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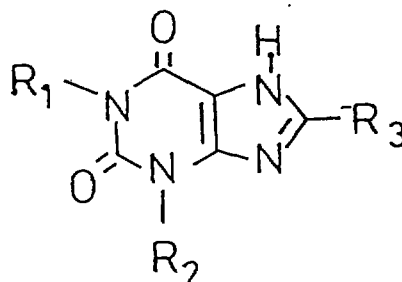
New xanthine derivatives with adenosine-
antagonistic activity

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The invention relates to new xanthine derivatives, processes for preparing them and their use as pharmaceutical compositions.

The new xanthines have the structure of general formula I



wherein

- R_1 is a C_{1-6} , preferably C_{1-4} alkyl group, a C_3 or C_4 alkenyl group or a C_3 or C_4 alkynyl group;
- R_2 is a C_3 or C_4 alkenyl group, a C_{1-6} , preferably C_{1-4} alkyl group, an optionally substituted benzyl group or a C_3 or C_4 alkynyl group;
- R_3 represents a C-linked saturated or unsaturated five, six or seven-membered heterocyclic ring which contains one or more heteroatoms selected from the group comprising oxygen and sulphur and may optionally carry one of the following groups:

C_{1-6} , preferably C_{1-4} alkyl, =O, -CHO, -CH₂OR₄, -CH₂OR₇, COOR₄, CONR₅R₆, whilst a furan or thiophene group may also contain one of the groups

-CH=CH-CONR₅R₆,

-CH=C (COOR₄)₂ (R_4 being identical or different),

-CH=C (COOR₄) (CONR₅R₆),

-CH=C (COOR₄) (CH₂OR₄) (R_4 being identical or different),

-CH=C (COOR₄) (CH₂OR₇),

-CH=C (CH₂OR₄)₂,

-CH=C (CH₂OR₇)₂,



$-\text{CH}=\text{C} (\text{CONR}_5\text{R}_6) \text{CH}_2\text{OR}_4,$

$-\text{CH}=\text{C} (\text{CONR}_5\text{R}_6) \text{CH}_2\text{OR}_7$ or nitro

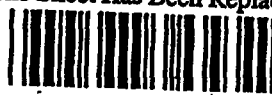
and the tetrahydrofuran group may also carry a group $-(\text{CH}_2)_2-\text{CONR}_5\text{R}_6$;

R_3 represents a C_{4-8} cycloalkene which may be substituted by C_{2-4} alkenyl,

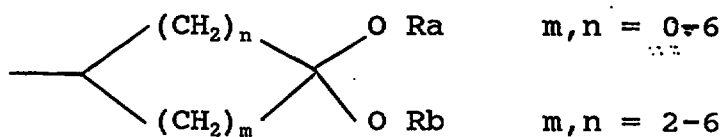
R_3 represents a C_{4-8} , preferably C_5 and C_6 , cycloalkanone or a C_4 to C_8 , preferably C_5 and C_6 cycloalkanol, which may be substituted in the α -position by C_{2-6} , preferably C_{2-4} , alkenyl, C_{2-6} , preferably C_{2-4} alkynyl, optionally substituted benzyl, CH_2OR_4 , CH_2COOR_7 or $(\text{CH}_2)_2\text{CN}$,

R_3 represents a C_3 to C_8 , preferably C_5 or C_6 cycloalkane, which may optionally be substituted by C_{1-6} , preferably C_{1-4} alkyl, $=\text{CH}_2$, $=\text{N}-\text{NH}-\text{aryl}$, preferably $=\text{N}-\text{NH}-\text{phenyl}$, wherein the aryl or phenyl group may be substituted, $=\text{N}-\text{NH}-\text{C}_1$ to C_6 alkyl, $=\text{NOH}$, $-\text{OCONH}-\text{aryl}$, preferably $-\text{OCONH}-\text{phenyl}$, wherein the aryl or phenyl group may be substituted, $\text{OCONH}-\text{C}_{1-6}$ alkyl, $-\text{OR}_4$, $-\text{OR}_7$, $-(\text{CH}_2)_1-\text{COOR}_4$, $-(\text{CH}_2)_1-\text{NR}_4\text{R}_4$ (R_4 being identical or different), $-(\text{CH}_2)_1-\text{CONR}_5\text{R}_6$, $-(\text{CH}_2)_1-\text{OR}_4$, $-(\text{CH}_2)_1-\text{OR}_7$, wherein 1 represents one of the numbers 0, 1, 2, 3 or 4, or a group $=\text{CAH}$ wherein A represents COOR_4 , CN , CONR_5R_6 , $\text{CH}=\text{CH}-\text{COOR}_4$, $\text{CH}=\text{CH}-\text{CONR}_5\text{R}_6$, CH_2OR_4 or CH_2OR_7 ,

or the cycloalkane is substituted by C_{1-6} , preferably C_{1-4} alkyl, vinyl, allyl, optionally substituted phenyl, optionally substituted C_{1-4} alkylphenyl, and has as a second substituent a hydroxyl group in a geminal position relative to the first substituent;



R₃ forms together with the cycloalkane a ketal of general formula

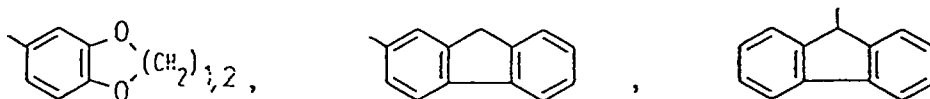


wherein

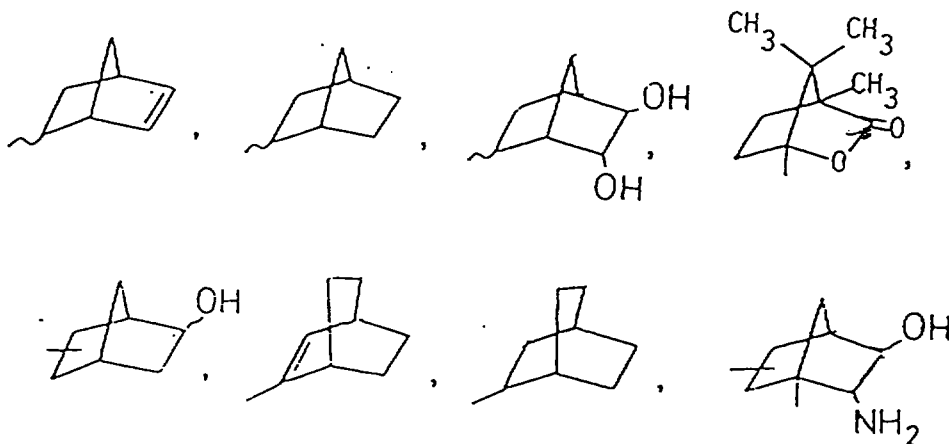
Ra represents C₁₋₄ alkyl and

Rb represents C₁₋₄ alkyl or Ra and Rb together form a C₂₋₃ alkylene group which may optionally be mono- or disubstituted by C₁₋₅ alkyl, C₁₋₅ alkyloxy-carbonyl, hydroxy C₁₋₅ alkyl, preferably hydroxymethyl;

R₃ represents an optionally substituted group of the formula



R₃ represents a group of formula

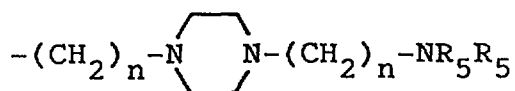


R₄ represents hydrogen, a C₁₋₁₃, preferably C₁₋₆ and C₁₁₋₁₃ alkyl group, an optionally substituted C₃₋₆ cycloalkyl group, an optionally substituted benzyl group, a C₃₋₁₃, preferably C₃₋₆ alkenyl, a propargyl group, a trityl



group,

- R_5 represents hydrogen, a C_{1-6} , preferably C_{1-4} alkyl group, an optionally substituted C_{3-6} cycloalkyl group;
- R_6 represents hydrogen, a C_{1-6} , preferably C_{1-4} alkyl group, an optionally substituted benzyl group, a group of general formula
- $$-(CH_2)_n-NR_5R_5,$$
- $$-((CH_2)_n-O-(CH_2)_m-O)_k-(CH_2)_n-NR_5R_5$$
- (wherein R_5 is identical or different);
- wherein $n = 2, 3, 4, 5, 6, 7$ or 8 , $m = 2, 3, 4, 5$ or 6 and $k = 0$ or 1 ,



(wherein R_5 is identical or different),

whilst the piperazine ring may be substituted by C_{1-4} alkyl, preferably methyl, a C-linked piperidinyll group which is optionally substituted by C_{1-4} alkyl or an N-linked benzyl group or

R_5 and R_6 together with the nitrogen atom form an optionally C_{1-4} -alkyl-substituted five or six or seven-membered ring which may contain a further heteroatom selected from the group comprising oxygen, sulphur and nitrogen, whilst the nitrogen atom may be substituted by the group R_4 ;

- R_7 represents an amino acid group, linked via the carbonyl function, of a naturally occurring amino acid, $-CO-(CH_2)_p-CH_3$ wherein $p=0$ to 13 , preferably $1, 2$ or 3 , menthoxyacetyl, a



camphanic acid group linked via a carbonyl group, abietinoyl, 4-aminobutyroyl, optionally substituted benzoyl, preferably trimethoxybenzoyl, a group of general formula $\text{CO} - \text{B}$, wherein B is an optionally substituted C-linked, 5, 6 or 7 membered heterocyclic group, and optionally the racemates, optically active compounds and pharmacologically acceptable acid addition salts thereof.

Preferred compounds of general formula I are those wherein

- R_1 represents an unbranched C_{3-4} alkyl group, an allyl or a propargyl group;
- R_2 represents an allyl group, a C_{3-4} alkyl group or a propargyl group;
- R_3 represents a group selected from among furan, tetrahydrofuran, tetrahydrofuranone, thiophene, dithiol, dithian or tetrahydropyran which may carry one of the following substituents: methyl, ethyl, propyl, butyl, CHO , CH_2OR_4 , CH_2OR_7 , COOR_4 , CONR_5R_6 ,
- R_3 represents a furan substituted by
- $-\text{CH}=\text{CH}-\text{CONR}_5\text{R}_6$, $-\text{CH}=\text{C}(\text{COOR}_4)_2$ (R_4 being identical or different),
 - $-\text{CH}=\text{C}(\text{COOR}_4)(\text{CONR}_5\text{R}_6)$,
 - $-\text{CH}=\text{C}(\text{COOR}_4)(\text{CH}_2\text{OR}_4)$ (R_4 being identical or different),
 - $-\text{CH}=\text{C}(\text{COOR}_4)(\text{CH}_2\text{OR}_7)$,
 - $-(\text{CH}_2)_n-\text{CONR}_5\text{R}_6$,
 - $-\text{CH}=\text{C}(\text{CH}_2\text{OR}_4)_2$,
 - $-\text{CH}=\text{C}(\text{CH}_2\text{OR}_7)_2$,
 - $-\text{CH}=\text{C}(\text{CONR}_5\text{R}_6)\text{CH}_2\text{OR}_4$ or

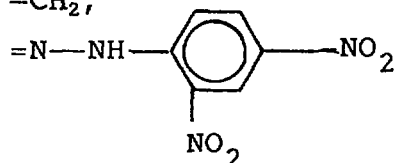
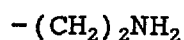
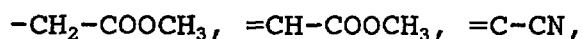
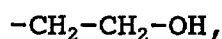
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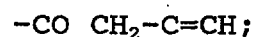
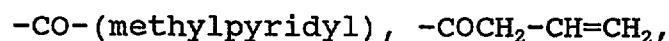
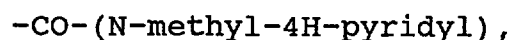


R_3 represents a cyclopentanyl or cyclohexanyl group, optionally substituted by methyl, ethyl, propyl, isopropyl, tert-butyl, allyl, vinyl, phenyl or benzyl, whilst a hydroxy group may be present as a geminal substituent;

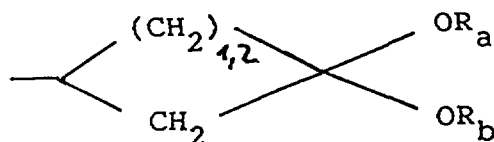
R_3 represents a cyclopentanyl or cyclohexanyl group, substituted by hydroxy, methoxy, ethoxy, propyloxy, trimethoxycarbonyl, isopropyloxy, optionally substituted benzyloxy, allyloxy, propargyloxy,



$=\text{NOH}$, $-\text{CH}_2\text{OH}$, OR_4 wherein R_4 = methyl or trityl, OR_7 wherein R_7 represents COCH_3 , COC_2H_5 , COC_3H_7 , CO tert-butyl, $-\text{CO}$ -phenyl or COCH_2 -phenyl, optionally substituted, CO -pyridyl,



R_3 represents a group



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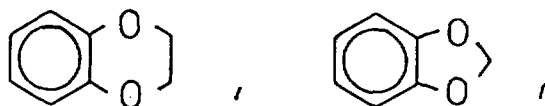


wherein R_a , R_b = CH_3 , C_2H_5 or R_3 and R_6 together represent $-\text{CH}_2-\text{CH}_2-$,

R_3 represents a cyclopentanone or cyclohexanone,

R_3 represents a cycloalkane or cycloalkene with 4 - 8 carbon atoms, which may optionally be substituted by a straight-chained or branched C_{2-4} alkenyl group; a cyclopentanone or cyclopentanol or cyclohexanone or cyclohexanol which may be substituted in α -position with respect to the keto or hydroxy group by C_{2-4} alkenyl, C_3 or C_4 alkynyl, benzyl, $-CH_2CH_2CN$, $(CH_2)_3NR_5R_5$ (wherein R_5 is the same or different), CH_2COOR_4 , or CH_2OR_4 , wherein R_4 may represent hydrogen, methyl, ethyl or propyl;

R_3 represents norbornane or norbornene, optionally substituted,



R_4 represents hydrogen, a C_{1-3} alkyl, a cyclopropyl group, a cyclopentyl group, benzyl, an aryl group, a propargyl group or a triphenylmethyl group;

R_5 represents hydrogen, a C_{1-3} alkyl group; a cyclopropyl group or a benzyl group;

R_6 represents hydrogen, methyl, ethyl, propyl, $-(CH_2)_n-NH_2$ ($n=2-8$), $-(CH_2)_n-NEt_2$ ($n=2,3$) or $-(CH_2)_3-O-(CH_2)_4-O-(CH_2)_3-NH_2$, N-benzyl-piperidin-4-yl, or R_5 and R_6 together with the nitrogen atom represent a piperidine, piperazine or morpholine group which may optionally be substituted by a C_{1-4} alkyl group, preferably methyl;

R_7 represents prolinoyl, $CO-(CH_2)_{0-3}-CH_3$, $(-)-$ menthoxyacetyl, a camphanic acid group linked via a



carbonyl group, abietinoyl, benzoyl, 4-aminobutyryl, 3,4,5-trihydroxybenzoyl, 3,4,5-trimethoxybenzoyl, a nicotinic acid, isonicotinic acid or picolinic acid group, an N-methylnicotinic acid group or an N-methyl-4H-nicotinic acid group, and optionally the acid addition salts thereof.

Particularly preferred compounds are the compounds of general formula I wherein R_3 forms an optionally substituted cyclopentane group in which the substituent is in the 3-position of the cyclopentane ring. It is particularly preferred for the group R_3 to represent 3-oxocyclopentane.

Examples of alkyl groups, including those which are constituents of other substituents, include methyl, ethyl, propyl, isopropyl, butyl, sec.-butyl, isobutyl, tert.-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl and examples of longer-chained alkyl groups include decanyl, undecanyl, dodecanyl and tridecanyl and the isomers thereof. Examples of alkenyl groups include allyl (provided that it does not form any enamines), propenyl, isopropenyl, butenyl and isobutenyl. (Et=ethyl).

Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl which may be substituted by C_{1-4} alkyl. A benzyl group, like a phenyl group, may be mono or polysubstituted by C_{1-4} alkyl, preferably methyl, or by C_{1-4} alkoxy, preferably methoxy, or by hydroxy and/or halogen such as fluorine, chlorine or bromine.

The term "aryl" indicates an aromatic ring system with 6 to 12 carbon atoms which may optionally be substituted by C_{1-4} alkyl, halogen, hydroxy, nitro, C_{1-4} alkoxy, amino, C_{1-4} alkylamino and/or C_{1-4} dialkylamino; the preferred aryl group is phenyl.

Examples include:

2-chlorophenyl, 2-bromophenyl, 3-fluorophenyl, 2,3-

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dichlorophenyl, 4-hydroxyphenyl, 2-methylphenyl, 4-methylphenyl, 3-ethylphenyl, 4-propylphenyl, 4-isopropylphenyl, 4-butylphenyl, 4-tert.-butylphenyl, 4-pentylphenyl, 2,4-dimethylphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 3-ethoxyphenyl, 2-propoxyphenyl, 4-butoxyphenyl, 2,4-dimethoxyphenyl, 3,4,5-trimethoxyphenyl, 2,4-dinitrophenyl, 4-nitrophenyl.

Examples of cyclic groups of general formula NR_5R_6 include: pyrrol, pyrroline, pyrrolidine, 2-methylpyrrolidine, 3-methylpyrrolidine, piperidine - optionally mono- or polysubstituted by C_{1-4} alkyl, piperazine, N-methylpiperazine, N-ethylpiperazine, N-n-propylpiperazine, N-benzylpiperazine, morpholine, thiomorpholine, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine in which the above-mentioned heterocyclic group may also be substituted by C_{1-4} alkyl, preferably methyl.

Examples of heterocyclic groups which may be linked via a carbon atom include thiophene, 2-methylthiophene, 2-nitrothiophene, furan, 2-nitrofuran, tetrahydrofuran, 2-methyltetrahydrofuran, 2-hydroxymethylfuran, tetrahydrofuranone, γ -butyrolactone, α -pyran, γ -pyran, 1,3-dioxolan, 1,2-oxathiolan, 1,2-oxathiepan, tetrahydro-pyran, thiolan, 1,3-dithian, 1,3-dithiolan, 1,3-dithiolene and furfural, in which the heterocyclic group may be substituted as specified in the definitions.

Examples of heterocyclic groups which may be linked via a carbon atom and contain at least one nitrogen atom include: pyridine, pyrrol, pyrroline, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, in which the above-mentioned heterocyclic groups may be substituted by C_{1-4} alkyl.

Examples of naturally occurring amino acids include alanine, valine, leucine, isoleucine, proline,

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phenylalanine, tryptophane, methionine, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, histidine, arginine, lysine.

The compounds according to the invention are adenosine antagonists; in particular they have a high affinity (up to 1.6 nM) for the A₁-receptor and a high selectivity for this receptor subtype.

In hippocampal slices the substances antagonise the adenosine-induced suppression of the humming peak after electrical stimulation. In vivo, an increased acetylcholine content can be detected in the rat's brain.

These results indicate that the xanthine derivatives described intensify the natural cell activity of cholinergic neurones in the brain and thus prove to be functional cholinomimetics with a central attack. EEG investigations on cats indicate a significant increase in vigilance.

Substances of this kind are of great interest for the symptomatic treatment of degenerative diseases of ageing such as senile dementia and Alzheimer's disease.

The high receptor affinity should make it possible to use low doses for treatment so that there are virtually no side effects which cannot be put down to the blocking of adenosine receptors. Similarly, because of the high A₁ selectivity of the compounds, A₂-dependent side effects should not occur. In addition to being used as geronto-psychoactive drugs and nootropics, the adenosine antagonists described could also be used to treat cardiac and circulatory disorders.

Other possible indications are degenerative diseases such as organic brain syndrome, Parkinson's disease, traumatic CNS damage, post/neurological deficit, respiratory depression (intoxication, post-op) and neonatal brain damage.

Pharmacological results are shown in Table Ia. The test methods correspond to those recited in the



following literary references:

- Lohse M.J., V. Lenschow and U. Schwabe (1984) Mol. Pharmacol. 26, 1-9;
 Virus, M.R., T. Baglajewski and M. Rachelovacki (1984) Neurotology of Agenig 5, 61-62;
 Daly, J.W., W. Padgett, M.T. Shamin, P. Butts-Lamb and J. Waters (1985) J. Med. Chem. 28, 487-492;
 Bruns, R.F., G.H. Lu and T.A. Pugsley (1986) Mol. Pharmacol. 29, 331-346

Table Ia

Examples according to Table I	K_i [nMol] (A_1)
22	$8 \cdot 10^{-9}$
24	$3 \cdot 10^{-9}$
28	$6 \cdot 10^{-9}$
33	$3 \cdot 10^{-9}$
39	$4 \cdot 10^{-9}$
40	$2 \cdot 10^{-9}$
45	$2 \cdot 10^{-9}$
49	$2 \cdot 10^{-9}$
50	$2 \cdot 10^{-9}$

The compounds according to the invention may be prepared by analogous methods known per se.

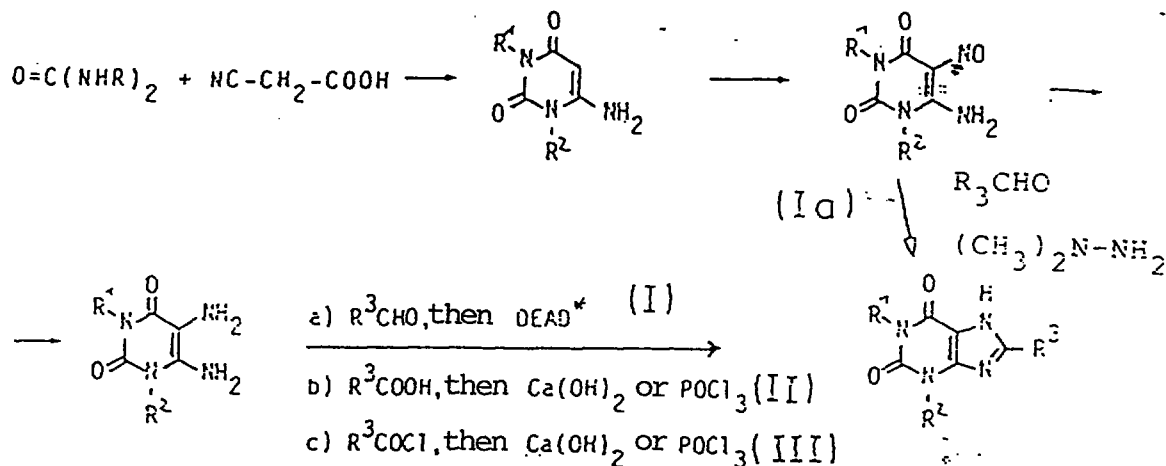
In general, 8-substituted 1,3-dialkylxanthines are obtained by reacting 1,3-dialkyldiaminouracils with aldehydes, carboxylic acids or carboxylic acid chlorides or by reacting 1,3-dialkyl-6-amino-5-nitrosouracils with aldehydes.

5,6-Diamino-1,3-dimethyluracil is commercially obtainable; derivatives substituted with other groups are prepared by reacting the corresponding dialkylurea with cyanoacetic acid with subsequent nitrosation and optional hydrogenation or reduction with dithionite to

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obtain the diamine (J. Org. Chem. 16, 1879 (1951) and Can. J. Chem. 46, 3413 (1968)).



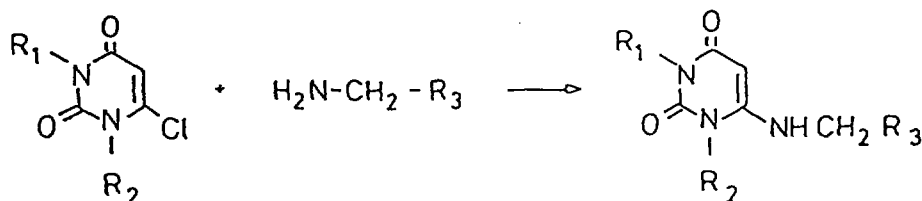
* Diethylazodicarboxylate

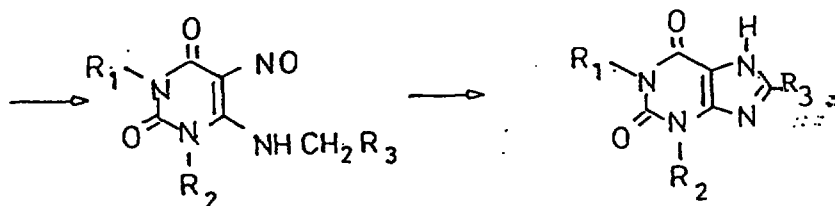
(The Roman numerals refer to the operating procedures described in the experimental section)

Xanthines with a benzyl group in the 3-position and a different group in the 1-position are obtained by 1-alkylation of corresponding precursor molecules which are substituted in the 3-position with a benzyl group and in the 8-position accordingly.

These can be obtained by reacting monobenzylurea and cyanoacetic acid to produce 6-amino-1-benzyluracil (L.-F. Tietze and Th. Eicher, Reaktionen und Synthesen, Georg Thieme Verlag, Stuttgart 1981, p. 322), alkylation with the desired group in the 3-position (XIV), nitrosation of the 5-position (XV) and hydrogenation to yield the 3-substituted 1-benzyl-5,6-diaminouracil (XVI). Aldehydes, carboxylic acids and acid chlorides used for the reaction with 5,6-diaminouracils can be prepared by methods known from the literature.

In suitable cases, the xanthines described may be produced by reacting 1,3-dialkyl-6-chlorobarbituric acids with $\text{H}_2\text{N}-\text{CH}_2-\text{R}_3$, followed by nitrosation and cyclisation (see J. Med. Chem. 32, 1231 (1989)).





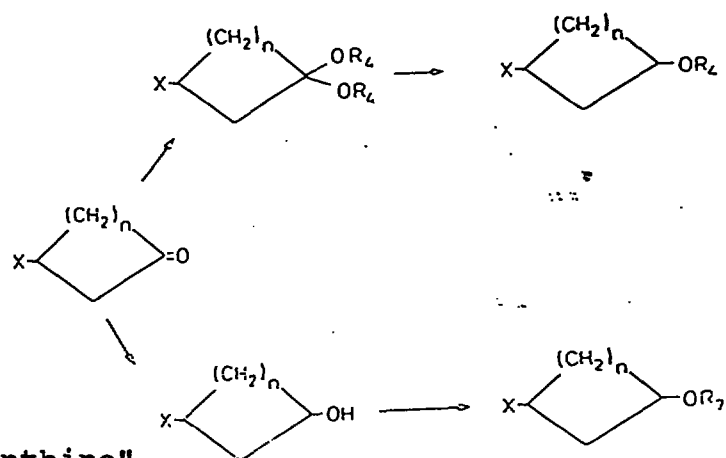
Using the processes thus described, it is possible to prepare xanthine derivatives in which R_3 has the following meaning, for example:

Thiophene, 2-methylthiophene, 2-nitrothiophene, furan, cyclohexan, cyclohexanone, tetrahydrofuranone, 1,3-dithiane, pyran, cyclobutane, cyclohexan, norbornene and others, provided that the corresponding aldehydes $R_3\text{CHO}$, carboxylic acids $R_3\text{COOH}$ or reactive derivatives thereof, already functionalised, can be reacted with the corresponding diaminouracil.

Other synthetic variations can then be effected on the "basic xanthine structures" thus obtained.

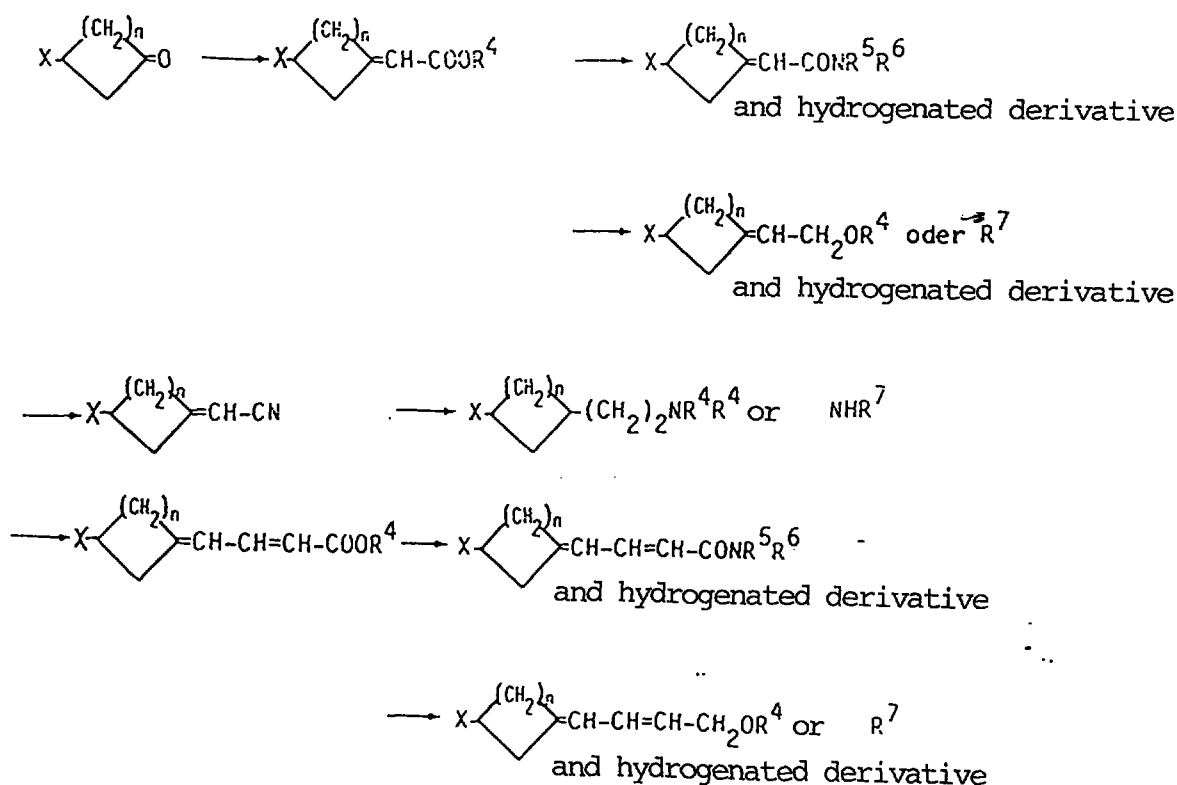
If desired, reactive functional groups can be protected in the usual way. Starting from the corresponding 8-cycloalkanones, the corresponding alcohols may be prepared by reduction and can then in turn be esterified with carboxylic acids or acid chlorides or reacted with isocyanates to form carbamates. By reacting the corresponding ketones with hydroxylamines the corresponding oximes may be obtained, or, with substituted hydrazines, the corresponding hydrazones. The ketone function can be ketalised with alcohols in the usual way. Reduction of the ketals - for example using $\text{LiAlH}_4/\text{AlCl}_3$ - yields the corresponding ethers. (In all the formulae which follow the positions of the groups are given solely by way of example without restricting the compounds according to the invention to the positions specified).



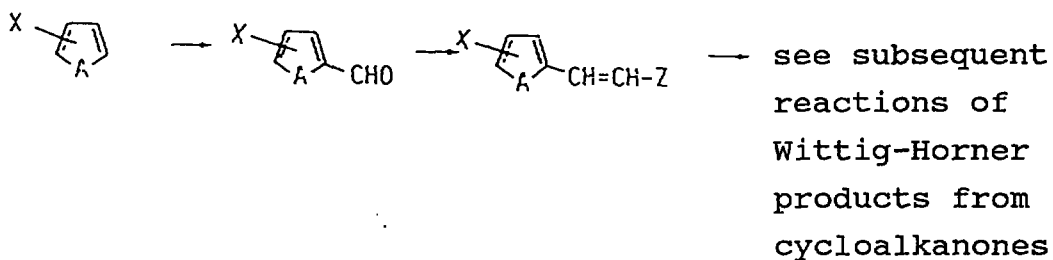


$n = 1 - 5$; $X = \text{"xanthine"}$

Wittig-Horner reactions on the ketone functions with phosphonic acid esters result in substituted olefins. By esterification of the carboxyl groups, amide formation and reduction to yield the alcohol with subsequent esterification or etherification, substituted compounds of the type specified below can be obtained, and these can subsequently be subjected to hydrogenation.

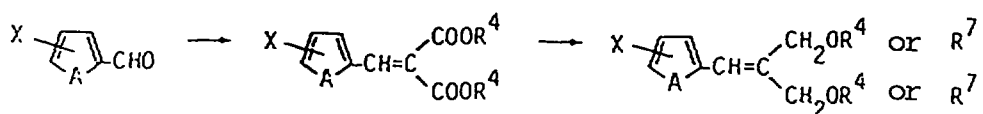


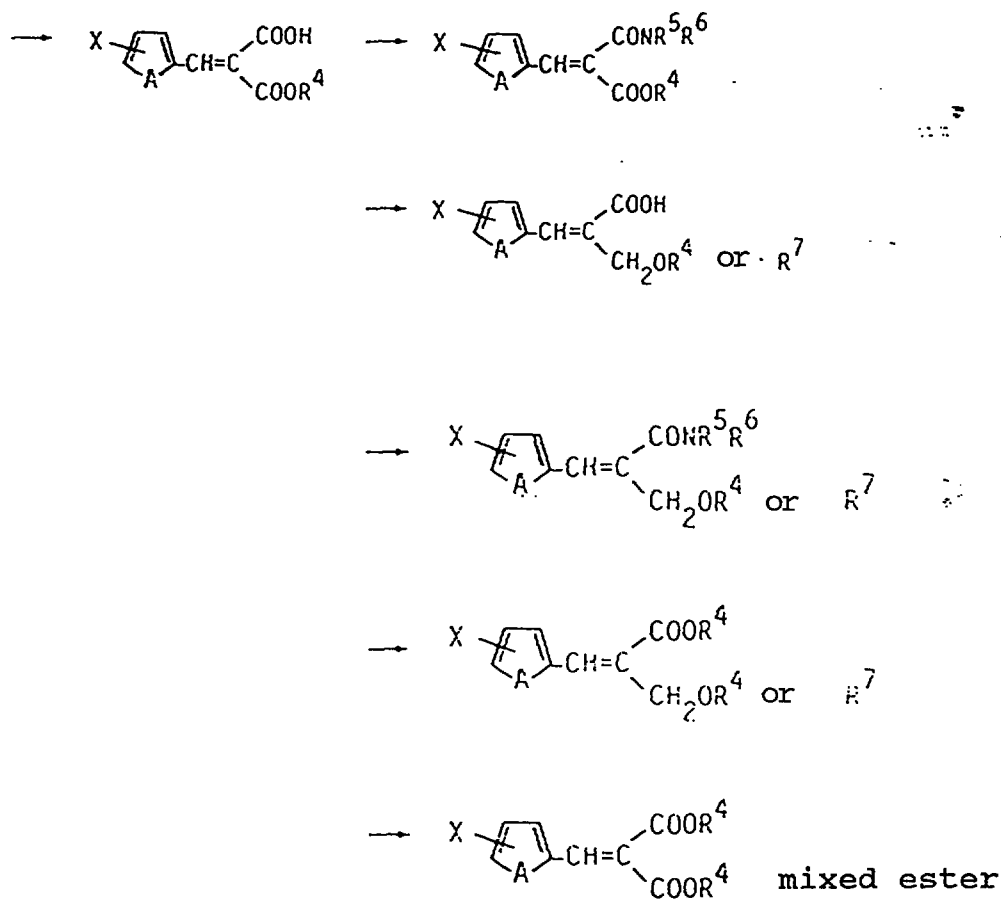
8-Furyl or 8-thiophenyl derivatives may be formylated according to Vilsmeier (IV). The aldehydes thus obtained are used as starting materials for Wittig-Horner reactions (X) with phosphonates; the products can be further derivatised in accordance with the methods specified above.



A = O, S; Z = extracting group, X = xanthine

The aldehydes are suitable for Knoevenagel reactions (XI) with malonic esters. The ester groups may be reduced to form alcohols and these may be esterified or etherified. Saponification of one of the ester groups yields the monocarboxylic acid. This serves as a starting material for the synthesis of "mixed-functional" derivatives. Thus, the combinations of ester (amide, alcohol (including esterified or etherified)/carboxylic acid, alcohol (including esterified or etherified)/amide, alcohol (including esterified or etherified)/ester, mixed ester may be obtained.



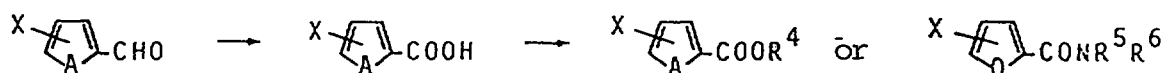


x = xanthine

A = O, S;

By reduction, the corresponding alcohols, which may be esterified and etherified, are obtainable from the aldehydes.

Reactions of oxidation yield carboxylic acids which may in turn be converted into the esters and amides.



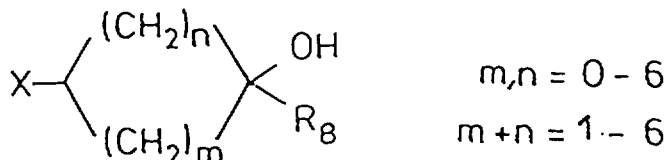
The double bond in 8-norbornenyl derivatives may be converted by reaction with KMnO_4 to yield the cis-diol. Reaction with m-chloroperbenzoic acid yields the epoxide

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which can be opened to yield the trans-diol, reacted with sodium azide to form the azido alcohol or reduced with lithium tetrahydridoalunate to yield the corresponding alcohol. The α -amino alcohol can be obtained by hydrogenation.

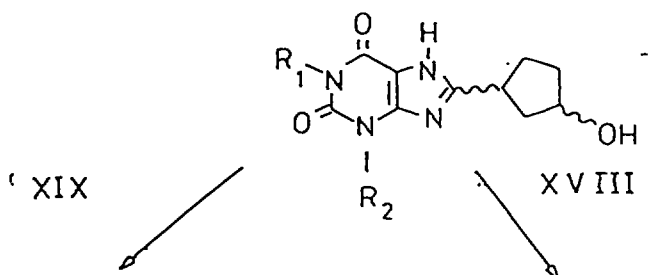
Starting from xanthine derivatives wherein R_3 represents a cycloalkanone, derivatives of general formula



wherein R₈ represents methyl, ethyl, butyl, tert.-butyl, vinyl, phenyl and benzyl, are obtained by Grignard reaction or by reacting with Li-organic reagents.

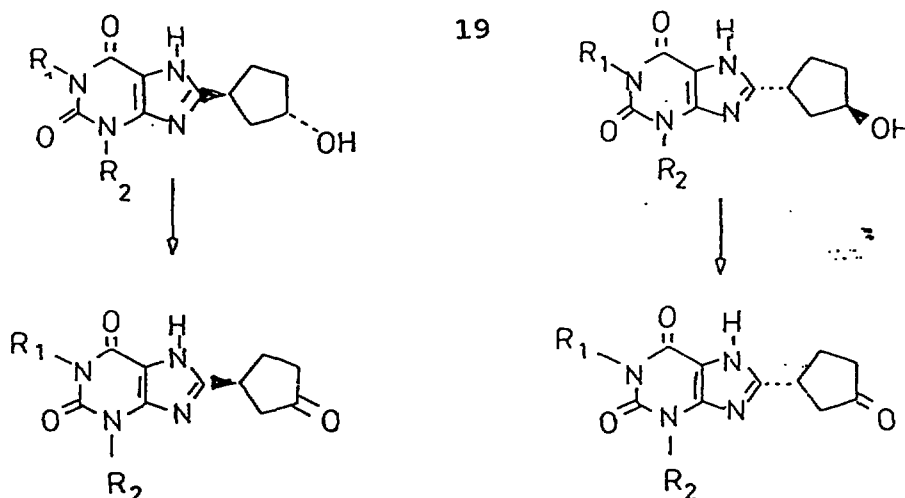
The above-mentioned cycloalkanones may be converted with the so-called Nozaki-Lombardo reagent into the corresponding methylene derivatives which can subsequently be reduced to yield the methyl compounds (J. Org. Chem. 50 (8), 1212 (1985) or after hydroboration with $\text{BH}_3 - \text{CH}_3\text{SCH}_3/\text{H}_2\text{O}_2$, OH^- yield the hydroxymethyl derivatives.

Reduction of the carbonyl group in optionally substituted cycloalkanones, e.g. using sodium tetrahydridoborate, produces the corresponding alcohols which can be esterified or etherified in the subsequent reaction steps. Enantiomerically pure xanthine derivatives which carry a cyclopentane group as the substituent R_3 may be prepared according to the following plan:



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The general procedures XVIII and XIX contain other details of stereospecific synthesis.

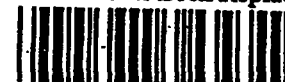
1,3-Dipropyl-8-[3-hydroxycyclopentyl]xanthine is esterified enantioselectively with lipases in organic solvents. By subsequent purification of the residual alcohol, according to the same process the (-)-rotatory enantiomer is obtained with a purity of more than 99.5%.

Reductive cleavage of the acetate first obtained using lithium aluminium hydride yields the optically enriched (+)-alcohol, which is obtained with an enantiomeric purity of more than 99.9% by reacting with a second lipase. From these optically pure substances a whole range of optically active xanthine derivatives can be obtained with substituted cyclopentane groups in the 8-position using the methods specified.

Suitable compounds according to the invention may be converted into the acid addition salts thereof using methods known per se.

Acids suitable for salt formation include for example hydrochloric, hydrobromic, hydriodic, hydrofluoric, sulphuric, phosphoric, acetic, propionic, butyric, caproic, valeric, oxalic, malonic, succinic, maleic, fumaric, lactic, tartaric, citric, malic, benzoic, p-hydroxybenzoic, p-aminobenzoic, phthalic, cinnamic, salicylic, ascorbic and methanesulphonic acid, 8-chlorotheophylline and the like.

The preferred acid addition salts are the hydrochlorides and hydrobromides.



General procedure I: cyclisation with aldehydeExample 11,3-Dipropyl-8-(1,4-benzodioxan-6-yl)xanthine

2.18 g (0.013 mol) of 1,4-benzodioxan-6-aldehyde, 80 ml of ethanol and 2.4 ml of glacial acetic acid are mixed together and 2.8 g (0.012 mol) of 5,6-diamino-1,3-dipropyluracil are added thereto. The clear solution is refluxed for 2½ hours and then cooled to 60°C. At this temperature, 2.1 ml (0.013 mol) of diethylazodicarboxylate are added dropwise and the viscous suspension produced is mixed with 80 ml of ethanol and refluxed for 2 hours. After a further 20 hours at ambient temperature the mixture is cooled to 5°C, the solid matter is filtered under suction and washed with ethanol and ether. 4.1 g of the title compound are obtained in the form of a grey solid (= 92% of theory), melting point 280-282°C.

General procedure Ia: cyclisation with aldehydesExample 1a1-Propyl-3-benzyl-8-(1,4-benzodioxan-6-yl)xanthine

2.9 g (0.01 mol) of 1-benzyl-3-propyl-5-nitroso-6-aminouracil are added to 60 ml of dimethylformamide together with 2.3 g (0.014 mol) of 1,4-benzodioxan-6-aldehyde, then 0.5 g (0.014 mol) of 1,1-dimethylhydrazine are added and the mixture is refluxed for 8 hours. After working up in the usual way, the crystalline residue is triturated with ethanol and filtered under suction. 1.0 g of the title compound is obtained in the form of yellow crystals, m.p. 290°C.

General procedure II: cyclisation with carboxylic acid

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Example 21,3-Dipropyl-8-(tetrahydropyran-4-yl)xanthine

3.2 g (0.025 mol) of tetrahydropyran-4-carboxylic acid, 4.0 g (0.025 mol) of carbonyldiimidazole and 85 ml of absolute methylene chloride are stirred for 30 minutes at ambient temperature. After the addition of 5.7 g (0.025 mol) of 5,6-diamino-1,3-dipropyluracil, the mixture is stirred for 4 hours at ambient temperature and then evaporated down in vacuo. The residue is combined with 130 ml of water and 11.6 g of calcium hydroxide, stirred for 30 minutes at 80°C and, after cooling, acidified with conc. HCl whilst cooling with ice. The mixture is extracted with ethyl acetate and the organic phase is dried and evaporated. Chromatography of the crystalline residue on silica gel (CH₂Cl₂/CH₃OH 99:1) yields 1.7 g of the title compound in the form of white crystals (15% of theory), m.p. 171-172°C.

Example 2a1,3-Dipropyl-8-(3-oxocyclopentyl)-xanthine

2.4 g (0.014 mol) of 1,4-dioxaspiro[4,4]nonan-7-carboxylic acid are dissolved in 56 ml of methylene chloride and after the addition of 2.2 g (0.014 mol) of carbonyldiimidazole stirred for 1 hour at ambient temperature. Then 3.2 g (0.014 mol) of 5,6-diamino-1,3-dipropyluracil are added and the mixture is stirred for a further 4 hours at ambient temperature. The solution is evaporated down in vacuo, the oily residue is mixed with 70 ml of water and 4.5 g of Ca(OH)₂ and stirred for 1 hour at 70°C. 100 ml of 50% NaOH are added, the mixture is stirred for a further hour at 70°C and for 16 hours at ambient temperature. Whilst being cooled with ice, the solution is adjusted to pH 6 with HCl and extracted with methylene chloride. After drying and



evaporation in vacuo the combined organic phases yield a crystalline residue which is recrystallised from ethanol using activated charcoal. 0.8 g (16%) of white crystals are obtained, m.p. 147-148°C.

The dioxolan protecting group is then hydrolysed with acid in the manner known from the literature and the title compound is obtained.

Example 2b

1,3-Dipropyl-8-(3-oxocyclopentyl)-xanthine

a) Preparation of 3-oxo-cyclopentane carboxylic acid

100.0 g of Methyl-3-oxocyclopentane carboxylate (0.7 mol) are mixed with 1000 ml of 2-molar hydrochloric acid and stirred for 10 hours at boiling temperature. The solution is cooled and fully concentrated by evaporation in vacuo. The residual water is drawn off 3 times with 50 ml of toluene each time (toluene is added to the residue and distilled off using a Rotavapor under a full water-jet vacuum and at a water bath temperature of 60-70°C). The crude yield is fractionally distilled in a high vacuum.
 1st fraction: Bp_{0.02} 20° - 110°C (yield: 1.2 g of oil)
 2nd fraction: Bp_{0.02} 110° - 116°
 yield: 4.7 g of partly crystalline oil
 3rd fraction: Bp_{0.02} 116° - 121°C
 yield: 74.0 g of colourless oil which later crystallised out.
 Yield 74.0 g (82.1% of theory)

8.8 g of 3-oxocyclopentane carboxylic acid (0.072 mol) are placed in 240 ml of absolute methylene chloride and at 20 - 25°C, with stirring, 11.6 g of carbonyldiimidazole are added and the resulting mixture is stirred for 2 hours at ambient temperature. The reaction mixture is evaporated to dryness in vacuo. The

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oily residue is mixed with 3200 ml of distilled water and 35 g of calcium hydroxide and stirred at 80°C for 0.5 hours. It is then cooled to 5°C and adjusted to pH 1-2 using conc. hydrochloric acid and extracted 3 times, each time with 100 ml of CH₂Cl₂. The combined organic phases are washed once with 100 ml of water, dried with magnesium sulphate, filtered and evaporated to dryness. The crude yield is purified over 350 g of silica gel S160 using about 4l of eluant CH₂Cl₂:CH₃OH 99:1. The clean fractions are evaporated to dryness. The crystalline residue is triturated with 100 ml of ether and filtered under suction.
Yield: 11.5 g of grey crystals (50.2% of theory)
M.p.: 164 - 168°C.

General procedure III: cyclisation with acid chloride

Example 3

1,3-Dipropyl-8-(4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]-heptan-3-on-1-yl)xanthine

1.2 g (5.4 mmol) of 5,6-diamino-1,3-dipropyluracil and 1.0 g of triethylamine (10 mmol) are dissolved in 50 ml of absolute methylene chloride. After the dropwise addition of 1.2 g (5.5 mmol) of camphanyl chloride, the mixture is stirred for 20 hours at ambient temperature and concentrated by evaporation in vacuo. The residue is mixed with 28 ml of water and 1.7 g of calcium hydroxide and stirred for 3 hours at 80°C. The cooled suspension is acidified whilst being cooled with ice and then extracted with methylene chloride. The combined organic phases are dried and evaporated down and the residue is purified by chromatography on silica gel (CH₂Cl₂/CH₃OH 99:1).

200 mg of the title compound are obtained in the form of white crystals (10% of theory), m.p. 200-201°C.



General procedure IV: Vilsmeier reactionExample 41,3-Dipropyl-8-(2-formylfuran-5-yl)xanthine

At 0-10°C 16.4 g (0.11 mol) of phosphorus oxychloride are added dropwise to 400 ml of absolute dimethylformamide. At 5-15°C a solution of 15.0 g (0.05 mol) of 1,3-dipropyl-8-furanylxanthine in 330 ml of dimethylformamide is added thereto. The mixture is stirred for 1 hour at ambient temperature and for 7 hours at 85°C. The mixture is poured onto 500 ml of ice and extracted with methylene chloride. The combined organic extracts are dried and evaporated down in vacuo and the residue is crystallised from ether. 12.1 g of the title compound are obtained in the form of brown crystals (73% of theory), m.p. 215-217°C.

General procedure V: oxidation of an aldehyde to form the acidExample 51,3-Dipropyl-8-(2-carboxyfuran-5-yl)xanthine

A solution of 0.26 g (1.5 mmol) of silver nitrate in 2 ml of water is shaken with a solution of 0.4 g of sodium hydroxide in 1 ml of water for 5 minutes. The grey-black silver oxide precipitate is filtered under suction and washed with water, then taken up in 5 ml of water and mixed with 1,3-dipropyl-8-[5-formyl-(2-furanyl)]xanthine. The mixture is heated to 50°C and a solution of 0.1 g of sodium hydroxide in 2 ml of water is slowly added dropwise. The resulting mixture is stirred for 15 minutes at 50°C and for 1 hour at ambient temperature and then filtered. The filtrate is acidified and mixed with methylene chloride, the precipitate formed is filtered under suction and washed



with methylene chloride and ether. 0.4 g of the title compound are obtained in the form of light brown crystals (77% of theory).

General procedure VI: Knoevenagel reaction

Example 6

1,3-Dipropyl-8-[2-(2,2'-bis(ethoxycarbonyl)vinyl)-furan-5-yl]xanthine

2.5 g (7.6 mmol) of 1,3-propyl-dipropyl-8-[5-formyl-(2-furanyl)]xanthine, 1.2 g (7.6 mmol) of diethylmalonate, 0.03 g (0.3 mmol) of piperidine, 0.09 g (1.5 mmol) of glacial acetic acid and 5 ml of benzene p.a. are combined and boiled for 6 hours using a water separator. After the mixture has cooled it is diluted with 10 ml of toluene, the solid matter is suction filtered and dissolved in 100 ml of warm methylene chloride. The solution is filtered, the filtrate is evaporated down in vacuo and the residue is recrystallised from propan-2-ol. 1.0 g of the title compound are obtained in the form of yellow crystals (28% of theory), m.p. 220-222°C.

General procedure VII: general preparation of amides

Example 7

1,3-Dipropyl-8-[2-(N,N-diethylaminocarbonyl)furan-5-yl]-xanthine

1.0 g (2.9 mmol) of 1,3-dipropyl-8-[2-carboxy-furan-5-yl]xanthine are dissolved in absolute dimethyl formamide and at 0-5°C 0.38 g of triethylamine and 0.45 g (3.3 mmol) of isobutylchloroformate are added thereto. The mixture is stirred for 2 hours at 0-5°C, then 0.34 g (2.9 mmol) of N,N-diethylamino-ethylamine are added, and the mixture is stirred for approximately



a further 12 hours in a thawing ice bath. The mixture is evaporated down in a high vacuum, methylene chloride and water are added, the mixture is made alkaline and extracted with methylene chloride. The organic phases are discarded, the aqueous phase is acidified and extracted once more. The combined organic extracts are dried, filtered and evaporated down and the residue is crystallised from ethyl acetate. 0.25 g of the title compound are obtained in the form of yellowish crystals, m.p. 247-250°C.

General procedure VIII: reduction of a ketone or aldehyde to form the alcohol

Example 8

1,3-Dipropyl-8-(1-hydroxycyclopent-3-yl)xanthine

0.5 g (1.6 mmol) of 1,3-dipropyl-8-(1-oxo-3-cyclopentyl)xanthine, 10 ml of ethanol and 0.1 g (2.6 mmol) of sodium tetrahydridoborate are stirred for 2½ days at ambient temperature. The mixture is evaporated down in vacuo and mixed with water and methylene chloride then the aqueous phase is acidified and extracted. The combined organic extracts are dried and evaporated down in vacuo. The residue is separated into the isomers by chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 95:5). From the 1st fraction, 0.4 g of the title compound are obtained in the form of white crystals (39% of theory), m.p. 174-176°C and from the 2nd fraction 0.4 g of the title compound are obtained in the form of white crystals (39% of theory), m.p. 191-193°C.



General procedure IX: acylation of an alcoholExample 91,3-Dipropyl-8-[1-((4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]-heptan-3-on-1-yl)carbonyloxy)cyclopentan-3-yl]xanthine

0.2 g (0.6 mmol) of 1,3-dipropyl-8-(1-hydroxy-3-cyclopentyl)xanthine and 0.24 g (3 mmol) of pyridine are mixed into 10 ml of absolute methylene chloride and after the addition of 0.2 g (0.9 mmol) of camphanyl chloride, the mixture is stirred for 4 hours at ambient temperature. Water is then added and the aqueous phase is separated off. The organic phase is dried and evaporated down in vacuo, then the residue is purified by chromatography on silica gel (CH₂Cl₂/CH₃OH 95:5). 50 mg of the title compound are obtained in the form of a yellowish oil.

General procedure X: Wittig-Horner reactionExample 101,3-Dipropyl-8-(1-cyanomethylenecyclopent-3-yl)xanthine

0.28 g (1.6 mmol) of diethylcyanomethane phosphonate are dissolved in 20 ml of absolute benzene and refluxed for 5 hours with 0.13 g (3.2 mmol) of a 60% sodium hydride dispersion. The mixture is evaporated down in vacuo and taken up in methylene chloride and water and then acidified. The aqueous phase is extracted and the combined organic extracts are dried and evaporated down. Subsequent chromatography of the residue on silica gel (CH₂Cl₂/CH₃OH 97:3) yields 0.1 g of the title compound in the form of a colourless oil (18% of theory).



General procedure XI: hydrogenation of double bondsExample 111,3-Dipropyl-8-(norbornan-2-yl)xanthine

1.0 g (3.1 mmol) of 1,3-dipropyl-8-(5-norbornen-2-yl)xanthine are hydrogenated under pressure in 30 ml of ethanol, with the addition of palladium/charcoal, until no further uptake of hydrogen can be detected. The catalyst is filtered off, the filtrate is concentrated by evaporation and the residue is chromatographed on silica gel ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99:1). 0.4 g of the title compound are obtained in the form of white crystals (39% of theory), m.p. 136-138°C.

General procedure XII: saponification of an esterExample 121,3-Dipropyl-8-(2-(2'-ethoxycarbonyl-2'-carboxyvinyl)-furan-5-yl)xanthine

3.2 g (6.8 mmol) of 1,3-dipropyl-8-[2-(2',2'-bis(ethoxycarbonyl)vinyl)-furan-5-yl]xanthine are added to a solution of 0.8 g (1.4 mmol) of potassium hydroxide in 20 ml of ethanol and the mixture is refluxed for 4 hours. After cooling, it is diluted with 50 ml of water and extracted with methylene chloride. The aqueous phase is acidified whilst being cooled with ice and the precipitate formed is filtered off and washed with water. 2.2 g of the title compound are obtained in the form of yellow crystals (73% of theory), m.p. 252-253°C.

General procedure XIII: reduction of an ester to obtain the alcohol

1.7 mmol of the ester are dissolved in 5 ml of tetrahydrofuran and added dropwise to a suspension of lithium alanate (0.04 g, 1.1 mmol) in 5 ml of



tetrahydrofuran. The mixture is stirred at ambient temperature for 36 hours and mixed with saturated diammonium tartrate solution. The aqueous phase is extracted with ethyl acetate, the combined organic extracts are dried and evaporated down in vacuo. The product is purified by crystallisation or by chromatography on silica gel.

General procedure XIV: N-alkylation

Example 13

1-Benzyl-3-propyl-6-aminouracil

3.0 g (0.014 mol) of 1-benzyl-6-aminouracil are stirred for 3 hours at 70°C with 2.2 g (0.018 mol) of n-propyl bromide, 4.2 ml of 15% sodium hydroxide solution and 7 ml of ethanol. The mixture is poured onto ice and extracted with methylene chloride. The organic phases are dried and evaporated down. The residual oil is crystallised from a mixture of methylene chloride and methanol. 1.62 g of the title compound are obtained in the form of white crystals (47% of theory), m.p. 189-192°C.

General procedure XV: nitrosation

Example 14

1-Benzyl-3-propyl-5-nitroso-6-aminouracil

2.0 g (7.7 mmol) of 6-amino-1-benzyl-3-propyluracil are heated to 80°C in 15 ml of water and mixed with a solution of 0.55 g of sodium nitrite in 3 ml of water. After the addition of 1 ml of glacial acetic acid a red solid is precipitated. The pH is adjusted to 4 and the suspension is stirred for a further 30 minutes at 80°C. After cooling, the crystals are filtered under suction and washed with water. 1.9 g of the title compound are



obtained in the form of reddish-violet crystals (86% of theory), m.p. 208-212°C/decomposition.

General procedure XVI: hydrogenation of the nitroso compound

The 3-substituted 6-amino-1-benzyl-5-nitrosouracil is taken up in methanol and, after the addition of Raney nickel, hydrogenated under pressure. The catalyst is filtered off, the filtrate is evaporated down and the residue is purified by crystallisation or chromatography.

General procedure XVII: etherification

Etherification of alcohols was carried out by deprotonation of the hydroxy function using a strong base (e.g. sodium hydride in tetrahydrofuran or dimethylformamide, sodium hydroxide) and reaction with an electrophile of the type R-X, wherein X may be halogen, tosyl, mesyl or the like.

General procedure XVIII:

Example 15

(+)-1,3-Dipropyl-8-(3-hydroxycyclopentyl)xanthine

- a) 2.0 g (6.2 mmol) of racemic 1,3-dipropyl-8-(3-hydroxycyclopentyl)xanthine are suspended in 2 l of absolute toluene and mixed with 640 mg of acetic anhydride and 2.0 g of lipase from *Candidacylindracea*, with vigorous stirring. After 6 hours at ambient temperature the enzyme is filtered off and washed with methanol. The combined filtrates are evaporated to dryness in vacuo and the residue is chromatographed with $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 95:5 on silica gel.



- b) 0.6 g of acetylated product are obtained, which is dissolved in 22 ml of absolute THF and, after the addition of 70 mg of lithium aluminium hydride, stirred for 2 hours at ambient temperature. Whilst the mixture is cooled with ice it is hydrolysed dropwise with 5 ml of H₂O, acidified and extracted with methylene chloride. The organic phase is dried and evaporated down and the residue is chromatographed with CH₂Cl₂/CH₃OH 95:5 on silica gel. 490 mg of alcohol are obtained with an optical rotation $[\alpha]_D^{20} = +12^\circ$ (c=0.4, methanol).
- c) The optically enriched alcohol is dissolved in 490 ml of absolute methylene chloride and mixed with 490 mg of acetic anhydride and 1.5 g of lipase "Amano P". The mixture is stirred for 24 hours at ambient temperature, filtered to remove the enzyme and the filtrate is evaporated to dryness in vacuo. Chromatography on silica gel using CH₂Cl₂/CH₃OH 95:5 yields 480 mg of alcohol of the title compound with an optical rotation $[\alpha]_D^{20} = +18.2$ (c = 0.5, CH₃OH); optical purity according to HPLC >99%.

General procedure XIX:

Example 16

(-)-1,3-Dipropyl-8-(3-hydroxy-cyclopentyl)xanthine

- a) 1.0 g of racemic 1,3-dipropyl-8-(3-hydroxy-cyclopentyl)xanthine are suspended in 1 l of absolute toluene and stirred with 320 g of acetic anhydride and 1.0 g of lipase from *Candida cylindracea* for 8 hours at ambient temperature. The mixture is filtered to remove the enzyme, then washed with methanol and the filtrates are



evaporated to dryness in vacuo. The residue is chromatographed on silica gel using $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 95:5. 0.45 g of crystalline residue is obtained, which is then triturated with ether and filtered under suction. This yields 350 mg of crystals with an optical rotation $[\alpha]_D^{20} = 13.7$ ($c = 0.4$, CH_3OH)

- b) The optically enriched alcohol is once again stirred in toluene with 110 mg of acetic anhydride and 350 mg of lipase from *Candida cylindracea* for 16 hours at ambient temperature. The mixture is worked up as described above. Yield: 200 mg of colourless crystals, optical rotation $[\alpha]_D^{20} = -20.2$ ($c = 0.5$, CH_3OH), enantiomeric purity according to HPLC >99.5%.

General procedure XIX:

Example 16

(+) and (-)-1,3-dipropyl-8-(3-oxocyclopentyl)xanthine

1.0 g of optically pure alcohol 28 is dissolved in 30 ml of absolute methylene chloride and after the addition of 1.1 g of pyridinium chlorochromate the mixture is stirred at ambient temperature for 2.5 hours. The mixture is washed twice with H_2O , the aqueous phases are extracted with methylene chloride and the combined organic phases are dried and evaporated down in vacuo. Purification is carried out by chromatography on silica gel using $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99:1, 98:2 and 97:3.

Depending on the optically pure alcohol used, the following compounds are obtained.

(+) alcohol yields

(-) 1,3-dipropyl-8-(3-oxocyclopentyl)xanthine

$[\alpha]_D^{20} = 8.3$ ($c = 0.5$, methanol);



(-) alcohol yields

(+) 1,3-Dipropyl-8-(3-oxocyclopentyl)xanthine

$[\alpha]_D^{20} - 8.0$ (c = 0.5, methanol).

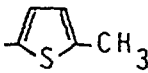
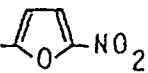
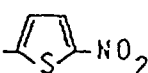
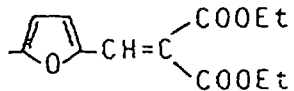
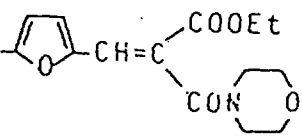
The official chemical abstract nomenclature of these compounds is: 8-(3-oxocyclopentyl)-1,3-dipropyl-7H-purin-2,6-dione.

The compounds listed in Table I can be prepared analogously to the procedures described or according to known analogous methods.

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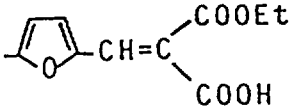
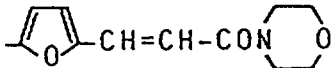
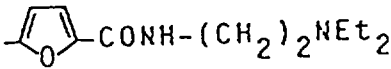
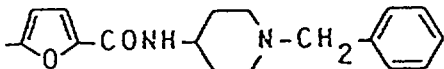
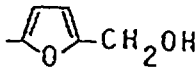
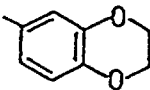


Table I

NO.	R ¹	R ²	R ³	M.pt(°C)
1	n-C ₃ H ₇	n-C ₃ H ₇		272-274
2	"	"		276-277
3	"	"		258-259
4	"	"		283-284
5	"	"		262-263
6	"	"		220-222
7	"	"		252-253

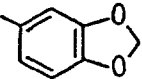
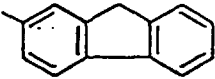
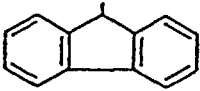
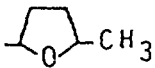
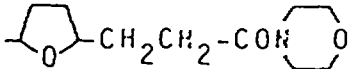
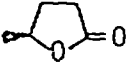
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No.	R ¹	R ²	R ³	M.pt (°C)
8	"	"		252-253
9	"	"		255
10	"	"		253-255
11	n-C ₃ H ₇	n-C ₃ H ₇		247-250
12	"	"		210-217
13	"	"		235-236
14	"	"		280-282

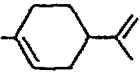
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NO.	R ¹	R ²	R ³	M.pt (°C)
15	"	"		291-294
16	"	"		> 300
17	"	"		228-229
18	CH ₃	CH ₃		228-230
19	CH ₃	CH ₃		148-150
20	n-C ₃ H ₇	n-C ₃ H ₇		135-137
21	"	"		195-196
22	"	"		171-172

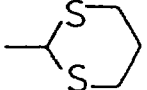
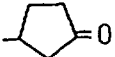
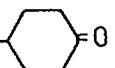
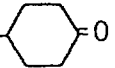
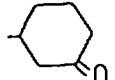
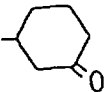
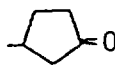
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No.	R ¹	R ²	R ³	Mp(°C)
23	CH ₃	CH ₃		275-277
24	n-C ₃ H ₇	n-C ₃ H ₇		213-213
25	"	"		205-207
26	"	"		197-198
27	"	"		80-83
28	"	"		186-187
29	CH ₃	CH ₃		260
30	n-C ₃ H ₇	n-C ₃ H ₇		179-181

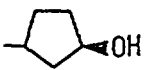
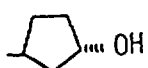
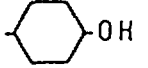
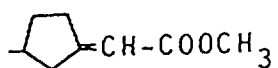
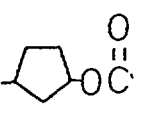
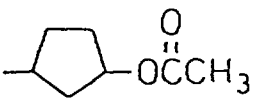
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NO.	R ¹	R ²	R ³	M.p ^t (°C)
31	"	"		197-198
32	CH ₃	CH ₃		273-275
33	n-C ₃ H ₇	n-C ₃ H ₇		165-167
34	"	"		138-140
35	CH ₃	CH ₃		292
36	"	"		210-220
37	n-C ₄ H ₉	n-C ₄ H ₉		142-150
38	CH ₃	CH ₃		292

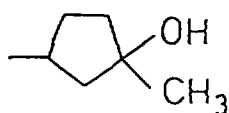
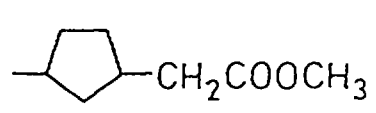
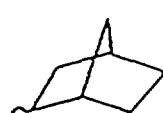
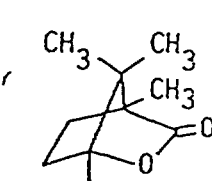
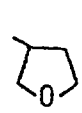
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No.	R ¹	R ²	R ³	Mp (°C)
39	n-C ₃ H ₇	n-C ₃ H ₇		174-176
40	"	"		191-193
41	CH ₃	CH ₃		277-280
42	n-C ₃ H ₇	n-C ₃ H ₇		213-216
43	"	"	 camphanic acid	101-112
44	"	"		156-157
45	"	"		166-168
46	"	"		144-148

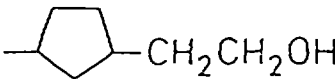
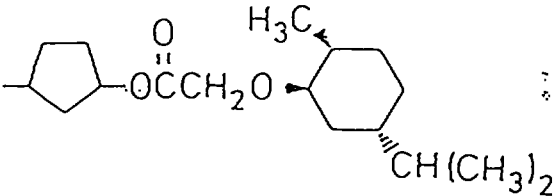
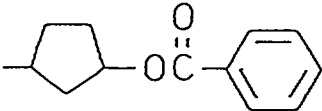
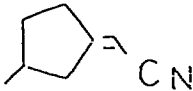
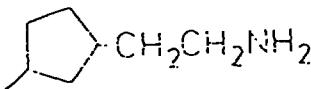
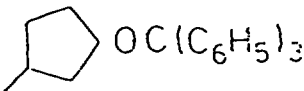
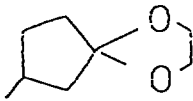
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NO.	R ¹	R ²	R ³	M.pt (°C)
47	"	"		151-152
48	"	"		146-147
49	"	"		137-139
50	"	"		136-138
51	"	"		200-201
52	"	"		162
53	"	"		180

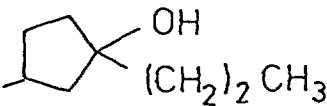
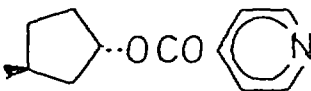
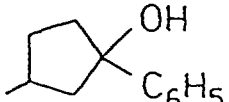
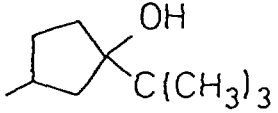
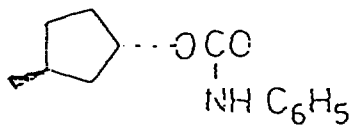
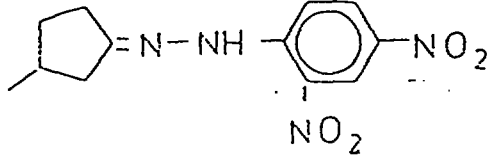
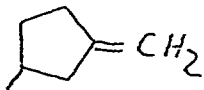
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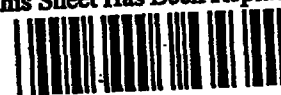
No.	R ¹	R ²	R ³	M.pt (°C)
54	"	"		164-165
55	"	"		134-135
56	"	"		148-151
57	"	"		128-147
58	"	"		199-203
59	"	"		167-168
60	"	"		155-157

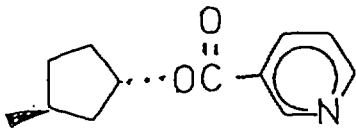
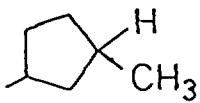
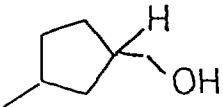
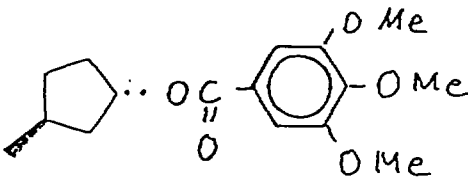
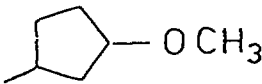
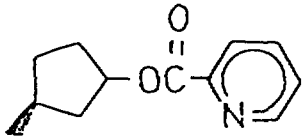
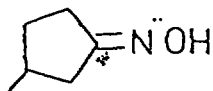
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No.	R ¹	R ²	R ³	M.pt (°C)
61	"	"		83-85
62	"	"		202-205
63	"	"		130-133
64	"	"		124-127
65	"	"		210-213
66	"	"		256-259
67	"	"		170-173

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No.	R ¹	R ²	R ³	M.pt (°C)
68	"	"		185-186
69	"	"		181-182
70	"	"		196-198 173-175
71	"	"		162-164
72	"	"		153-154
73	"	"		155-156
74	"	"		234-236

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No.	R ¹	R ²	R ³	M.pt (°C)
75	"	"	 =O (S)	172-173
76	"	"	 =O (R)	174-175
77	"	"	 OH (SS)	188-189
78	"	"	 OH (RR)	182-183

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The compounds of general formula (I) may be used either on their own or in conjunction with other active substances according to the invention, possibly in conjunction with other pharmacologically active substances. Suitable forms for administration include, for example, plain or coated tablets, capsules, suppositories, solutions, syrups, emulsions or dispersible powders. Tablets may be produced, for example, by mixing the active substance or substances with known excipients, e.g. inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for obtaining delayed release such as carboxymethylcellulose, cellulose acetate phthalate or polyvinyl acetate. The tablets may also consist of several layers.

Coated tablets may be produced accordingly by coating cores made in the same way as the tablets with the substances normally used for tablet coating, such as collidone or shellac, gum arabic, talc, titanium dioxide or sugar. In order to obtain delayed release or prevent incompatibilities, the core may also consist of several layers. Similarly, the tablet coating may consist of several layers in order to obtain delayed release, and the excipients mentioned above for the tablets may be used.

Syrups of the active substances or combinations of active substances according to the invention may additionally contain a sweetener such as saccharin, cyclamate, glycerol or sugar and a flavour-enhancing agent, e.g. a flavouring such as vanillin or orange extract.

They may also contain suspension adjuvants or thickeners such as sodium carboxymethylcellulose, wetting agents, e.g. condensation products of fatty alcohols with ethylene oxide, or preservatives such as

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p-hydroxybenzoates.

Injection solutions are prepared in the usual way, e.g. by adding preservatives such as p-hydroxybenzoates or stabilizers such as alkali metal salts of ethylenediamine-tetraacetic acid and the resulting solutions are transferred into injection vials or ampoules.

Capsules containing one or more active substances or combinations of active substances may be prepared, for example, by mixing the active substances with inert carriers such as lactose or sorbitol and encapsulating the mixture in gelatine capsules.

Suitable suppositories may be produced, for example, by mixing the active substances or combinations of active substances envisaged therefore with conventional carriers such as neutral fats or polyethylene glycol or the derivatives thereof.

The Examples which follow illustrate the invention without restricting its scope:

Examples of pharmaceutical formulations

<u>A) Tablets</u>	<u>per tablet</u>
Active substance	100 mg
Lactose	140 mg
Corn starch	240 mg
Polyvinylpyrrolidone	15 mg
Magnesium stearate	<u>5 mg</u>
	500 mg

The finely ground active substance, lactose and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, granulated whilst wet and dried. The granulate, the remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to form tablets of

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suitable shape and size.

B) <u>Tablets</u>	<u>per tablet</u>
Active substance	80 mg
Corn starch	190 mg
Lactose	55 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone	15 mg
Sodium carboxymethyl starch	23 mg
Magnesium stearate	<u>2 mg</u>
	400 mg

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and combined with the remaining corn starch and water to form granules which are dried and screened. The sodium carboxymethyl starch and magnesium stearate are added and thoroughly mixed and the mixture is compressed to form tablets of suitable size.

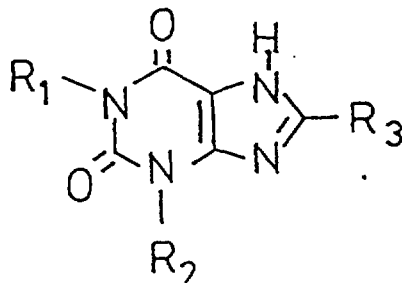
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Claims

1. New xanthines of general formula I



wherein

R_1 is a C_{1-6} , preferably C_{1-4} alkyl group, a C_3 or C_4 alkenyl group or a C_3 or C_4 alkynyl group;

R_2 is a C_3 or C_4 alkenyl group, a C_{1-6} , preferably C_{1-4} alkyl group, an optionally substituted benzyl group or a C_{3-4} alkynyl group;

R_3 represents a C-linked saturated or unsaturated five, six or seven-membered heterocyclic ring which contains one or more heteroatoms selected from the group comprising oxygen and sulphur and may optionally carry one of the following groups:

C_{1-6} , preferably C_{1-4} alkyl, $-CHO$, $-CH_2OR_4$, $-CH_2OR_7$, $COOR_4$, $CONR_5R_6$, whilst a furan or thiophene group may also contain one of the groups

$-CH=CH-CONR_5R_6$,

$-CH=C (COOR_4)_2$ (R_4 being identical or different),

$-CH=C (COOR_4) (CONR_5R_6)$,

$-CH=C (COOR_4) (CH_2OR_4)$ (R_4 being identical or different),

$-CH=C (COOR_4) (CH_2OR_7)$,

$-CH=C (CH_2OR_4)_2$,

$-CH=C (CH_2OR_7)_2$,

$-CH=C (CONR_5R_6)CH_2OR_4$,

$-CH=C (CONR_5R_6)CH_2OR_7$ or nitro

and the tetrahydrofuran group may also carry a



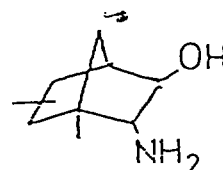
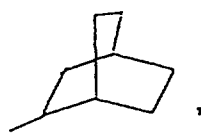
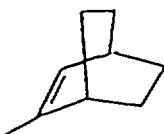
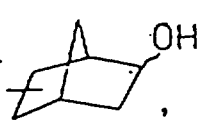
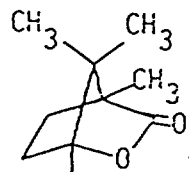
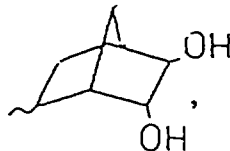
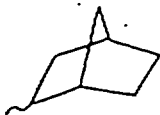
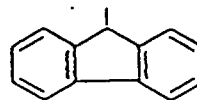
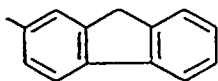


group $-(CH_2)_2-CONR_5R_6$;

- R_3 represents a C_{4-8} cycloalkene which may be substituted by C_{2-4} alkenyl,
- R_3 represents a C_{4-8} , preferably C_5 and C_6 , cycloalkanone or a C_4 to C_8 , preferably C_5 and C_6 cycloalkanol, which may be substituted in the α -position by C_{2-6} , preferably C_{2-4} , alkenyl, C_{2-6} , preferably C_{2-4} alkynyl, optionally substituted benzyl, CH_2OR_4 , CH_2COOR_7 or $(CH_2)_2CN$,
- R_3 represents a C_3 to C_8 , preferably C_5 or C_6 cycloalkane, which may optionally be substituted by C_{1-6} , preferably C_{1-4} alkyl, $=CH_2$, $=N-NH$ -aryl, preferably $=N-NH$ -phenyl, wherein the aryl or phenyl group may be substituted, $=N-NH-C_1$ to C_6 alkyl, $=NOH$, $-OCONH$ -aryl, preferably $-OCONH$ -phenyl, wherein the aryl or phenyl group may be substituted,
 $OCONH-C_{1-6}$ alkyl, $-OR_4$, $-OR_7$, $-(CH_2)_1-COOR_4$, $-(CH_2)_1-NR_4R_4$ (R_4 being identical or different), $-(CH_2)_1-CONR_5R_6$, $-(CH_2)_1-OR_4$, $-(CH_2)_1-OR_7$, wherein 1 represents one of the numbers 0, 1, 2, 3 or 4, or a group $=CAH$ wherein A represents $COOR_4$, CN , $CONR_5R_6$, $CH=CH-COOR_4$, $CH=CH-CONR_5R_6$, CH_2OR_4 or CH_2OR_7 ,
- or the cycloalkane is substituted by C_{1-6} , preferably C_{1-4} alkyl, vinyl, allyl, optionally substituted phenyl, optionally substituted C_{1-4} alkylphenyl, and has as a second substituent a hydroxyl group in a geminal position relative to the first substituent;
- R_3 forms together with the cycloalkane a ketal of general formula



Rb represents C₁₋₄ alkyl or Ra and Rb together form a C₂₋₃ alkylene group which may optionally be mono- or disubstituted by C₁₋₅ alkyl, C₁₋₅ alkyloxycarbonyl, hydroxy C₁₋₅ alkyl, preferably hydroxymethyl;

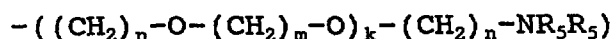
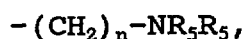
Cc1ccc(cc1)OCCOC2=CC=CC=C2

R₅ represents hydrogen, a C₁₋₆, preferably C₁₋₄



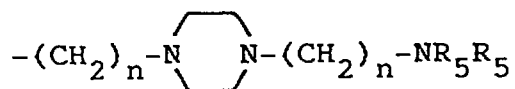
alkyl group, an optionally substituted C₃₋₆ cycloalkyl group;

R₆ represents hydrogen, a C₁₋₆, preferably C₁₋₄ alkyl group, an optionally substituted benzyl group, a group of general formula



(wherein R₅ is identical or different)

wherein n = 2, 3, 4, 5, 6, 7 or 8, m = 2, 3, 4, 5 or 6 and k = 0 or 1,



(wherein R₅ is identical or different),

whilst the piperazine ring may be substituted by C₁₋₄ alkyl, preferably methyl, a C-linked piperidinyl group which is optionally substituted by C₁₋₄ alkyl or an N-linked benzyl group or

R₅ and R₆ together with the nitrogen atom form an optionally C₁₋₄-alkyl-substituted five or six or seven-membered ring which may contain a further heteroatom selected from the group comprising oxygen, sulphur and nitrogen, whilst the nitrogen atom may be substituted by the group R₄;

R₇ represents an amino acid group, linked via the carbonyl function, of a naturally occurring amino acid, -CO-(CH₂)_p-CH₃ wherein p=0 to 13, preferably 1, 2 or 3, menthoxyacetyl, a camphanic acid group linked via a carbonyl group, abietinoyl, 4-aminobutyroyl, optionally substituted benzoyl, preferably





trimethoxybenzoyl, a group of general formula
 $\text{CO} - \text{B}$, wherein B is an optionally substituted
 C-linked, 5, 6 or 7 membered heterocyclic
 group,
 and optionally the racemates, optically active
 compounds and pharmacologically acceptable
 acid addition salts thereof.

2. Xanthines of general formula I wherein

R_1 represents an unbranched C_{3-4} alkyl group, an allyl
 or a propargyl group;

R_2 represents an allyl group, a C_{3-4} alkyl group or a
 propargyl group;

R_3 represents a group selected from among furan,
 tetrahydrofuran, tetrahydrofuranone, thiophene,
 dithiol, dithian or tetrahydropyran which may carry
 one of the following substituents: methyl, ethyl,
 propyl, butyl, CHO, CH_2OR_4 , CH_2OR_7 , COOR_4 , CONR_5R_6 ,

R_3 represents a furan substituted by
 $-\text{CH}=\text{CH}-\text{CONR}_5\text{R}_6$, $-\text{CH}=\text{C}(\text{COOR}_4)_2$ (R_4 being identical or
 different),
 $-\text{CH}=\text{C}(\text{COOR}_4)(\text{CONR}_5\text{R}_6)$,
 $-\text{CH}=\text{C}(\text{COOR}_4)(\text{CH}_2\text{OR}_4)$ (R_4 being identical or
 different),
 $-\text{CH}=\text{C}(\text{COOR}_4)(\text{CH}_2\text{OR}_7)$,
 $-(\text{CH}_2)_n-\text{CONR}_5\text{R}_6$,
 $-\text{CH}=\text{C}(\text{CH}_2\text{OR}_4)_2$,
 $-\text{CH}=\text{C}(\text{CH}_2\text{OR}_7)_2$,
 $-\text{CH}=\text{C}(\text{CONR}_5\text{R}_6)\text{CH}_2\text{OR}_4$ or
 $-\text{CH}=\text{C}(\text{CONR}_5\text{R}_6)\text{CH}_2\text{OR}_7$;

R_3 represents a cyclopentanyl or cyclohexanyl group,
 optionally substituted by methyl, ethyl, propyl,



isopropyl, tert-butyl, allyl, vinyl, phenyl or benzyl, whilst a hydroxy group may be present as a geminal substituent;

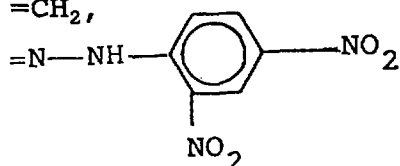
R_3 represents a cyclopentanyl or cyclohexanyl group, substituted by hydroxy, methoxy, ethoxy, propyloxy, trimethoxycarbonyl, isopropyloxy, optionally substituted benzyloxy, allyloxy, propargyloxy,

$-\text{CH}_2-\text{CH}_2-\text{OH}$,

$-\text{CH}_2-\text{COOCH}_3$, $=\text{CH}-\text{COOCH}_3$, $=\text{C}-\text{CN}$,

$-(\text{CH}_2)_2\text{NH}_2$

$=\text{CH}_2$,



$=\text{NOH}$, $-\text{CH}_2\text{OH}$, OR_4 wherein R_4 = methyl or trityl,

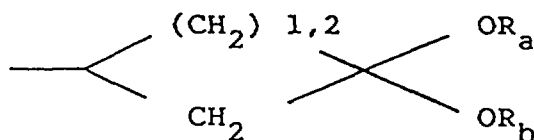
OR_7 wherein R_7 represents COCH_3 , COC_2H_5 , COC_3H_7 , CO tert-butyl, $-\text{CO}$ -phenyl or COCH_2 -phenyl, optionally substituted, CO -pyridyl,

$-\text{CO}$ -(N-methyl-4H-pyridyl),

$-\text{CO}$ -(methylpyridyl), $-\text{COCH}_2-\text{CH}=\text{CH}_2$,

$-\text{CO CH}_2-\text{C}=\text{CH}$;

R_3 represents a group



wherein R_a , R_b = CH_3 , C_2H_5 or R_a and R_b together represent $-\text{CH}_2-\text{CH}_2-$,

R_3 represents a cyclopentanone or cyclohexanone,

R_3 represents a cycloalkane or cycloalkene with 4 - 8 carbon atoms, which may optionally be substituted by a straight-chained or branched C_{2-4} alkenyl

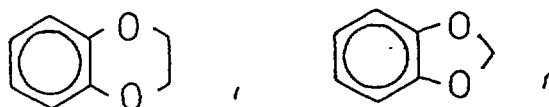
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group; a cyclopentanone or cyclopentanol or cyclohexanone or cyclohexanol which may be substituted in α -position with respect to the keto or hydroxy group by C_{2-4} alkenyl, C_3 or C_4 alkynyl, benzyl, $-CH_2CH_2CN$, $(CH_2)_3NR_5R_5$ (wherein R_5 is the same or different), CH_2COOR_4 , or CH_2OR_4 , wherein R_4 may represent hydrogen, methyl, ethyl or propyl;

R_3 represents norbornane or norbornene, optionally substituted,



R_4 represents hydrogen, a C_{1-3} alkyl, a cyclopropyl group, a cyclopentyl group, benzyl, an aryl group, a propargyl group or a triphenylmethyl group;

R_5 represents hydrogen, a C_{1-3} alkyl group; a cyclopropyl group or a benzyl group;

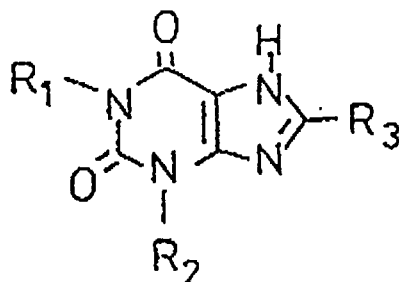
R_6 represents hydrogen, methyl, ethyl, propyl, $-(CH_2)_n-NH_2$ ($n=2-8$), $-(CH_2)_nNEt_2$ ($n=2,3$) or $-(CH_2)_3-O-(CH_2)_4-O-(CH_2)_3-NH_2$, N-benzyl-piperidin-4-yl, or R_5 and R_6 together with the nitrogen atom represent a piperidine, piperazine or morpholine group which may optionally be substituted by a C_{1-4} alkyl group, preferably methyl;

R_7 represents prolinoyl, $CO-(CH_2)_{0-3}-CH_3$, $(-)-$ menthoxyacetyl, a camphanic acid group linked via a carbonyl group, abietinoyl, benzoyl, 4-aminobutyroyl, 3,4,5-trihydroxybenzoyl, 3,4,5-trimethoxybenzoyl, a nicotinic acid, isonicotinic acid or picolinic acid group, an N-methylnicotinic



acid group or an N-methyl-4H-nicotinic acid group,
and optionally the acid addition salts thereof.

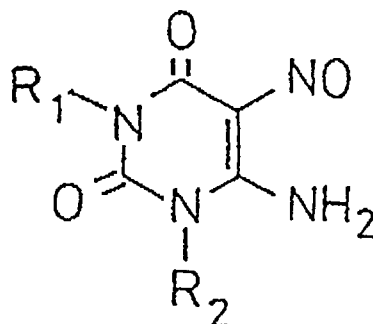
3. Process for preparing xanthines of general formula



I

wherein R_1 , R_2 and R_3 are defined as in claim 1 or 2,
characterised in that

a) a compound of general formula

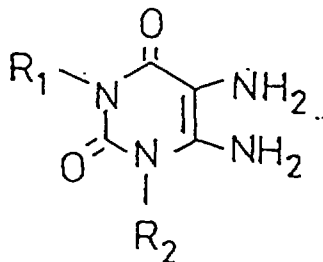


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wherein R_1 and R_2 are defined as hereinbefore, is
reacted with a compound of general formula $\bar{R}_3$ CHO -
wherein R_3 is as hereinbefore defined and any
functional groups in R_3 have to be protected - and
subsequently cyclised with N,N-dimethylhydrazine;
or

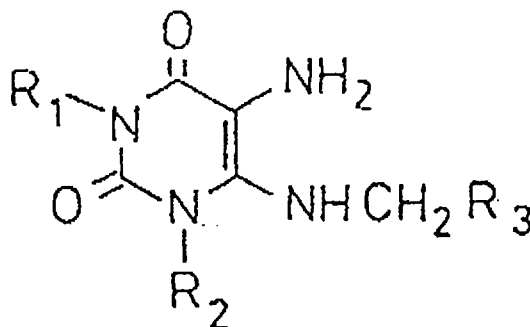
b) a compound of general formula



is reacted with a compound of general formula $R_3\text{CHO}$, $R_3\text{COOH}$ or a reactive derivative thereof - whilst any functional groups in R_3 have to be protected - and subsequently cyclised to form the xanthine of general formula I; or

- c) a compound of general formula

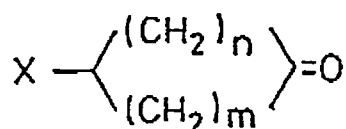
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wherein R_1 , R_2 and R_3 are defined as hereinbefore, is cyclised to form a compound of general formula I,

and subsequently a compound prepared according to a, b or c is optionally further treated using methods known per se, as follows:

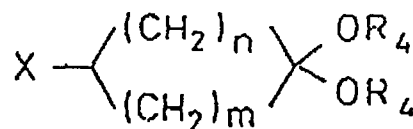
- d) a compound of general formula 1



$$\begin{aligned} m, n &= 0 - 6 \\ m + n &= 2 - 6 \end{aligned}$$

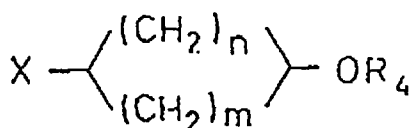
wherein X represents the xanthine group, is converted

- 1) into a compound of formula



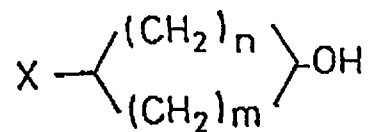
"

or

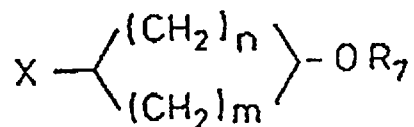


or

2) into a compound

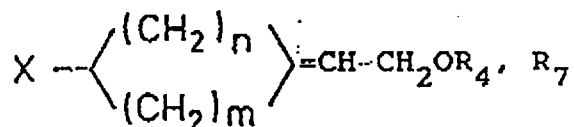
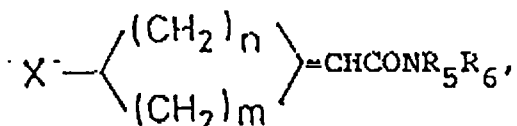
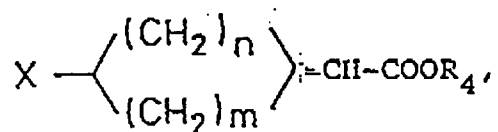


or



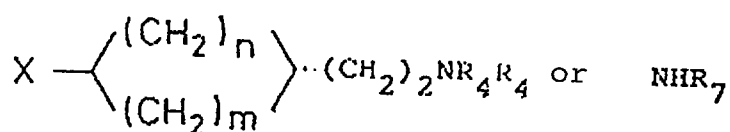
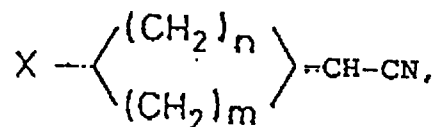
or

3) into a compound



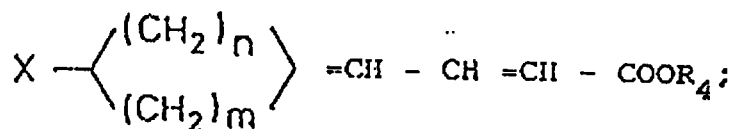
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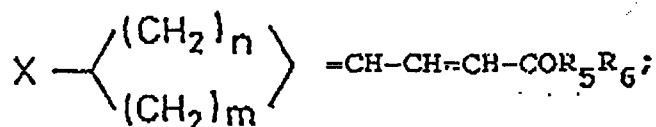
4) into a compound



or

5) into a compound

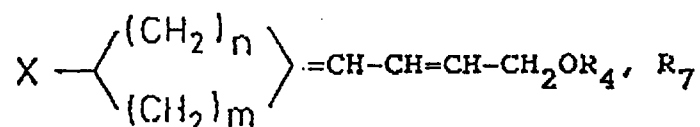




which may optionally be hydrogenated,

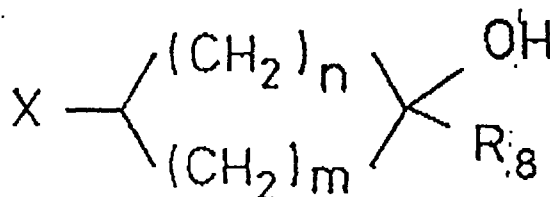
or

6) into a compound



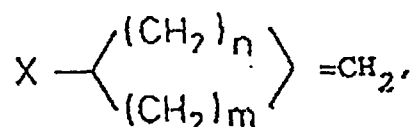
or

7) by Grignard reaction or by reaction with Li-organic reagents into a compound of general formula



or

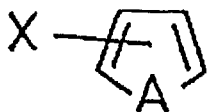
8) by reaction with the Nozaki-Lombardo reagent into a compound



which is reduced to yield the methyl derivative or converted with $\text{BH}_3/\text{CH}_3\text{SCH}_3/\text{H}_2\text{O}_2/\text{OH}^-$ into the corresponding hydroxymethyl compound;

or

e) a compound of general formula

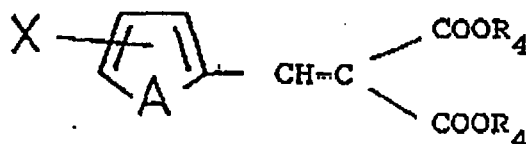


wherein X represents the xanthine group and A

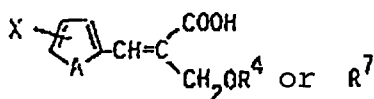
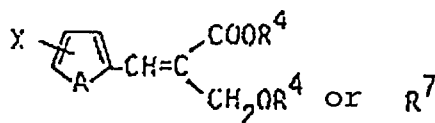
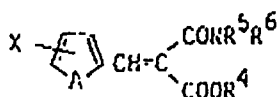
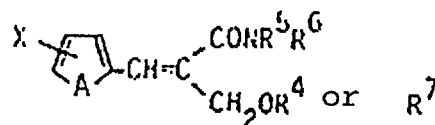
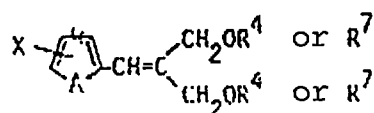




represents oxygen or sulphur, is formylated and then optionally reacted with malonic acid esters to yield compounds of the structure



which can then be converted by analogous methods known per se to compounds of the structure

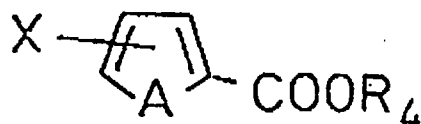


or

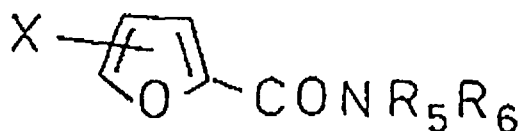
f) an aldehyde of formula



is converted into the acid or the ester of formula



or if A = 0 in the amide of formula





or

- g) 8-norbornenyl derivatives of general formula I are transformed by reaction with KMnO_4 into the cis-diol or converted with m-chloroperbenzoic acid into the epoxide, which can be opened up to form the trans-diol, reacted with sodium azide to form the azido alcohol or reduced with lithium tetrahydroalunate to yield the corresponding alcohol;

whilst in the reaction specified above the groups R_4 , R_5 , R_6 and R_7 are defined as in claim 1 or 2;

- h) suitable compounds of general formula I can be converted into the acid addition salts thereof by methods known per se.

4. Use of a compound of general formula I according to claim 1 or 2 as a pharmaceutical composition.

5. Use of a compound of general formula I according to claim 1 or 2 as a pharmaceutical composition with an adenosine-antagonistic activity.

6. Pharmaceutical preparations containing as active substance one or more compounds of general formula I or the physiologically acceptable acid addition salts thereof in conjunction with conventional excipients and/or carriers.

7. Process for preparing pharmaceutical preparations according to claim 6, characterised in that compounds of general formula I are processed with conventional galenic excipients and/or carriers to obtain conventional pharmaceutical forms for administration.

