3-Alkylxanthines, processes for their preparation and compositions for use in the treatment of chronic obstructive airway disease and cardiac disease

Description

Technical Field

The present invention relates to novel, pharmacologically active compounds and methods for their preparation. The invention also relates to pharmaceutical compositions containing the compounds. More particularly, the novel compounds of the invention are intended for use in the treatment of chronic obstructive airway disease (COAD) or cardiac disease.

The object of the present invention is to provide xanthine derivatives which have a bronchodilatory and cardiotonic potency but which do not elicit convulsions.

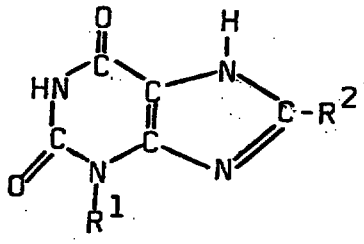
Background Art

Theophylline and various salts thereof are used in the treatment of chronic obstructive airway disease (COAD) and cardiac disease. Major therapeutic effects of theophylline are to relax bronchial smooth muscle and stimulate heart muscle. The major drawback with theophylline therapy is that the drug with a significant frequency produces toxic side-effects; most common are nausea and gastric distress, most serious are convulsions, which may lead to death.

Xanthine derivatives substituted with methyl in position 1 are disclosed in U.S. 4 089 959 as having bronchodilatory activity.

Disclosure of the Invention

It has been found according to the present invention that compounds of the formula



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and the physiologically acceptable salts thereof, wherein R^1 is n-propyl, n-butyl, isobutyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexylmethyl, and R^2 is hydrogen or methyl, provided that R^2 is methyl when R^1 is n-propyl, n-butyl or isobutyl, possess bronchodilatory and cardiotonic potency but do not elicit convulsions. This advantageous property makes the compounds of the invention valuable in the treatment of chronic obstructive airway disease (COAD) and of cardiac disease.

The present invention includes pharmaceutically acceptable salts of compounds of formula (1) with pharmaceutically acceptable bases. By the term "pharmaceutically acceptable salts" is meant salts the cations of which are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial pharmacological properties of the parent compounds of general formula (1) are not vitiated by side effects ascribable to those cations. Suitable salts include the alkali metal, e.g. sodium and potassium, and ammonium salts and salts of amines known in the art to be pharmaceutically acceptable, e.g. glycine, ethylene diamine, choline, diethanolamine, triethanolamine, octadecylamine, diethylamine, triethylamine, 1-amino-2-propanol,2-amino-2-(hydroxymethyl)propane-1,3-diol and 1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol.

Pharmaceutically acceptable salts may be prepared by the reaction together of stoichiometric quantities of a compound of formula (1) and the appropriate base, that is to say, a base as described immediately hereinbefore, for example at an elevated temperature, with or without an appropriate solvent, preferably followed by recrystallisation from an appropriate solvent, for example a hydroxylic solvent, e.g. water, of the salt so formed.

In clinical practice the compounds of the present invention will normally be administered orally, rectally, nasally, sublingually, by injection or by inhalation in the form of a pharmaceutical preparation comprising the active ingredient in the form of the original compound or optionally in the form of a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier which may be a solid, semi-solid or liquid diluent or an ingestible capsule, and such preparations comprise a further aspect of the invention. Usually the active substance will comprise between 0.1 and 99% by weight of the preparation, for example between 0.5 and 20% for preparations intended for injection and between 0.1 and 50% for preparations intended for oral administration.

To produce pharmaceutical preparations in the form of dosage units for oral application containing a compound of the invention the active ingredient may be mixed with a solid, pulverulent

carrier, for example lactose, saccharose, sorbitol, mannitol, a starch such as potato starch, corn starch, amylopectin, laminaria powder or citrus pulp powder, a cellulose derivative, polyvinylpyrrolidone or gelatin and also may include lubricants such as magnesium or calcium stearate or a Carbowax® or other polyethylene glycol waxes and compressed to form tablets or cores for dragées. If dragées are required, the cores may be coated, for example with concentrated sugar solutions which may contain gum arabic, talc and/or titanium dioxide, or alternatively with a film forming agent dissolved in easily volatile organic solvents or other suitable solvent or mixtures of organic solvents. Dyestuffs can be added to these coatings for example, to distinguish between different contents of active substance. For the preparation of soft gelatin capsules (pearl-shaped closed capsules) consisting of gelatin and, for example, glycerol as a plasticizer, or similar closed capsules, the active substance may be admixed with a Carbowax® or a suitable oil as e.g. sesam oil, olive oil, or arachis oil. Hard gelatin capsules may contain granulates of the active substance with solid, pulverulent carriers such as lactose, saccharose, sorbitol, mannitol, starches (for example potato starch, corn starch or amylopectin), cellulose derivatives, polyvinylpyrrolidone or gelatin, and may also include magnesium stearate or stearic acid as lubricants.

A compound of the invention may also be formulated as a sustained action dosage form using suitable excipients. Different methods may be used for the availability control e.g. diffusion process and ion exchange. Methods using the diffusion process may be exemplified by products involving coated granules or particles, matrix imbedded drug and slightly soluble forms.

Effervescent powders are prepared by mixing the active ingredient with non-toxic carbonates or hydrogen carbonates of e.g. sodium, potassium or calcium, such as calcium carbonate, potassium carbonate and potassium hydrogen carbonate, solid, non-toxic acids as tartaric acid, ascorbic acid, and citric acid, and for example aroma.

Liquid preparations for oral application may be in the form of elixirs, syrups or suspensions, for example solutions containing from about 0.1% to 20% by weight of active substance, sugar and a mixture of ethanol, water, glycerol, propylene glycol and optionally aroma, saccharin and/or carboxymethyl-cellulose as a dispersing agent.

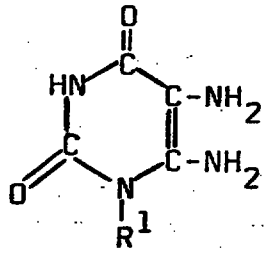
For parenteral application by injection preparations may comprise an aqueous solution or suspension of the active substances according to the invention, desirably in a concentration of 0.5—10%, and optionally also a stabilzing agent and/or buffer substances in aqueous solution. Dosage units of the solution may advantageously be enclosed in ampoules.

The dosage at which the active ingredients are administered may vary within a wide range and will depend on various factors such as for example the individual requirements of each patient. A suitable oral dosage range is from 50 to 1000 mg given 1—4 times a day. A suitable dosage range at parenteral administration is from 20 to 500 mg.

The pharmaceutical compositions containing the active ingredients may suitably be formulated so that they provide doses within these ranges either as single dosage units or as multiple dosage units.

The compounds of the invention can be prepared by any of the following methods.

A. Reacting a compound of the formula



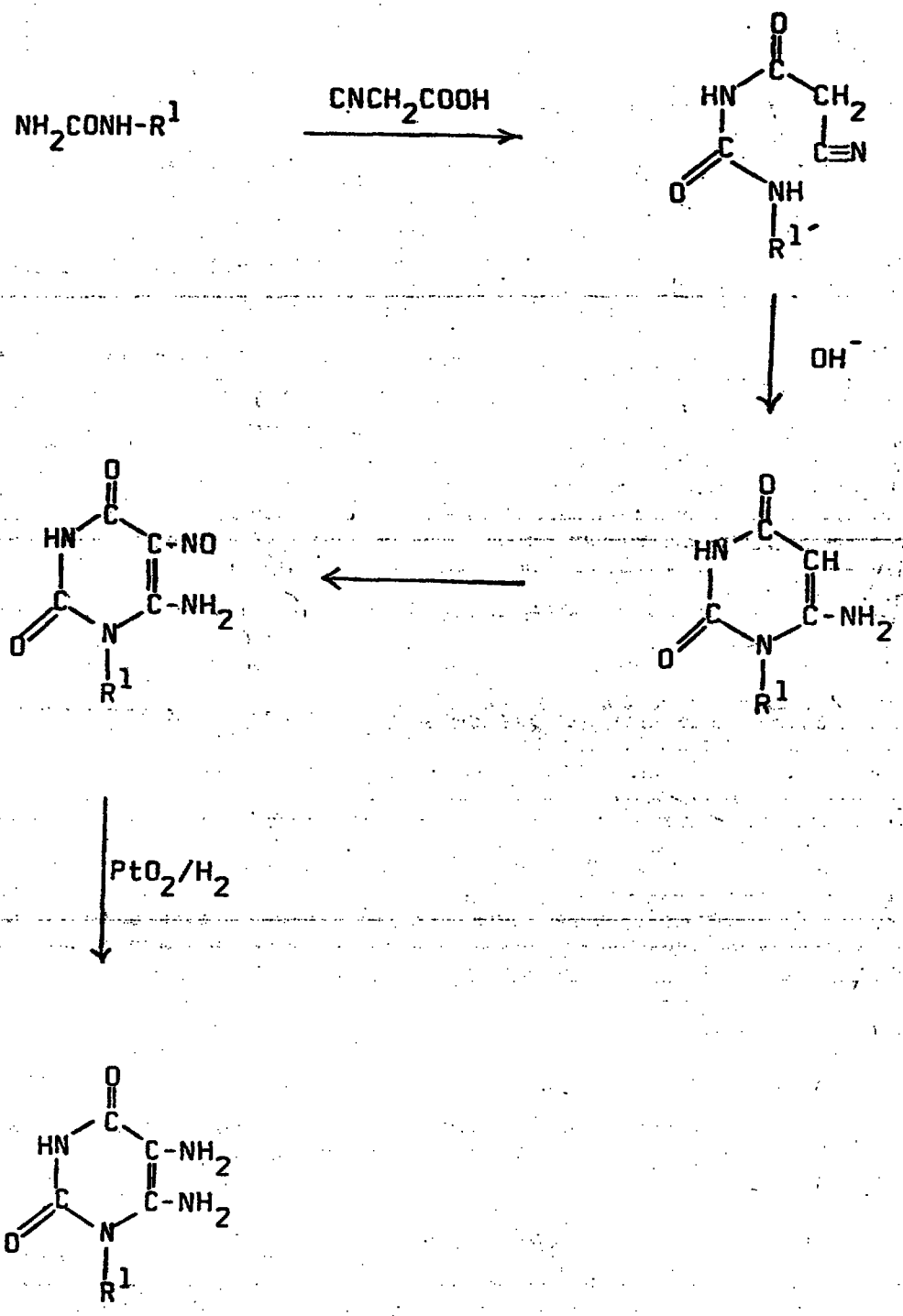
with a compound of the formula

$$R^2—X$$

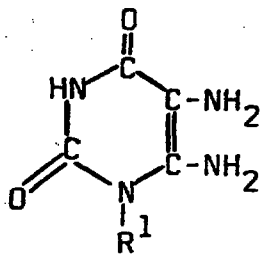
wherein R^1 is n-propyl, n-butyl, isobutyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexylmethyl, R^2 is hydrogen or methyl, X is —COOH, $—CONH_2$ or —OC—O—CO—R^2, provided that R^2 is methyl when R^1 is n-propyl, n-butyl or isobutyl and, if necessary, submitting the obtained product to dehydration.

The dehydration may be carried out for instance by heating the reaction mixture in the absence of solvent or by heating the mixture with alkali or by boiling the mixture in a high-boiling solvent.

The starting material of the compounds prepared according to this route can be obtained for instance as illustrated in the reaction scheme below, wherein the radical R^1 has the meaning given in this specification.



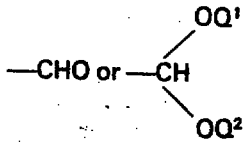
B. Reacting a compound of the formula



with a compound of the formula

$$R^2—X^1$$

wherein R^1 is n-propyl, n-butyl, isobutyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexylmethyl, R^2 is hydrogen or methyl, X^1 is



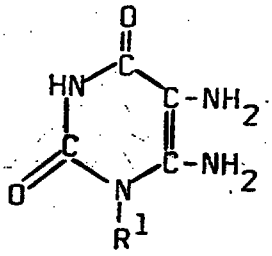
provided that R^2 is methyl when R^1 is n-propyl, n-butyl or isobutyl, and submitting the obtained product to oxidative cyclization.

Q^1 is hydrogen or an alkyl group with 1—3 carbon atoms and Q^2 is an alkyl group with 1—3 carbon atoms. Preferably Q^1 and Q^2 are methyl or ethyl.

For the oxidative cyclization a variety of agents can be used, e.g. thionyl chloride, $SOCl_2$.

Intermediates

The compounds of the formula



wherein R^1 is n-pentyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexylmethyl are not previously described in the literature. They are valuable starting materials for the preparation via methods A and B of the compounds of the invention. The preparation of the starting material is described in connection with the description of method A.

Best mode of carrying out the invention

The best result when carrying out this invention will be obtained when the compound 3-cyclopentyl-3,7-dihydro-1H-purine-2,6-dione is used.

Working Examples

Example 1

Preparation of 3-cyclopropyl-3,7-dihydro-1H-purine-2,6-dione VI

a) Preparation of 6-amino-1-cyclopropyl-2,4-(1H,3H)-pyrimidinedione II

To a solution of 64 g (0.75 mol) cyanoacetic acid and 250 ml of acetic anhydride was added 70 g (0.7 mol) of cyclopropylurea. The solution was stirred at 60—70°C for 2 hours. After cooling white crystals were filtered off and washed with ethanol. Yield 76.7 g (66%) (I). This was suspended in 200 ml of hot water and 55 ml of 5 N NaOH was added in portions so the solution the whole time was basic. The reaction mixture was refluxed for 20 minutes and then neutralized with 5 N HCl. After cooling, white crystals were filtered off. Yield 31.7 g (42%) (II) NMR.

b) Preparation of 6-amino-1-cyclopropyl-5-nitroso-2,4-(1H,3H)-pyrimidinedione III

31.7 g (0.19 mol) of 6-amino-1-cyclopropyl-2,4-(1H,3H)-pyrimidinedione (II) was suspended in 250 ml water. To this was added 45 ml of 5 N HCl and 15 g of $NaNO_2$ (0.22 mol) which was dissolved in water. The reaction mixture was stirred for 2 hours and after cooling, the red crystals were filtered off and washed with water. Yield 31.9 g (86%) (III) NMR.

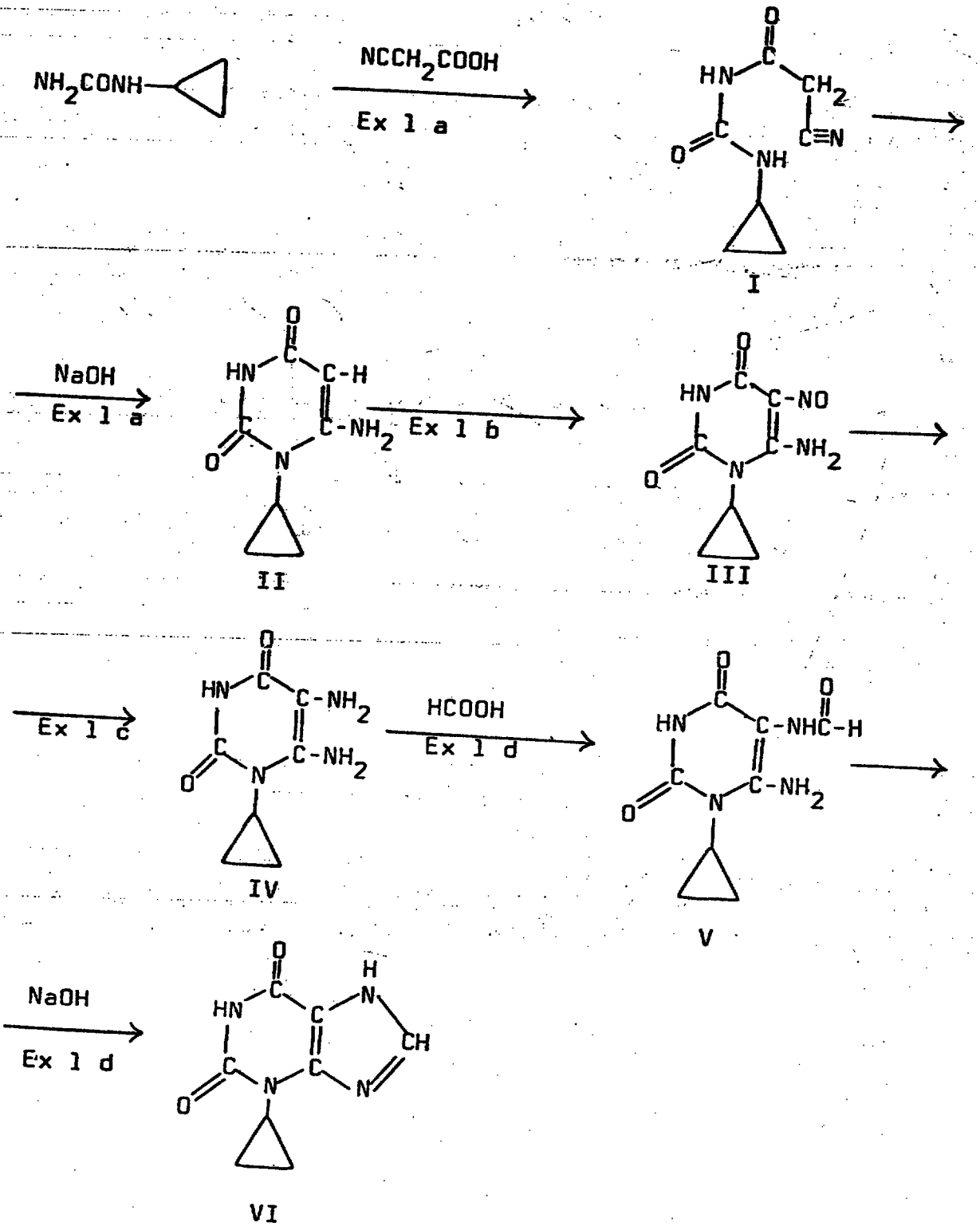
c) Preparation of 1-cyclopropyl-5,6-diamino-2,4-(1H,3H)-pyrimidinedione IV

15.9 g of 6-amino-1-cyclopropyl-5-nitroso-2,4-(1H,3H)-pyrimidinedione (III) was catalytically hydrogenated in 1 liter of DMF and in the presence of 0.1 g PtO_2 for 4 hours and at room temperature and at a pressure of 200 kPa. The catalyst and the crystals were filtered off and washed with ethanol. Yield 12.9 g (87%) (IV).

d) Preparation of 3-cyclopropyl-3,7-dihydro-1H-purine-2,6-dione VI

A solution of 12 g of 1-cyclopropyl-5,6-diamino-2,4-(1H,3H)-pyrimidinedione (IV) in 50 ml of formic acid was refluxed for 2 hours. The hot solution was filtered and 30 ml of chloroform was added and ether was then added slowly. The received crystals were filtered off. Yield 11.2 g (V). The amide (V) was refluxed in 40 ml of 2 N NaOH for 1 hour and then neutralized with 5 N HCl. The crystals were filtered off. Yield 7 g (60%) (VI) NMR (see Table I).

Reaction scheme:



Example 2.

Preparation of 3-cyclobutyl-3,7-dihydro-1H-purine-2,6-dione XII

a) Preparation of 6-amino-1-cyclobutyl-2,4-(1H,3H)-pyrimidinedione VIII

To a solution of 30 g (0.35 mol) cyanoacetic acid and 100 ml of acetic anhydride was added 36.1 g (0.32 mol) of cyclobutylurea. The solution was stirred at 60—70°C for 2 hours. After cooling, white crystals were filtered off and washed with ethanol. Yield 36.4 g (63%) (VII). This was suspended in 100 ml of hot water and 50 ml of 2 N NaOH was added in portions so the solution the whole time was basic. The reaction mixture was refluxed for 20 minutes. After cooling, white crystals were filtered off. Yield 3.6 g (20%) (VIII) NMR.

b) Preparation of 6-amino-1-cyclobutyl-5-nitroso-2,4-(1H,3H)-pyrimidinedione IX

3 g (0.0166 mol) of 6-amino-1-cyclobutyl-2,4-(1H,3H)-pyrimidinedione (VIII), was suspended in 25 ml water. To this was added 4 ml of 5 N HCl and 1.3 g of $NaNO_2$ (0.019 mol) which was dissolved in water. The reaction mixture was stirred for 3 hours and the red crystals were filtered off and washed with water. Yield 3.1 g (89%) (IX) NMR.

c) Preparation of 1-cyclobutyl-5,6-diamino-2,4-(1H,3H)-pyrimidinedione X

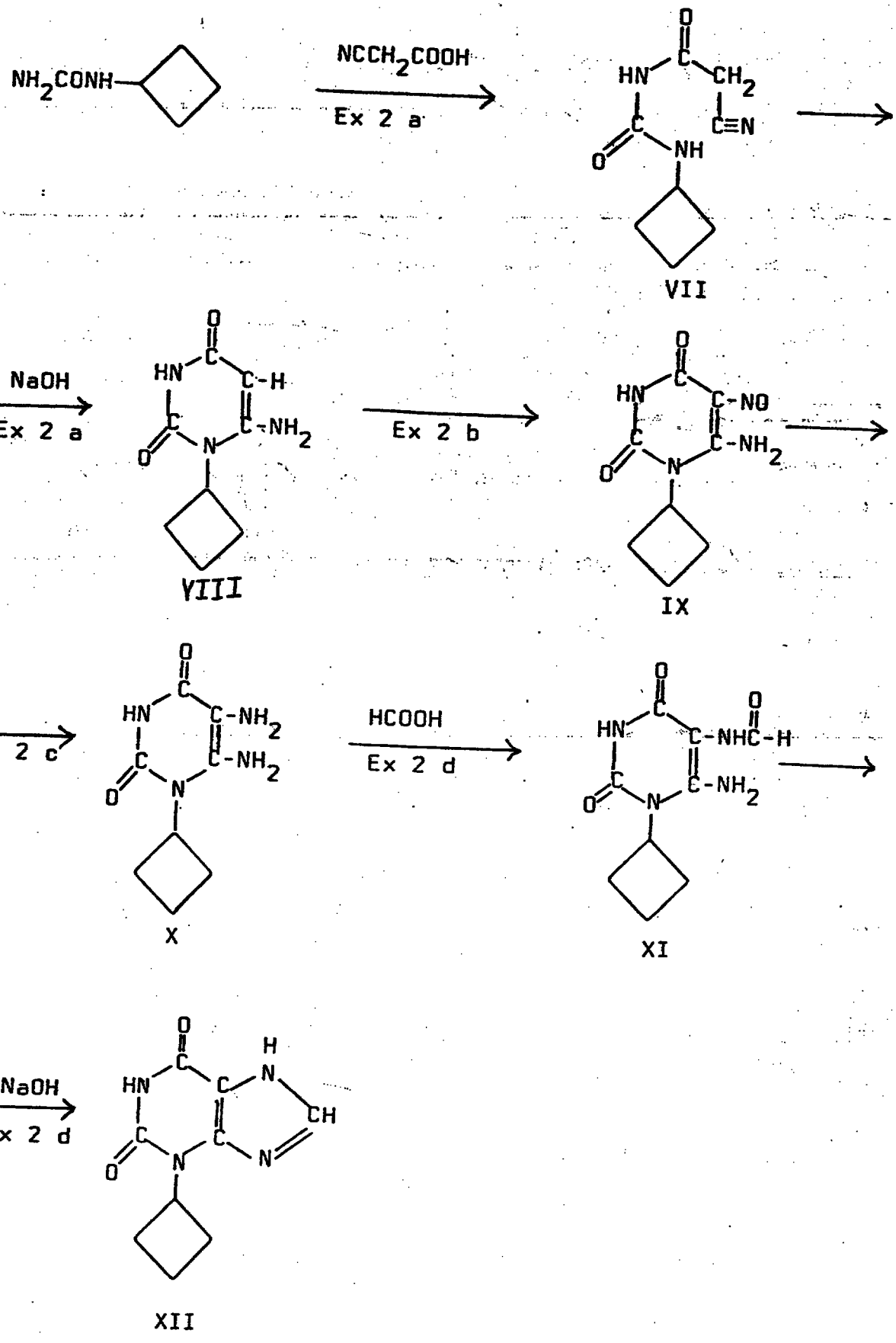
6.9 g of 6-amino-1-cyclobutyl-5-nitroso-2,4-(1H,3H)-pyrimidinedione (IX) was catalytically hydrogenated in 250 ml of DMF and in the presence of 0.1 g PtO_2 for 2 hours and at room temperature and at a pressure of 200 kPa. The catalyst and the crystals were filtered off and washed with ethanol. Yield 3.5 g (54%) (X).

d) Preparation of 3-cyclobutyl-3,7-dihydro-1H-purine-2,6-dione XII

A solution of 3,5 g of 1-cyclobutyl-5,6-diamino-2,4-(1H,3H)-pyrimidinedione (X) in 20 ml of formic acid was refluxed for 2 hours. The hot solution was filtered and 20 ml of chloroform was added and ether was then added slowly. The received crystals were filtered off. Yield 2.7 g (XI).

The amide (XI was refluxed in 20 ml of 2 N NaOH for 1 hour and then neutralized with 5 N HCl. The crystals were filtered off and recrystallized from 150 ml ethanol. Yield 1.4 g (38%) (XII) NMR (see Table I).

Reaction scheme:



Example 3

Preparation of 3-cyclopentyl-3,7-dihydro-1H-purine-2,6-dione XVIII

a) Preparation of 6-amino-1-cyclopentyl-2,4-(1H,3H)-pyrimidinedione XIV

To a solution of 136 g (1.6 mol) cyanoacetic acid and 400 ml of acetic anhydride was added 192 g (1.5 mol) of cyclopentylurea. The solution was stirred at 60—70°C for 2 hours. After cooling white crystals were filtered off and washed with ethanol. Yield 192 g (66%) (XIII). This was stirred in 500 ml of hot water and 195 ml of 5 N NaOH was added in portions so the solution the whole time was basic. The reaction mixture was refluxed for 20 minutes and then neutralized with 5 N HCl. After cooling, white crystals of cyclopentylurea were filtered off (159 g). The filtrate was evaporated and the residue was refluxed with 200 ml of 1 N NaOH. After cooling the cyclopentylurea was filtered off and the filtrate was neutralized with 5 N HCl. The crystals were filtered off. Yield 3.8 g (2%) (XIV) NMR.

b) Preparation of 6-amino-1-cyclopentyl-5-nitroso-2,4-(1H,3H)-pyrimidinedione XV

12.4 g (0.064 mol) of 6-amino-1-cyclopenyl-2,4-(1H,3H)-pyrimidinedione (XIV) was suspended in 200 ml water. To this was added 14 ml of 5 N HCl and 4.8 g of $NaNO_2$ (0.07 mol) which was dissolved in water. The reaction mixture was stirred for 1 hour and washed with water. Yield 12.9 g (90%) (XV) NMR.

c) Preparation of 1-cyclopentyl-5,6-diamino-2,4-(1H,3H)-pyrimidinedione XVI

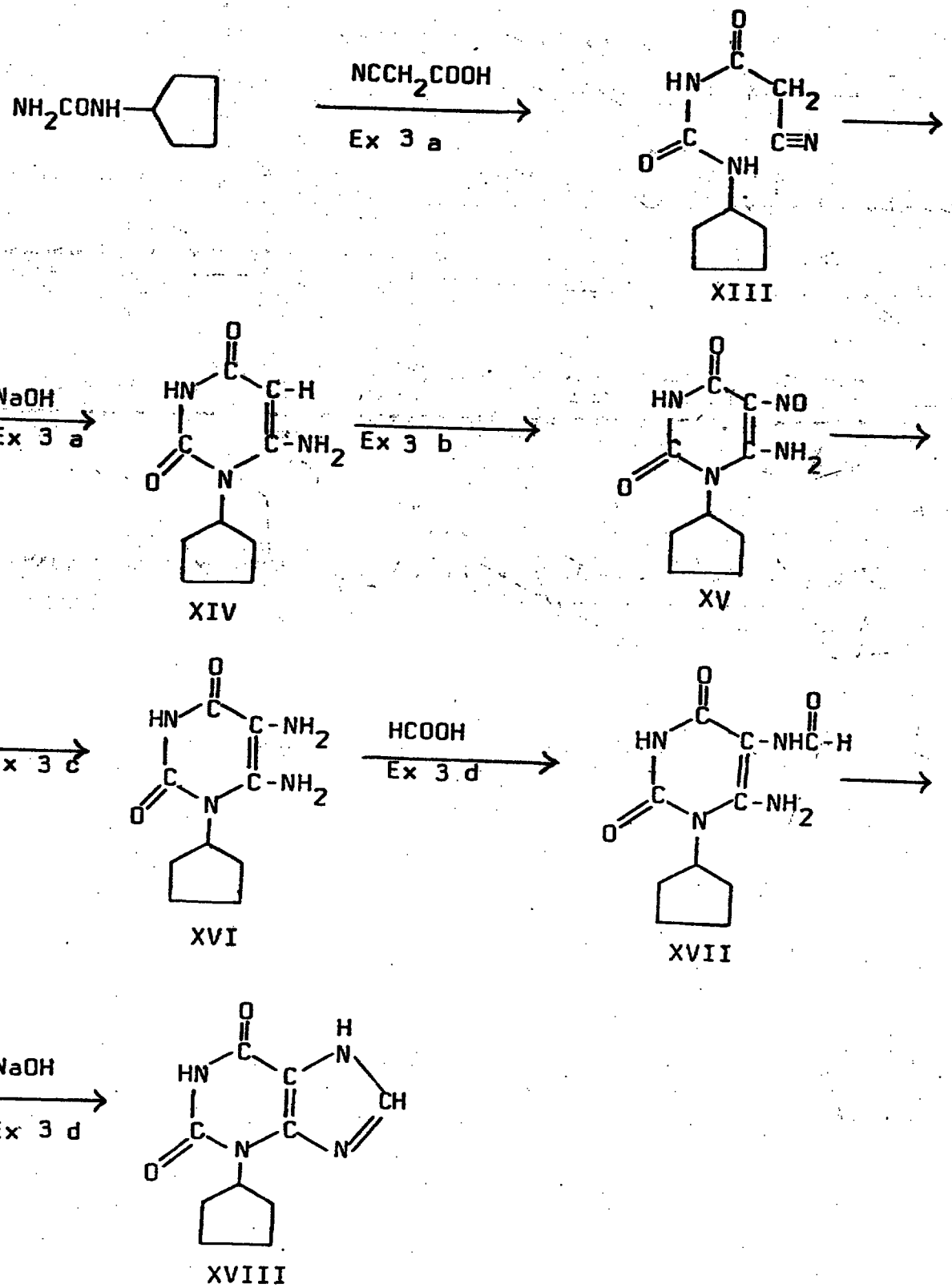
12.9 g of 6-amino-1-cyclopentyl-5-nitroso-2,4-(1H,3H)-pyrimidinedione (XV) was catalytically hydrogenated in 30 ml of 2N HCl and in the presence of 0.1 g PtO_2 for 3 hours and at room temperature and at a pressure of 200 kPa. The catalyst was filtered off and the filtrate was neutralized with 5 N NaOH. The crystals were filtered off. Yield 6.1 g (50%) (XV).

d) Preparation of 3-cyclopentyl-3,7-dihydro-1H-purine-2,6-dione XVIII

A solution of 6.1 g of 1-cyclopentyl-5,6-diamino-2,4-(1H,3H)-pyrimidinedione (XVI) in 25 ml of formic acid was refluxed for 1 hour. The hot solution was filtered and 20 ml of chloroform was added and ether was then added slowly. The received crystals were filtered off. Yield 5.9 g (XVII).

The amide (XVII) was refluxed in 30 ml of 2 N NaOH for 1 hour and then neutralized with 5 N HCl. The crystals were filtered off and recrystallized from 400 ml ethanol. Yield 3.4 g (53%) (XVIII) NMR (see Table I).

Reaction scheme:



Example 4

Preparation of 3,7-dihydro-3-cyclohexylmethyl-1H-purine-2,6-dione XXIV

a) Preparation of 6-amino-1-cyclohexylmethyl-2,4-(1H,3H)-pyrimidine-dione (XX) was performed according to the description of Example 3 a.

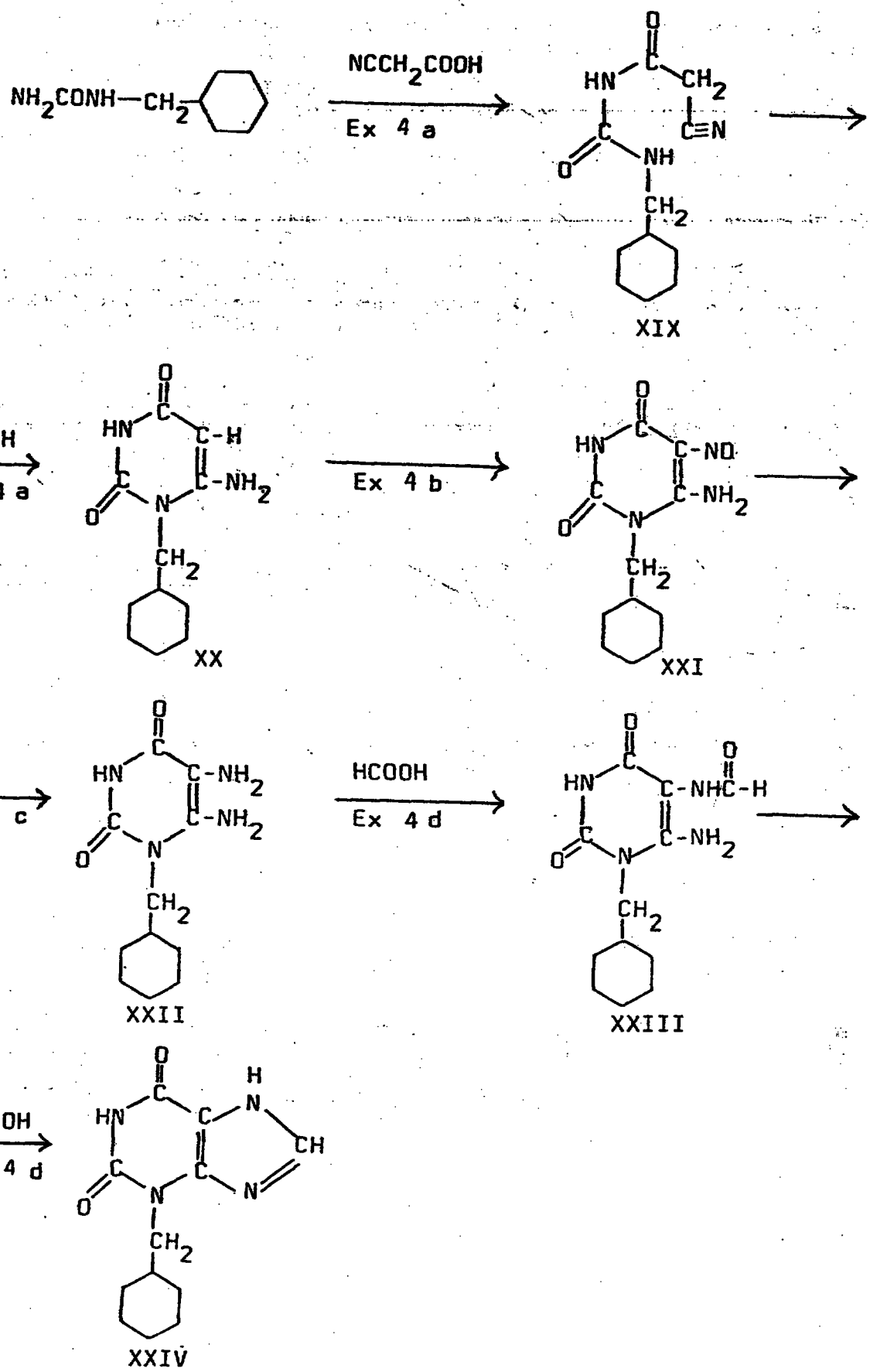
b) Preparation of 6-amino-1-cyclohexylmethyl-5-nitroso-2,4-(1H,3H)-pyrimidinedione (XXI) was performed according to the description of Example 3 b.

c) Preparation of 5,6-diamino-1-cyclohexylmethyl-2,4-(1H,3H)-pyrimidinedione (XXII) was performed according to the description of Example 2 c.

d) Preparation of 3,7-dihydro-3-cyclohexylmethyl-1H-purine-2,6-dione XXIV

2 g of 5,6-diamino-1-cyclohexylmethyl-2,4-(1H,3H)-pyrimidine dione (XXII) was refluxed in 10 ml of formic acid for 1 h. 5 ml of chloroform was added and ether was then added slowly. The received crystals were filtered off. Yield 2.1 g (XXIII). The amide (XXIII) was refluxed in 15 ml of 2 N NaOH for 1 hour and then neutralized with 5 N HCl. Yield 1.7 g (XXIV) NMR (see Table I)

Reaction scheme:



Example 5

Preparation of 3,7-dihydro-3-(2,2-dimethylpropyl)-1H-purine-2,6-dione XXIX

a) Preparation of 6-amino-1-(2,2-dimethylpropyl)-2,4-(1H,3H)-pyrimidinedione (XXVI) was performed according to the description of Example 3 a.

b) Preparation of 6-amino-1-(2,2-dimethylpropyl)-5-nitroso-2,4-(1H,3H)-pyrimidine dione (XXVII)

To a solution of 7.0 g of XXVI in 50 ml of DMSO was added 8 ml of 5 N HCl and 2.7 g of $NaNO_2$ dissolved in 5 ml of water. The reaction mixture was stirred 10 minutes at 50°C and then 100 ml of water was added. The red crystals were filtered off. Yield 6 g (XXVII).

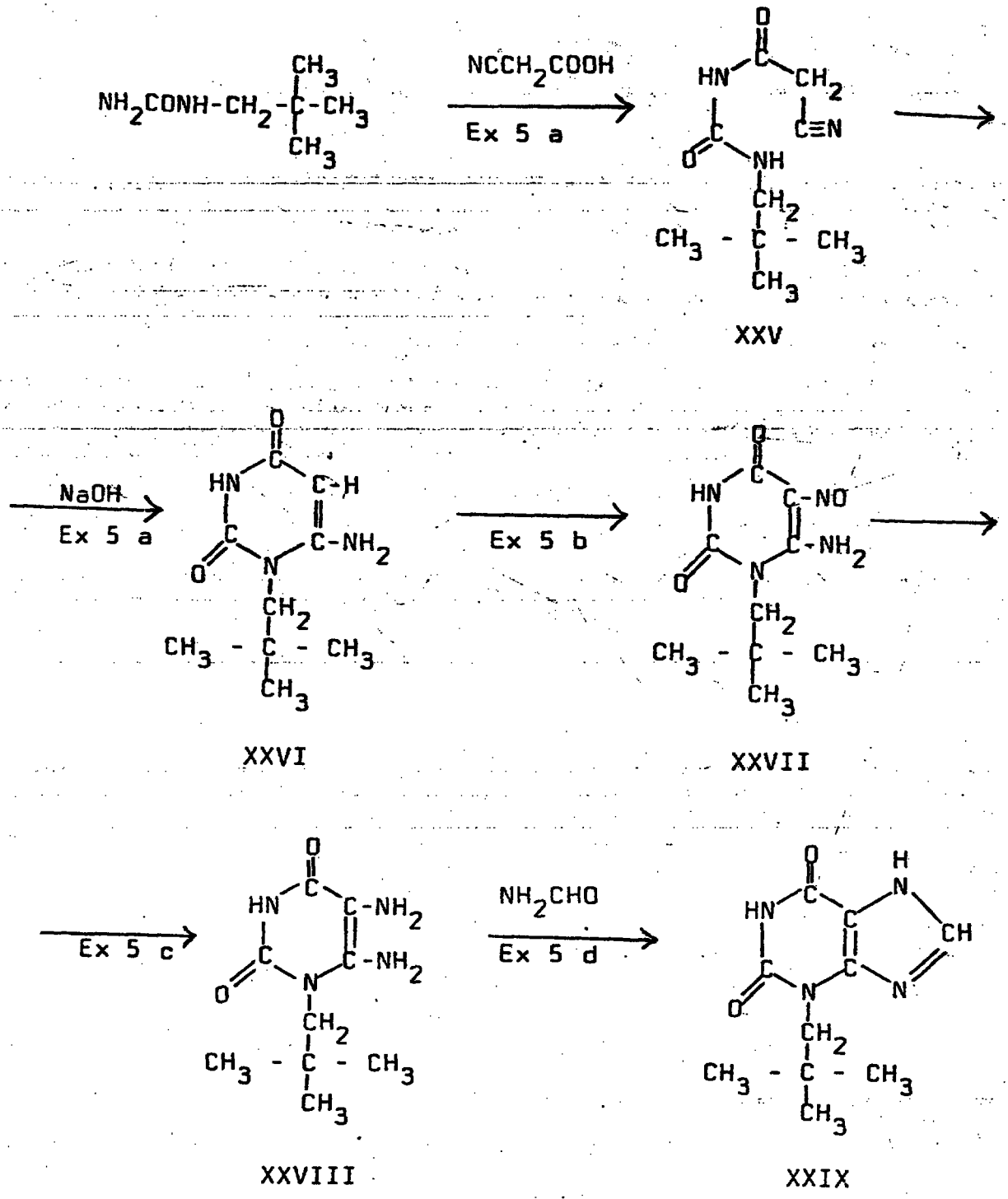
c) Preparation of 5,6-diamino-1-(2,2-dimethylpropyl)-2,4-(1H,3H)-pyrimidinedione (XXVIII)

To a suspension of 6.0 g of XXVII in 100 ml of water was added 13.0 g of sodium dithionite in portions. The green crystals were filtered off and washed with water. Yield 4.0 g (XXVIII).

d) Preparation of 3,7-dihydro-3-(2,2-dimethylpropyl)-1H-purine-2,6-dione (XXIX)

4.0 g of XXVIII was refluxed in 20 ml of formamide for 30 minutes. After cooling 30 ml of ethanol was added and the yellow crystals were filtered off and recrystallized from 15 ml of DMF. Yield 2.0 g (XXIX) NMR (see Table I).

Reaction scheme:



Example 6

Preparation of 3,7-dihydro-8-methyl-3-cyclohexylmethyl-1H-purine-2,6-dione XXX

1 g of 5,6-diamino-1-cyclohexylmethyl-2,4-(1H,3H)-pyrimidine dione (XXII) was refluxed in 5 ml of acetic acid for 1 hour. 2 ml of chloroform was added and ether was then added slowly. The received crystals of the amide were filtered off. Yield 1 g.

The amide was refluxed in 10 ml of 2 N NaOH for 1 hour and then neutralized with 5 N HCl. The crystals were filtered off and recrystallized from 80 ml of ethanol. Yield 0.6 g (XXX) NMR (see Table I).

Example 7

Preparation of 3-cyclopentyl-3,7-dihydro-8-methyl-1H-purine-2,6-dione XXXI

1.6 g of 1-cyclopentyl-5,6-diamino-2,4-(1H,3H)-pyrimidine dione (XVI) was refluxed in 10 ml of acetic acid for 15 min. 10 ml of chloroform was added and ether was then added slowly. The received crystals of the amide were filtered off. Yield 2.0 g.

The amide was refluxed in 5 ml of 2 N NaOH for 1 hour and then neutralized with 5 N HCl. The crystals were filtered off and recrystallized from 25 ml of 80% ethanol. Yield 0.7 g (XXXI) NMR (see Table I).

Example 8

Preparation of 3,7-dihydro-3-(2,2-dimethylpropyl)-8-methyl-1H-purine-2,6-dione XXXIV

10.4 g of 5,6-diamino-1-(2,2-dimethylpropyl)-2,4-(1H,3H)-pyrimidine dione (XXVIII) was refluxed in 75 ml of acetic acid for 1 hour. 50 ml of chloroform was added and ether was then added slowly. The received crystals were filtered off. Yield 11.4 g. The amide was refluxed in 50 ml of 1 N NaOH for 1 hour and then neutralized with 5 N HCl. Yield 7.2 g (XXXIV). NMR (see Table I).

Example 9

Preparation of 3,7-dihydro-8-methyl-3-(2-methylpropyl)-1H-pyrine-2,6-dione XXXV

10 g of 5,6-diamino-1-(2-methylpropyl)-2,4-(1H,3H)-pyrimidinedione was refluxed in 50 ml of acetic acid for 1 hour. 30 ml of chloroform was added and ether was then added slowly. The received crystals were filtered off. Yield 10.8 g. The amide was refluxed in 30 ml of 2 n NaOH for 1 hour and then neutralized with 5 N HCl. The crystals were filtered off and recrystallized from 50 ml of acetic acid. Yield 3.3 g. NMR (see Table I).

TABLE I

NMR data in δ

Solvent DMSO-d_6 ($\delta = 2.83$)

		R_3	R_8	N_1H	N_7H
Ex 1d	D 4161 (VI)	1H 3,20 m 4H 1,22m	1H 8.35s	11,23b	13,80b
Ex 2d	D 4164 (XII)	4H 2,36 m 1H 5,42 p 2H 3,43p	1H 8,40s	11,43b	13,83b
Ex 3d	D 4132(XVIII)	1H 5,53 p 8H 2,17m	1H 8,40s	11,43b	13,94b
Ex 4d	D 4138 (XXIV)	2H 4,14 d 11H 1,63m	1H 8,37s	11,37b	13,90b
Ex 5d	D 4034 (XXIX)	2H 4,16 s 9H 1,23 s	1H 8,27s	11,40b	13,84b
Ex 6	D 4137 (XXX)	2H 4,10 d 11H 1,60 m	3H 2,70s	11,27b	13,45b
Ex 7	D 4134 (XXXI)	1H 5,50 p 8H 2,20 m	3H 2,68s	11,30b	13,43b
Ex 8	D 4070 (XXXIV)	2H 4,08 s 9H 1,23 s	3H 2,67s	11,24b	13,40b
Ex 9	D 4169 (XXXV)	2H 4,05 d 1H 2,50 h 6H 1,10 d	3H 2,63s	11,10b	13,27b

The following Examples illustrate how the compounds of the invention can be incorporated in pharmaceutical compositions.

Example 10

Aerosol for inhalation

Active substance	1.50 g
"Miglyol" (Registered Trade Mark)	0.20 g
"Frigen" (Registered Trade Mark) 11/12/113/114	ad 100.0 g

"Frigen" is used to denote the halogenated hydrocarbons.
"Frigen" 114 is 1,2-dichloro-1,1,2,2-tetrafluorethane,
"Frigen" 113 is 1,1-difluoro-2,2-dichlorotrifluorotrichloroethane, "Frigen" 11 is trichloromonofluoromethane and "Frigen" 12 is dichlorodifluoromethane. "Miglyol" denotes a triglyceride of saturated vegetable oils. Or a pulver aerosol where the active substance is mixed with lactose.

Example 11

Tablets

Each tablet contains:	
Active substance	20.0 mg
Maize starch	25.0 mg
Lactose	190.0 mg
Gelatin	1.5 mg
Talc	12.0 mg
Magnesium stearate	1.5 mg
	250.0 mg

Example 12

Suppositories

Each suppository contains:	
Active substance	50.0 mg
Ascorbyl palmitate	1.0 mg
Suppository base (Imhausen H)	ad 2.000.0 mg

Example 13

Injection solution

Active substance	2.000 mg
Sodium hydroxide	0.310 mg
Sodium pyrosulphite	0.500 mg
Disodium edetate	0.100 mg
Sodium chloride	8.500 mg
Sterile water for injection	ad 1.00 g

Sublingual tablets

Example 14

Each tablet contains:

Active substance	20.0 mg
Lactose	85.0 mg
Agar	5.0 mg
Talc	5.0 mg

Pharmacological tests

Acute toxicity studies in mice

Male NMRI mice, weighing 20—26 g, starved for 6 h were used. The compounds, dissolved in 0.5 M NaOH and 0.85% NaCl-solution (pH 10.6—12.1) were administered as follows:

a) intravenously, 0.1 ml/10 g at an injection rate of 0.3 ml per minute

b) orally, 0.1 ml/10 g

At least seven dose levels, doses increasing in a geometric progression with a factor 1.2, were examined. Each dose was given to 5 animals. The animals were observed for signs of toxicity during 14 days after administration. The position of extremities in dead animals indicated whether they had died in convulsions or not.

In acute toxicity studies it was observed that many xanthine compounds elicit convulsions. This was also repeatedly shown to occur with theophylline. However, no sign of convulsive activity (such as tonically stretched hindlegs of dead animals) was observed in animals given the compounds of this invention.

Additionally, convulsive activity was studied by slowly infusing drugs into the tail veins of albino mice. In this study it was confirmed that 1-alkyl substituted xanthines (theophylline and caffeine) consistently produced tonic convulsions, and that with the compounds of the invention death occurred without signs of tonic convulsions. (Table II).

Isolated guinea-pig trachea

Guinea-pigs of both sexes, weighing between 150 and 250 g, were killed by a blow on the head and bled. The trachea was removed and cut spirally yielding one or two preparations. The tracheal preparations were mounted in organ baths containing Krebs solution maintained at 37°C and bubbled with carbogen (95% O_2 + 5% CO_2). Isometric tension reflecting mainly activity in circular tracheal muscle was recorded by means of a force displacement transducer. Initial tension was set at 0.5 g which was the approximate basal tension kept during the experiment. Evaluation of relaxant effects was done when the preparations had contracted to a stable tension by the addition of carbocholine 0.1 µg/ml to the bath. EC_{50} values, i.e. molar concentrations of xanthines required to produce 50% maximum response were obtained from log concentration response lines and used to calculate the potency of theophylline relative to that of the test drug. After washing out the drugs the trachea resumed its basal tone and was left to stabilize for at least 15 min. before the next drug evaluation was performed. Between two evaluations of theophylline the effect of the test drug was examined and its EC_{50} value was compared with the mean of the previous and following EC_{50} values of theophylline. In the Table II the potency ratios are illustrated. Theophylline is one by definition and a value larger than one indicate that the drug is more potent than theophylline.

Isolated guinea-pig hearts

From the bled guinea-pigs, the hearts were immediately removed and perfused with oxygenated Krebs solution at 37° according to Langendorff. The heart was mounted in a thermostatically controlled organ bath (25 ml) containing Krebs solution. A saline-filled, open-end polyethylene catheter was inserted into the right ventricle through the pulmonary artery. The catheter was fixed to the pulmonary artery by a ligature just above the valvular plane. It was connected to a pressure transducer (P23 AC), making it possible to record changes in intraventricular pressure. From these, the contraction frequency was obtained. Drugs were given as single bolus injections into the perfusion solution.

TABLE II

Compound	Guinea-Pig trachea Potency ratios of theophylline	Convulsion test mice i.v. Effects	Death mg/kg i.v.	Guinea-Pig heart Potency ratios of theophylline Chronotrop
Theophylline	1	tonic conv. 30/30	446.3 ± 9.6	1
Caffein	~1	tonic conv. 20/20	391.7 ± 17.7	0.5
D 4034 XXIX	3	loss of balance salivation	519.1 ± 16.6	3
D 4070 XXXIV	1.8	loss of balance	693.3 ± 22.2	1.5
D 4138 XXIV	5	loss of balance salivation	543.6 ± 31,7	15
D4137 XXX	4	loss of balance salivation	493.1 ± 19.4	10
D 4132 XVIII	5.65	loss of balance salivation	593 ± 21.9	3.4
D 4134 XXXI	5.85			
D 4164 XII	3.8	loss of balance (clonic/tonic conv. 3/10)	519.2 ± 16.86	2.1
D 4161 VI	0.5	single twitches and clonic conv. 1/10 loss of balance	1030 ± 39.3	
D 4169 XXXV	10.3	loss of balance single clonic conv.	488.2 ± 8.1	4

VI = 3-cyclopropyl-3,7-dihydro-1H-purine-2,6-dione
XII = 3-cyclobutyl-3,7-dihydro-1H-purine-2,6-dione
XVIII = 3-cyclopentyl-3,7-dihydro-1H-purine-2,6-dione
XXIV = 3,7-dihydro-3-cyclohexylmethyl-1H-purine-2,6-dione
XXIX = 3,7-dihydro-3-(2,2-dimethylpropyl)-1H-purine-2,6-dione
XXX = 3,7-dihydro-8-methyl-3-cyclohexylmethyl-1H-purine-2,6-dione
XXXI = 3-cyclopentyl-3,7-dihydro-8-methyl-1H-purine-2,6-dione
XXXIV = 3,7-dihydro-3-(2,2-dimethylpropyl)-8-methyl-1H-purine-2,6-dione.
XXXV = 3,7-dihydro-8-methyl-3-(2-methylpropyl)-1H-purine-2,6-dione

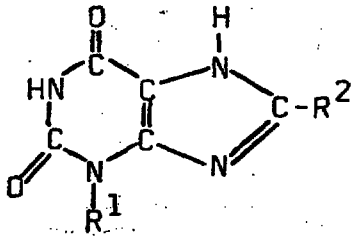
Legend to table

The left column lists molar ratios for bronchodilatation between theophylline and various xanthine compounds. Toxic symptoms occuring before death in mice receiving constant rate infusion of drug i.v. are accounted for in the middle column. Tonic convulsions (conv.) is a consistent effect by theophylline and caffeine (30 out of 30 and 20 out of 20 respectively tested animals had marked tonic convulsions). Each other compound was tested in 10 animals and in no case a tonic convulsion was induced. The notes indicate, however, that a few animals receiving D 4164, D 4161 or D 4169 exhibited a clonic-type of convulsion or a mixed clonic/tonic type of convulsion, however, of very moderate intensity compared to the effect seen by theophylline and caffeine. The far right column indicates cardiotonic activity as positive chronotropic potency.

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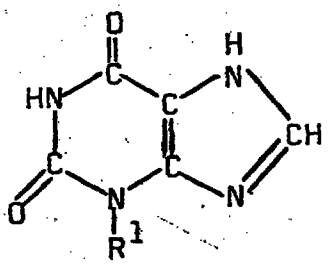
Claims

1. A compound of the formula



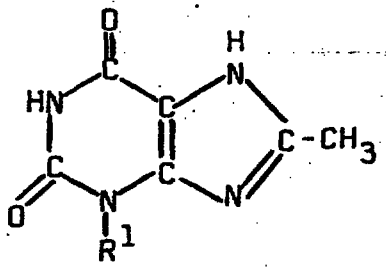
or a physiologically acceptable salt thereof, in which formula R^1 is n-propyl, n-butyl, isobutyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexylmethyl and R^2 is hydrogen or methyl, provided that R^2 is methyl when R^1 is n-propyl, n-butyl or isobutyl.

2. A compound according to claim 1 with the formula



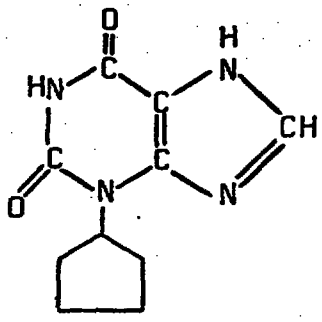
or a physiologically acceptable salt thereof, wherein R^1 is n-pentyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexylmethyl.

3. A compound according to claim 1 with the formula



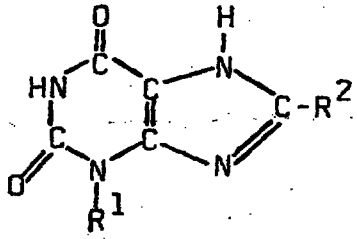
or a physiologically acceptable salt thereof, wherein R^1 is n-propyl, n-butyl, isobutyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexylmethyl.

4. A compound according to claim 1 with the formula



* C L M S *

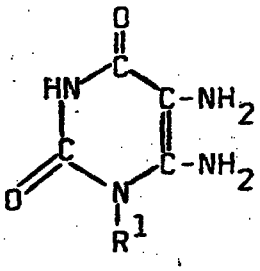
5. A method for the preparation of a compound of the formula



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or a physiologically acceptable salt thereof, in which formula R^1 is n-propyl, n-butyl, isobutyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexylmethyl and R^2 is hydrogen or methyl, provided that R^2 is methyl when R^1 is n-propyl, n-butyl or isobutyl, characterized by

a) reacting a compound of the formula

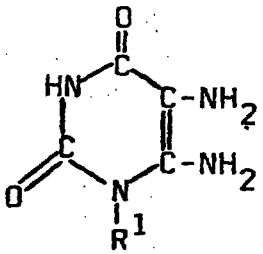


with a compound of the formula

$$R^2—X$$

wherein R^1 and R^2 have the definitions given above and X is —COOH, —$CONH_2$ or —OC—O—CO—R^2 and, if necessary, submitting the obtained product to dehydration, or

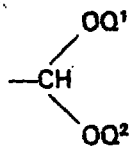
b) reacting a compound of the formula



with a compound of the formula

$$R^2—X^1$$

wherein R^1 and R^2 have the definitions given above and X^1 is —CHO or



wherein Q^1 is hydrogen or an alkyl group with 1—3 carbon atoms and Q^2 is an alkyl group with 1—3 carbon atoms, and submitting the obtained product to oxidative cyclization, whereafter, if desired, the compound obtained in any of the routes a)-b) is converted into a physiologically acceptable salt.

6. A process according to claim 5, characterized in that a compound according to claims 2—4 is prepared.

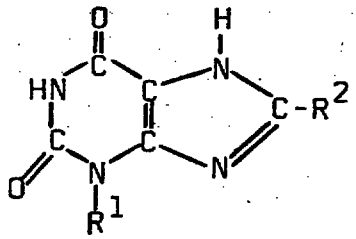
7. A pharmaceutical preparation comprising as active ingredient an effective amount of a compound according to claim 1 in association with a pharmaceutically acceptable carrier for use in the treatment of chronic obstructive airway disease or cardiac disease.

8. A pharmaceutical preparation according to claim 7 comprising as active ingredient a compound according to any of claims 2—4 in association with a pharmaceutically acceptable carrier.

9. A pharmaceutical preparation according to either of claims 7—8 in dosage unit form.

Patentansprüche

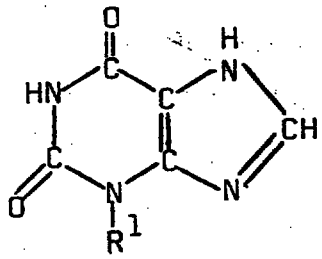
1. Eine Verbindung der Formel



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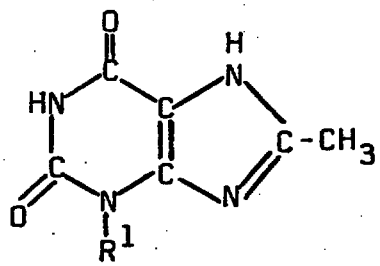
oder ein physiologisch verträgliches Salze derselben, in welcher Formel R^1 n-Propyl, N-Butyl, Isobutyl,n-Pentyl, 2-Methylbutyl, 3-Methylbutyl, 2,2-Dimethylpropyl, Cyclopropyl, Cyclobutyl, Cyclopentyl oder Cyclohexylmethyl und R^2 Wasserstoff oder Methyl ist, wobei R^2 Methyl ist, wenn R^1 n-Propyl, n-Butyl oder Isobutyl ist.

2. Verbindung nach Anspruch 1 der Formel



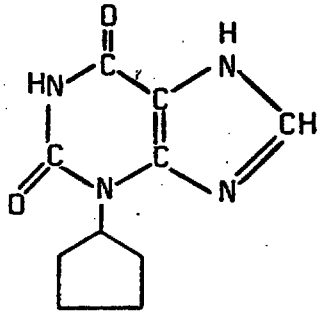
oder ein physiologisch verträgliches Salz derselben, worin R^1 n-Pentyl, 2-Methylbutyl, 3-Methylbutyl, 2,2-Dimethylpropyl, Cyclopropyl, Cyclobutyl, Cyclopentyl oder Cyclohexylmethyl ist.

3. Verbindung nach Anspruch 1 der Formel



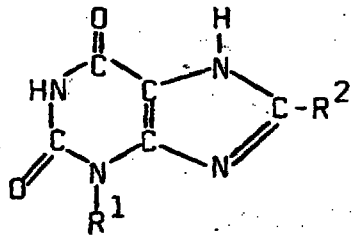
oder ein physiologisch verträgliches Salz derselben, worin R^1 n-Propyl, n-Butyl, Isobutyl, n-Pentyl, 2-Methylbutyl, 3-Methylbutyl, 2,2-Dimethylpropyl, Cyclopropyl, Cyclobutyl, Cyclopentyl oder Cyclohexylmethyl ist.

4. Verbindung nach Anspruch 1 der Formel



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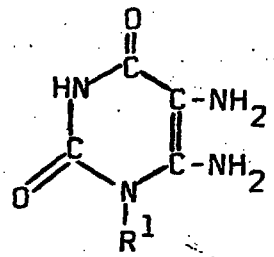
5. Verfahren zur Herstellung einer Verbindung der Formel



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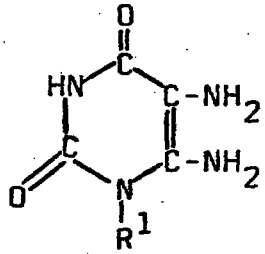
oder ein physiologisch verträglichen Salzes derselben, in welcher Formel R^1 n-Propyl, n-Butyl, Isobutyl, n-Pentyl, 2-Methylbutyl, 3-Methylbutyl, 2,2-Dimethylpropyl, Cyclopropyl, Cyclobutyl, Cyclopentyl oder Cyclohexylmethyl bedeutet und R^2 Wasserstoff oder Methyl bedeutet, wobei R^2 Methyl ist, wenn R^1 n-Propyl, n-Butyl oder Isobutyl ist, dadurch gekennzeichnet, daß man

a) eine Verbindung der Formel

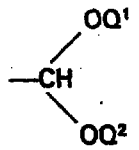


mit einer Verbindung der Formel R^2—X umsetzt, worin R^1 und R^2 die obigen Bedeutungen haben und X —COOH, —$CONH_2$ oder —OC—O—CO—R^2 ist, und, wenn erforderlich, das erhaltene Produkt einer Dehydratation unterzieht oder

b) eine Verbindung der Formel



mit einer Verbindung der Formel R^2—X^1 umsetzt, worin R^1 und R^2 die obigen Bedeutungen haben und X^1 —CHO oder



ist, worin Q^1 Wasserstoff oder eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen und Q^2 eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen ist, und das so erhaltene Produkt einer oxidativen Cyclisierung unterzieht,
wonach man gegebenenfalls die auf einem der Wege a) bis b) erhaltene Verbindung in ein physiologisch verträgliches Salz umwandelt.

6. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß eine Verbindung nach einem der Ansprüche 2 bis 4 hergestellt wird.

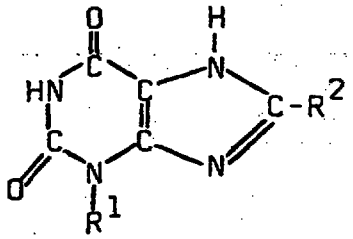
7. Pharmazeutisches Präparat, enthaltend als aktiven Bestandteil eine wirksame Menge einer Verbindung nach Anspruch 1 in Kombination mit einem pharmazeutisch verträglichen Trägermaterial für die Verwendung bei der Behandlung von chronischen, die Luftwege versperrenden Erkankungen oder Herzkrankheiten.

8. Pharmazeutisches Präparat nach Anspruch 7, das als aktiven Bestandteil eine Verbindung nach einem der Ansprüche 2 bis 4 in Kombination mit einem pharmazeutisch verträglichen Trägermaterial enthält.

9. Pharmazeutisches Präparat nach einem der Ansprüche 7 und 8 in der Form von Dosierungseinheiten.

Revendications

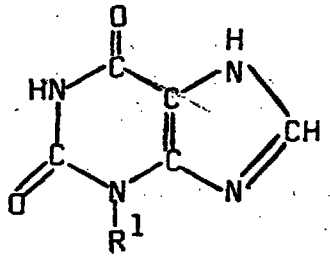
1. Composé de formule



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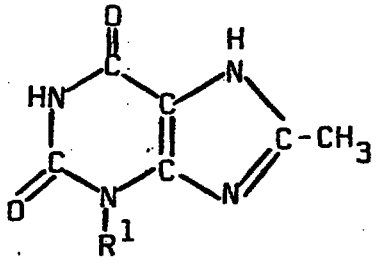
ou l'un de ses sels physiologiquement acceptables, formule dans laquelle R^1 est le radical n-propyle-n-butyle, isobutyle, n-pentyl, 2-méthylbutyle, 3-méthylbutyle, 2,2-diméthylpropyle, cyclopropyle, cyclobutyle, cyclopentyle ou cyclohexylméthyle et R^2 soit le groupe méthyle quand R^1 est le radical n-propyle, n-butyle ou isobutyle.

2. Composé selon la revendication 1, de formule



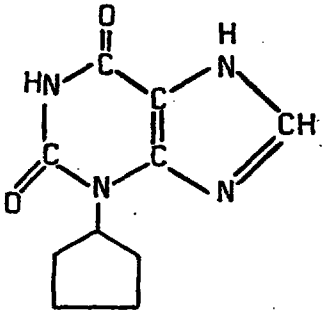
ou l'un de ses sels physiologiquement acceptables, où R^1 est le radical n-pentyle, 2-méthylbutyle, 3-méthylbutyle, 2,2-diméthylpropyle, cyclopropyle, cyclobutyle, cyclopentyle ou cyclohexylméthyle.

3. Composé selon la revendication 1, de formule

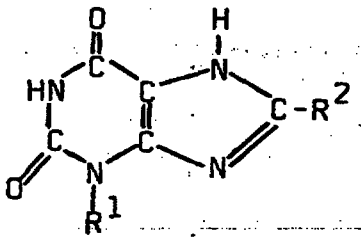


ou l'un de ses sels physiologiquement acceptables, où R^1 est le radical n-propyle, n-butyl, isobutyle, n-pentyle, 2-méthylbutyle, 3-méthylbutyle, 2,2-diméthylpropyle, cyclopropyle, cyclobutyle, cyclopentyle ou cyclohexylméthyle.

4. Composé selon la revendication 1, de formule

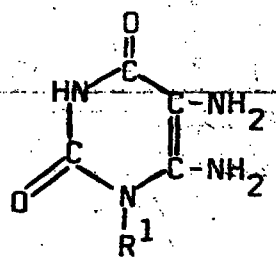


5. Procédé pour la préparation d'un composé de formule



ou l'un de ses sels physiologiquement acceptables ou R^1 est le radical n-propyle, n-butyle, isobutyle, n-pentyle, 2-méthylbutyle, 3-méthylbutyle, 2,2-diméthylpropyle, cyclopropyle, cyclobutyle, cyclopentyle ou cyclohexylméthyle et R^2 est l'hydrogène ou le groupe méthyle, sous réserve que R^2 soit le groupe méthyle quand R^1 est le radical n-propyle, n-butyle ou isobutyle, caractérisé en ce que

a) on fait réagir un composé de formule

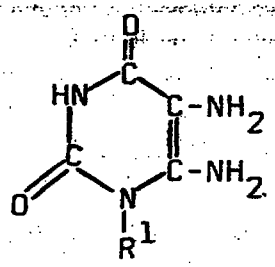


avec un composé de formule

$$R^2—X$$

où R^1 et R^2 ont les définitions données ci-dessus et X est —COOH, $—CONH_2$ ou —OC—O—CO—R^2 et, si besoin est, on soumet le produit obtenu à une déshydratation, ou

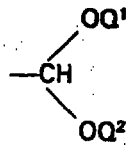
b) on fait réagir un composé de formule



avec un composé

$$R^2—X^1$$

où R^1 et R^2 ont les définitions données ci-dessus et X^1 est —CHO ou



où Q^1 est l'hydrogène ou un groupe alcoyle à 1—3 atomes de carbone et Q^2 est un groupe alcoyle à 1—3 atomes de carbone, et l'on soumet le produit obtenu à une cyclisation oxydante, après quoi, si on le souhaite, on convertit le composé obtenu par l'une quelconque des voies a)-b) en un sel physiologiquement acceptable.

6. Procédé selon la revendication b, caractérisé en ce qu'on prépare un composé selon l'une quelconque des revendications 2—4.

7. Préparation pharmaceutique comprenant en tant que principe actif une quantité efficace d'un composé selon la revendication 1, en association avec un véhicule pharmaceutiquement acceptable,

* C L M S *

destinée à l'utilisation dans le traitement de maladies chroniques obstruant les voies respiratoires ou de maladies cardiaques.

8. Préparation pharmaceutique selon la revendication 7, comprenant en tant que principe actif un composé selon l'une quelconque des revendications 2—4, en association avec un véhicule pharmaceutiquement acceptable.

9. Préparation pharmaceutique selon l'une ou l'autre des revendications 7—8, sous forme de dose unitaire.