamidoxime in 40 ml of anhydrous acetone is acylated

in the presence of 0.86 g of sodium hydrogen carbonate using a solution of 1.13 g of chloroacetyl chloride and 5.0 ml of acetone. 2.1 g of O-chloroacetyl-2-(3-methylxanthin-7-yl)-acetamidoxime are obtained. The product is dried at 105°C and a pressure of 133 Pa for 40 minutes until the weight is constant. The residue is crystallised from methanol. 1.6 g of 3,7-dihydro-3-methyl-7-[(5-chloromethyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione are obtained.

Example 8

a) A mixture of 1.5 g of 3-[(methylxanthin-7-yl)-methyl]-5-chloromethyl-1,2,4-oxadiazole, 10 ml of diethylamine and 10 ml of toluene is heated on a water bath for 8 hours with stirring in a sealed flask provided with a magnetic stirrer. The reaction mixture is then concentrated, the residue is washed with water, dissolved in 5 ml of hot ethanol and clarified using active carbon. The hydrochloride is formed using ethanolic hydrogen chloride and crystallised from water. 1.4 g of 3,7-dihydro-3-methyl-7-[(5-diethylaminomethyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione hydrochloride are obtained.

b) 1.41 g of O-chloroacetyl-2-(3-methylxanthin-7-yl)-acetamidoxime prepared according to Example 7 in 15 ml of toluene are treated dropwise with 1.5 ml of diethylamine with vigorous stirring. The reaction mixture is then heated to boiling for 8 hours and subsequently concentrated. The residue is washed with water. The hydrochloride is formed in ethanol and crystallised from water. 1.2 g of 3,7-dihydro-3-methyl-7-[(5-diethylaminomethyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione hydrochloride are obtained.

c) 2.38 g of 2-(3-methylxanthin-7-yl)-acetamidoxime in 20 ml of pyridine are reacted with 3.0 g of diethylaminoacetyl chloride with stirring at a temperature not exceeding 20°C. The reaction mixture is then heated on a water bath for 2 hours and concentrated. The residue is washed with water. The hydrochloride is formed using ethanolic hydrogen chloride and crystallised from water. 2.1 g of 3-[(3-methylxanthin-7-yl)-methyl]-5-diethylaminomethyl-1,2,4-oxadiazole hydrochloride are obtained.

d) A mixture of 2.38 g of 2-(3-methylxanthin-7-yl)-acetamidoxime, 200 ml of toluene, 1.36 g of sodium ethylate and 3.46 g of ethyl β-diethylaminopropionate is heated to boiling for 12 hours with stirring in a flask provided with a water separator. The reaction mixture is then concentrated under reduced pressure, the pH value is then set at 7 and the precipitate is washed with water and dried. The hydrochloride is formed in ethanol. 2.0 g of 3,7-dihydro-3-methyl-7-[(5-diethylaminomethyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione hydrochloride are obtained.

Example 9

2.38 g of 2-(3-methylxanthin-7-yl)-acetamidoxime in 25 ml of ethanol are heated to boiling for 20 hours with stirring with a solution of 0.45 g of sodium in 25 ml of ethanol and with 3.12 g of ethyl cyclohexane carboxylate. The reaction mixture is then concentrated, the residue is mixed with water and the pH value is set at 7. The residue is crystallised from aqueous ethanol. 2.51 g of 3,7-dihydro-3-methyl-7-[(5-cyclohexyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione are obtained; melting point 245 to 248°C.

Example 10

2.38 g of 2-(3-methylxanthin-7-yl)-acetamidoxime are reacted with 3.28 g of ethyl phenyl acetate and sodium ethylate in ethanol in the manner described in Example 9. 2.7 g of 3,7-dihydro-3-methyl-7-[(5-benzyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione are obtained; melting point 188 to 190°C.

Example 11

2.52 g of 3-(3-methylxanthin-7-yl)-propionic acid amidoxime in 4.0 ml of ethyl acetate are heated to boiling for 5 hours with a solution of 0.46 g of sodium in 25 ml of ethanol. The reaction mixture is then filtered while hot, the filtrate is then evaporated, the residue is treated with 20 ml of water and the pH value is set at 7. The precipitate is crystallised from water. 1.7 g of 3,7-dihydro-3-methyl-7-[2-(5-methyl-1,2,4-oxadiazol-3-yl)-ethyl]-1H-purine-2,6-dione are obtained; melting point 258 to 260°C.

Example 12

A mixture of 2.52 g of 3-(3-methylxanthin-7-yl) propionic acid amidoxime, 25 ml of toluene, 1.12 g of pulverised potassium hydroxide and 3.70 g of ethyl β-piperidinopropionate is heated to boiling for 10 hours with stirring in a flask provided with a water separator. The reaction mixture is then evaporated. The residue is treated with water, the pH value is then set at 7 and the precipitate separated out is washed with water. The hydrochloride is formed in ethanol. 2.6 of 3,7-dihydro-3-methyl-7-{2-[5-(2-piperidinoethan-1-yl)-1,2,4-oxadiazol-3-yl]-ethyl}-1H-purine-2,6-dione hydrochloride are obtained.

Example 13

A solution of 2.66 g of 4-(3-methylxanthin-7-yl) butyric acid amidoxime in 4.0 ml of ethyl acetate is heated to boiling for 6 hours with a solution of 0.46 g of sodium in 25 ml of ethanol. The reaction mixture is then worked up in the manner described in Example 3. 1.8 g of 3,7-dihydro-3-methyl-7-[3-(5-methyl-1,2,4-oxadiazol-3-yl)-propyl]-1H-purine-2,6-dione are obtained.

Examples 14 to 34

The compounds listed in Table IV are prepared in a manner analogous to the above examples. The groups A or substituents R^1 of formula I and the preparation process are given in Table IV.

Table IV

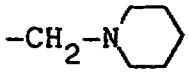
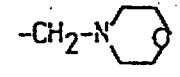
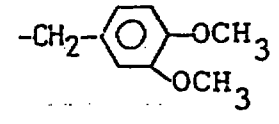
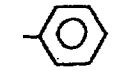
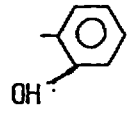
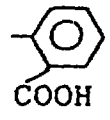
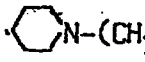
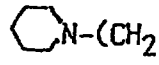
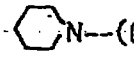
Example No.	A	R^1	Process according to Example
14	$-CH_2-$	CH_3CH_2-	3
15	$-CH_2-$	$CH_3CH_2CH_2-$	3
16	$-CH_2-$	$CH_3(CH_2)_3-$	3
17	$-CH_2-$	$CH_3(CH_2)_4-$	4
18	$-CH_2-$	$(CH_3)_2CH-$	3
19	$-CH_2-$	$HOCH_2CH_2-$	3
20	$-CH_2$		8
21	$-CH_2$		8
22	$-CH_2-$		3
23	$-CH_2$	$-(CH_2)_3COOH$	3
24	$-CH_2-$		3
25	$-CH_2-$		3

Table IV, continuation

Example No.	A	R^1	Process according to Example
26	$-CH_2-$		6
27	$-CH_2-CH_2-$	$(C_2H_5)_2NCH_2-$	8
28	$-CH_2-CH_2-$		8
29	$-CH_2-CH_2-$	$(C_2H_5)_2N(CH_2)_2-$	8
30	$-(CH_2)_3-$	$(C_2H_5)_2N(CH_2)_2-$	8
31	$-(CH_2)_3-$		8
32	$-(CH_2)_4-$	CH_3-	4
33	$-(CH_2)_4-$	$(C_2H_5)_2N(CH_2)_2-$	8
34	$-(CH_2)_4-$		8

B) Formulation examples

Example 35

a) Tablets

Component	Amount (g)
3,7-Dihydro-3-methyl-7-[(5-methyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione	10.0
Wheat starch	130.0
Calcium phosphate	199.0
Magnesium stearate	1.0
Total weight	340.0.

The above components are mixed; the mixture is ground and pressed to form 1,000 tablets having a total weight of 340 mg each and an active ingredient content of 10 mg each.

b) Repository dragees

Component	Amount (g)
3,7-Dihydro-3-methyl-7-[(5-methyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione	50.0
Carboxymethylcellulose	300.0
Stearic acid	20.0
Cellulose acetate phthalate	30.0
Total weight	400.0.

The active ingredient, the carboxymethylcellulose and the stearic acid are thoroughly ground with a solution of the cellulose acetate phthalate in 200 ml of ethyl acetate and pressed to form dragees of 400 mg. The dragee cores are coated with sugar-containing 5 % strength aqueous polyvinylpyrrolidone solution in known manner. The active ingredient content of the dragees is 50 mg.

b) Syrup

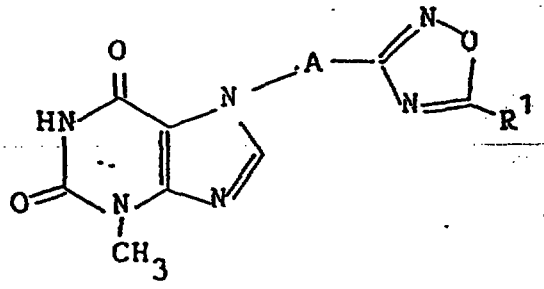
Component	Amount
3,7-Dihydro-3-methyl-7-[3-(5-(2-diethylaminoethyl)-1,2,4-oxadiazol-3-yl)-propyl]-1H-purine-2,6-dione hydrochloride	5 g
Lemon syrup	200 ml
Benzoic acid solution	20 ml
Water	100 ml
Sugar syrup	ad 1,000 ml.

The active ingredient is dissolved in warm water. After adding 500 ml of sugar syrup, the other components are added and the mixture is made up to 1,000 ml using sugar syrup. The syrup obtained has an active ingredient content of 5 mg/ml.

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Patent claims

1. Oxadiazolylalkylpurine derivatives of the general formula I,



(I),

wherein:
A denotes C_{1-4} alkylene, and
R^1 denotes C_{1-6} alkyl, hydroxyalkyl, haloalkyl, carboxyalkyl, C_{5-6} cycloalkyl, aminoalkyl of the general formula $-(CH_2)_n-NR^2R^3$, wherein
n denotes 1, 2 or 3, and
R^2 and R^3 each independently denote hydrogen or C_{1-4} alkyl, or, together with the nitrogen atom to which they are bound, form a 5-membered or 6-membered heterocyclic ring optionally containing a second nitrogen atom or an oxygen atom, or
R^1 denotes phenyl, hydroxyphenyl, carboxyphenyl, benzyl or dimethoxybenzyl
and their acid adddition salts and salts formed using inorganic bases, in particular the pharmaceutically suitable salts.

2. The following compounds according to claim 1:
3,7-dihydro-3-methyl-7-[(5-methyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[(5-ethyl)-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[(5-propyl)-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione;

3,7-dihydro-3-methyl-7-[(5-butyl)-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[(5-pentyl)-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[(5-prop-2-yl)-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[(5-cyclohexyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[(5-chloromethyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[(5-(2-hydroxyethyl)-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[(5-diethylaminomethyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[(5-piperidinomethyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[(5-morpholinomethyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[(5-benzyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[(5-(3,4-dimethoxybenzyl)-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[(5-(3-carboxypropyl)-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[(5-phenyl-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[(5-(2-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione, and
3,7-dihydro-3-methyl-7-[(5-(2-carboxyphenyl)-1,2,4-oxadiazol-3-yl)-methyl]-1H-purine-2,6-dione.

3. The following compounds according to claim 1:
3,7-dihydro-3-methyl-7-[2-(5-methyl-1,2,4-oxadiazol-3-yl)-ethyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[2-(5-diethylaminomethyl-1,2,4-oxadiazol-3-yl)-ethyl]-1H-purine-2,6-dione;

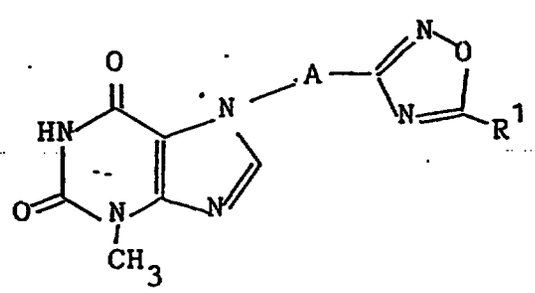
* C L M S *

3,7-dihydro-3-methyl-7-[2-(5-piperidinomethyl-1,2,4-oxadiazol-3-yl)-ethyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[2-(5-(2-piperidinoethan-1-yl)-1,2,4-oxadiazol-3-yl)-ethyl]-1H-purine-2,6-dione, and
3,7-dihydro-3-methyl-7-[2-(5-(2-diethylaminoethan-1-yl)-1,2,4-oxadiazol-3-yl)-ethyl]-1H-purine-2,6-dione.

4. The following compounds according to claim 1:
3,7-dihydro-3-methyl-7-[3-(5-methyl-1,2,4-oxadiazol-3-yl)-propyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[3-(5-(2-diethylaminoethan-1-yl)-1,2,4-oxadiazol-3-yl)-propyl]-1H-purine-2,6-dione, and
3,7-dihydro-3-methyl-7-[3-(5-(2-piperidinoethan-1-yl)-1,2,4-oxadiazol-3-yl)-propyl]-1H-purine-2,6-dione.

5. The following compounds according to claim 1:
3,7-dihydro-3-methyl-7-[4-(5-methyl-1,2,4-oxadiazol-3-yl)-butyl]-1H-purine-2,6-dione;
3,7-dihydro-3-methyl-7-[4-(5-(2-diethylaminoethan-1-yl)-1,2,4-oxadiazol-3-yl)-butyl]-1H-purine-2,6-dione, and
3,7-dihydro-3-methyl-7-[4-(5-(2-piperidinoethyl)-1,2,4-oxadiazol-3-yl)-butyl]-purine-2,6-dione.

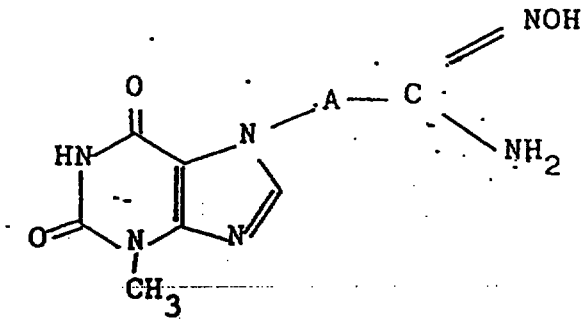
6. Process for preparing the oxadiazolylalkylpurine derivatives of the general formula I according to claims 1 to 5



(I)

with A and R^1 as in claim 1,
and their salts,
characterised in that

a) an amidoxime of the general formula II



(II),

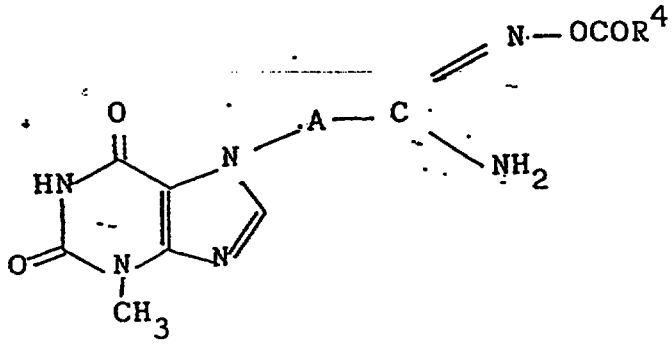
wherein A has the above meaning,

is reacted with a carboxylic acid of the general formula III,

$$R^4\text{-COOH} \qquad \text{(III)},$$

wherein R^4 has the meaning of R^1 or denotes a group which can be converted to the group R^1, or a reactive derivative thereof, and if required the group R^4 is converted to a group R^1, or

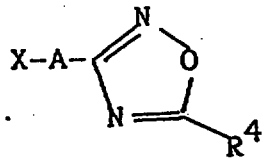
b) an amidoxime of the general formula II, wherein A has the above meaning, is reacted with a carboxylic acid of the general formula III, wherein R^4 has the above meaning, or a reactive derivative thereof, the compound of the general formula IV formed



(IV),

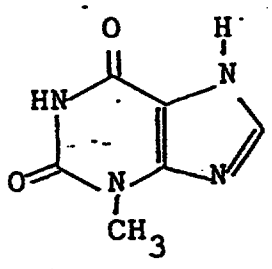
wherein A and R^4 have the above meaning, is cyclised after or without isolation by cleaving water, and if required the group R^4 is converted to a group R^1, or

c) an oxadiazole derivative of the general formula V



(V),

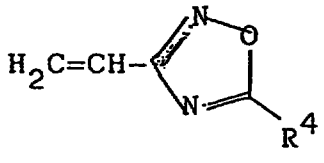
wherein R^4 and A have the above meaning and X denotes halogen or a sulphonate group,
is reacted with 3-methylxanthine of the formula VI



(VI)

or the sodium or potassium salt thereof in the presence of a basic catalyst, and if required the group R^4 is converted to a group R^1.

7. Process for preparing compounds of the general formula I according to claim 1, wherein A denotes the group $-(CH_2)_2-$ and R^1 has the above meaning, characterised in that an olefin of the general formula VII,



(VII),

* C L M S *

wherein R^4 has the above meaning,
is reacted with 3-methylxanthine of the formula VI in the presence of a basic catalyst, and if required the group R^4 is converted to a group R^1, and if required the compound of the formula I thus obtained is converted to a therapeutically suitable salt.

8. Pharmaceutical agent, characterised by containing a compound of the general formula I according to claim 1 or 2 or a therapeutically suitable salt thereof.