Xanthine derivatives and pharmaceutical preparations containing these derivatives for use in the treatment of chronic obstructive airway disease and cardiac disease

Field of the Invention

The present invention relates to a novel group of compounds which have a relaxing effect on the bronchial smooth muscle and pharmaceutical compositions containing them for use in treating chronic obstructive airway disease (COAD) or cardiac disease.

Background of the Invention

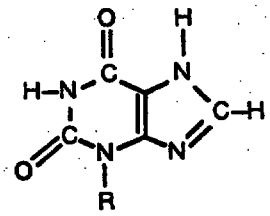
Theophylline and various salts thereof are used in the treatment of chronic obstructive airway disease (COAD) and cardiac disease. Major therapeutic effects of theophylline are to relax bronchial smooth muscle and stimulate heart muscle. The major drawback with theophylline therapy is that the drug with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

Certain biological aspects of several xanthine derivatives are disclosed in Chemical Abstracts, Vol. 81, No. 23, 9 December 1974, pages 541—2, Abstract No. 152277f, and in Biochemistry, Vo. 16, (15), 1977, pages 3316—3321 (Kramer et al.).

The present invention relates to the treatment of COAD and cardiac disease with xanthine derivatives which have a favourable ratio between bronchodilator potency and toxic potency compared to theophylline.

Detailed Description of the Invention

The present invention relates to the use of a compound of the formula

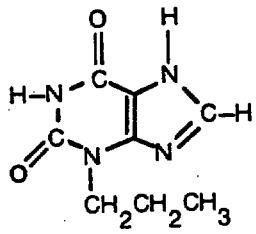


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and therapeutically acceptable salts thereof, wherein R is the group

$-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$ or $-CH_2CH(CH_3)_2$

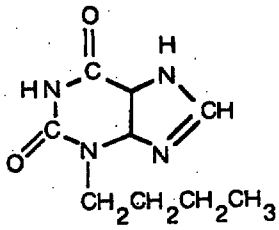
Formula I includes the compound of the formula



D 4028

This compound is disclosed in the Bull. Chem. Soc. Jap. 1973, 46 (2), pages 506—9, where a method for its preparation is described.

Formula 1 includes also the compound of the formula

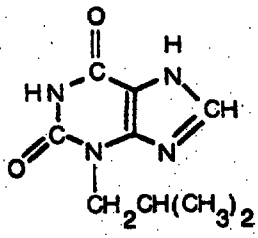


D 4031

This compound is disclosed in the Bull Chem. Soc. Jap. 1973, 46 (2), pages 506—9, where a method for its preparation is described.

Formula 1, finally, includes the compound of the formula

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D 4030

This compound is disclosed in the J. Chem. Soc. 1962, page 1866, where a method for its preparation is described.

When carefully evaluated the publications mentioned above is found to disclose no pharmacological use of the substances of the invention.

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 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 gelatine 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 coating for example, to distinguish between different contents of active substance. For the preparation of soft gelatine capsules (pearlshaped closed capsules) consisting of gelatine 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 gelatine 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 amylpectin), cellulose derivatives, polyvinylpyrrolidone or gelatine, 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 such 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, saccharine and/or carboxymethylcellulose 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

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indicates a better therapeutic index than theophylline.

TABLE 1

Compound (.)	Guinea-Pig Trachea $ED_{50}(TA)/ED_{50}(.)$	$LD_{50}(TA)/LD_{50}(.)$	$ED_{50}(TA)/ED_{50}(.)$ $LD_{50}(TA)/LD_{50}(.)$	Guinea-Pig heart Potency ratios of theophylline	
				chronotrop	inotrop
4028	3.4 [2.6, 4.4]	1.3 [1.1, 1.5]	2.7 [2.0, 3.6] (≥2.1)	2	2.5
4030	3.5 [2.5, 4.8]	1.9 [1.7, 2.3]	1.8 [1.2, 2.6] (≥1.3)	5	2
4031	2.8 [2.0, 3.7]	1.4 [1.1, 1.6]	2.0 [1.4, 2.9] (≥1.5)	5	2

[ ] denotes two-sided 95% confidence interval

( ) denotes one-sided 95% confidence interval

TABLE 2

Acute toxicity studies in mice

Compound (.)	LD_{50} ± SE i.v. mg/kg	LD_{50} i.v. mmoles/kg	LD_{50} ± SE p.o. mg/kg	LD_{50} p.o. mmoles/kg	Ratio LD_{50} p.o. / LD_{50} i.v.	Ratio i.v. LD_{50} TA/(.)	Ratio p.o. LD_{50} TA/(.)
Theophylline Na-salt	202.5 ± 10.9	1.01	444.7 ± 43.7	2.22	2.2	1	1
D 4028*	157.4 ± 7.1	0.81	501.1 ± 54.0	2.55	3.1	1.24	0.87
D 4030	109.3 ± 5.9	0.52	303.8 ± 26	1.45	2.8	1.94	1.53
D 4031	158.2 ± 8.8	0.75	407.6 ± 10.7	1.95	2.6	1.35	1.14

*For reasons of calculation the highest i v dose level without any lethal effect for the compound D 4028 was used as if one test animal had died. This means that the toxicity of this compound may be slightly lower than indicated by the figures in the table.

The following examples will illustrate the preparation of the compounds of the invention.

Example 1

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

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

To a solution of 47 g (0.55 mol) cyanoacetic acid and 100 ml of acetic anhydride was added 50 g (0.49 mol) of n-propylurea. The solution was stirred at 60—70°C for 1 hour. After cooling white crystals were filtered off and washed with ethanol. Yield 56.2 g (68%) (I). This was stirred in 100 ml of hot water and 60 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 and then neutralized with 5 N HCl. After cooling, white crystals were filtered off. Yield 34.3 g (61%) (II) NMR.

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

To 34.3 g (0.20 mol) of 6-amino-1-propyl-2,4-(1H,3H)-pyrimidinedione (II), dissolved in 900 ml hot water, was added 45 ml of 5 N HCl and 15 g of $NaNO_2$ (0.22 mol) which was dissolved in water. After cooling the red crystals were filtered off and washed with water. Yield 33.3 g (83%) (III) NMR.

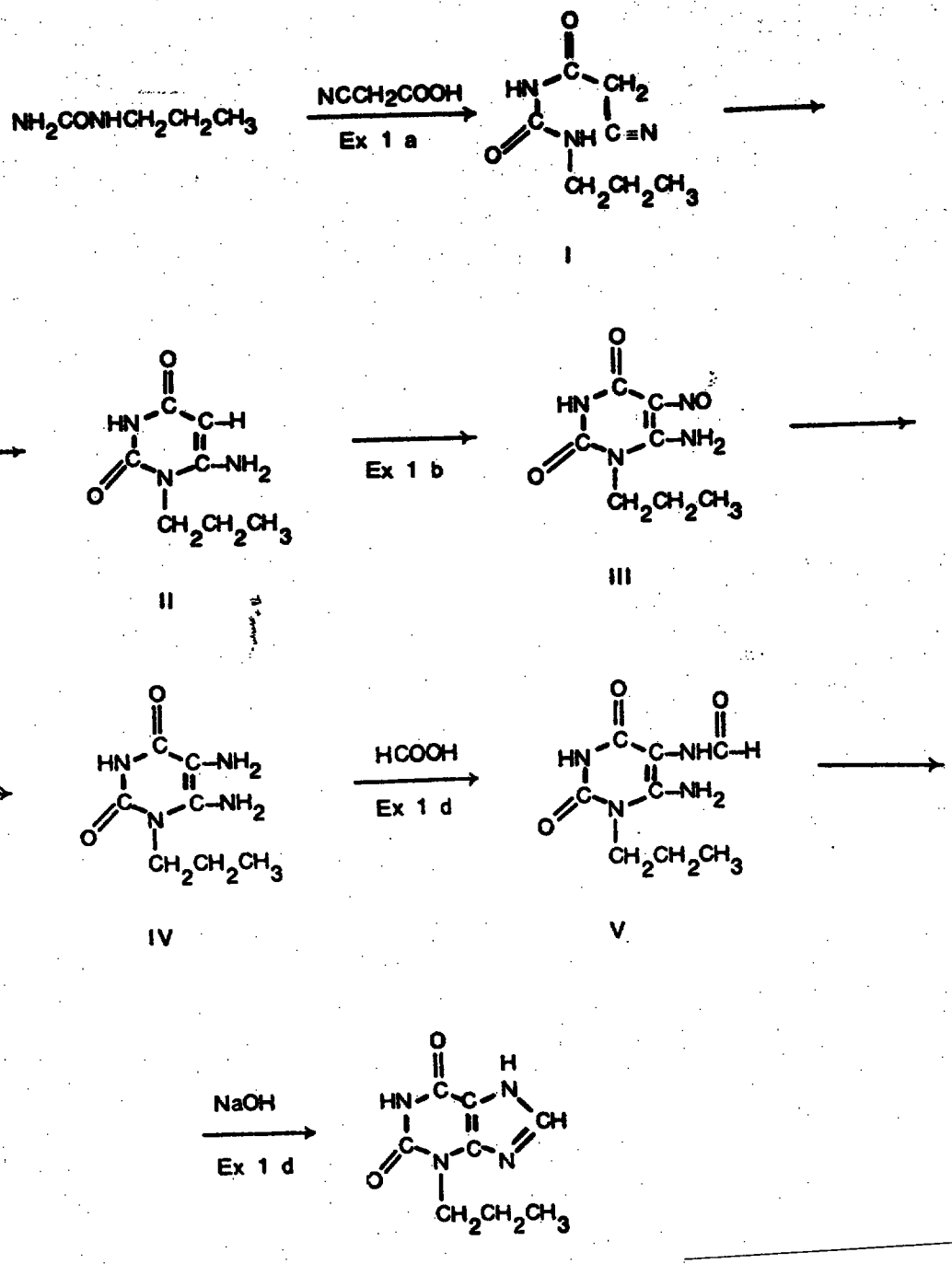
c/ Preparation of 5,6-diamino-1-propyl-2,4-(1H,3H)-pyrimidinedione IV

33.3 g of 6-amino-5-nitroso-1-propyl-2,4-(1H,3H)-pyrimidinedione (III) was catalytically hydrogenated in 800 ml of DMF 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 and the crystals were filtered off and washed with ethanol. Yield 29 g (93%) (IV).

d/ Preparation of 3,7-dihydro-3-propyl-1H-purine-2,6-dione VI

A solution of 29 g of 5,6-diamino-1-propyl-2,4-(1H,3H)-pyrimidine-dione (IV) in 100 ml of formic acid was refluxed for 2 hours. The hot solution was filtered and 50 ml of chloroform was added and ether was then added slowly. The received crystals were filtered off. Yield 30.9 g (V).

The amide (V) was refluxed in 90 ml of 2 N NaOH for 2 hours and then neutralized with 5 N HCl. The crystals were filtered off and recrystallized from 1.9 l ethanol. Yield 21.2 g (68%) (VI) NMR.



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Example 2
Preparation of 3-butyl-3,7-dihydro-1H-purine-2,6-dione (XII)

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

To a solution of 46 g (0.55 mol) cyanoacetic acid and 100 ml of acetic anhydride was added 58 g (0.5 mol) of n-butylurea. The solution was stirred at 70°C for 2 hours. After cooling white crystals were filtered off and washed with ethanol. Yield 68 g (74%) (VII). This was stirred in 500 ml of water and 20 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 50.6 g (75%) (VIII), NMR.

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

To 50.6 g (0.276 mol) of 6-amino-1-butyl-2,4-(1H,3H)-pyrimidinedione (VIII) dissolved in 1.8 l of water at 80°C was added 60 ml of 5 N HCl and 20 g (0.29 mol) of $NaNO_2$ which was dissolved in water. After cooling the red crystals were filtered off and washed with water. Yield 52.8 g (97%) (IX), NMR.

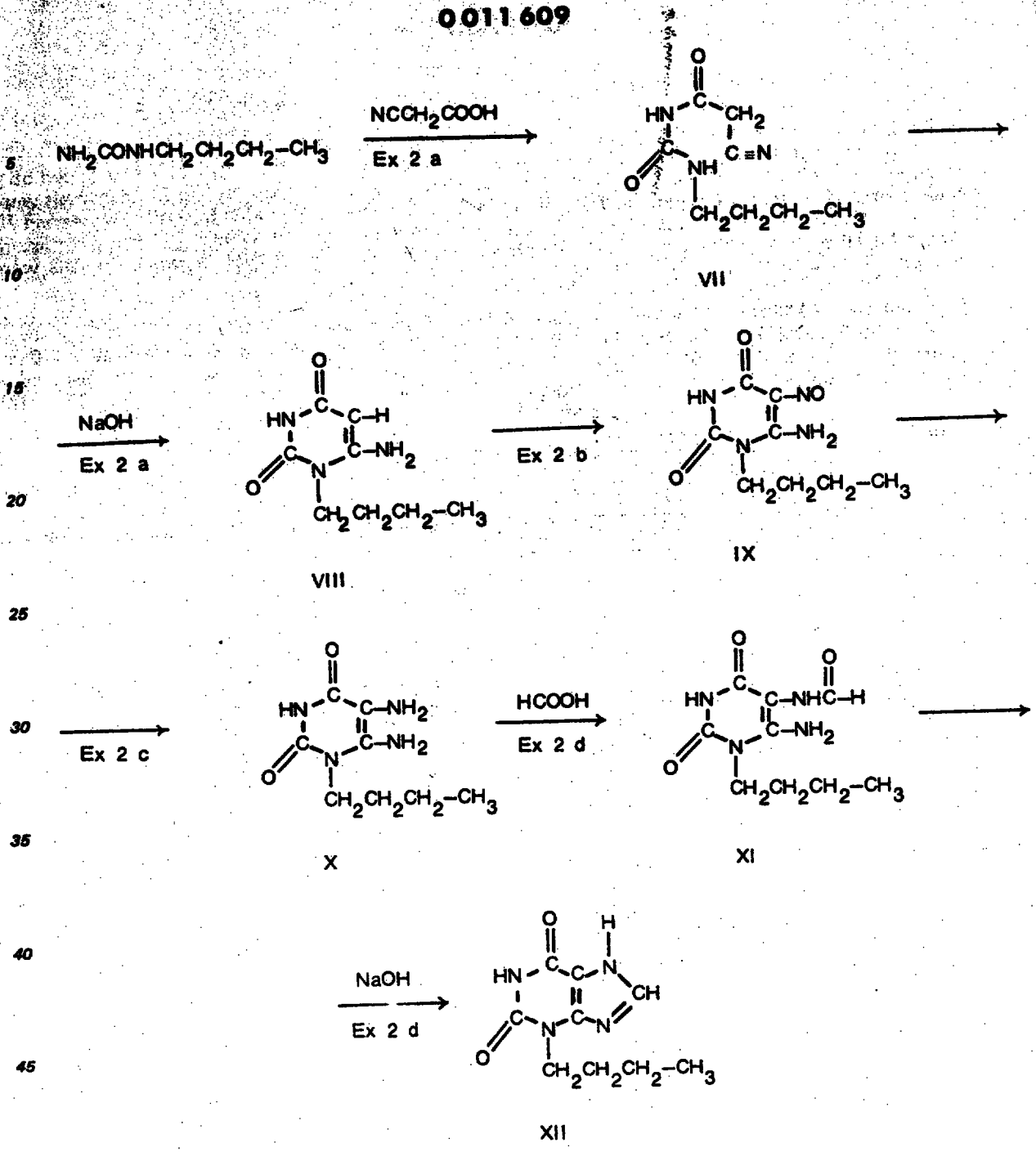
c/ Preparation of 1-butyl-5,6-diamino-2,4-(1H,3H)-pyrimidinedione (X)

52,8 g (0.27 mol) of 6-amino-1-butyl-5-nitroso-2,4-(1H,3H)-pyrimidinedione (IX) was dissolved in 1 l of DMF at 90°C and catalytically hydrogenated in the presence of 0,1 g PtO_2 for 18 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 36.6 g (67%) (X), NMR.

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

A solution of 36,6 g of 1-butyl-5,6-diamino-2,4-(1H,3H)-pyrimidinedione (X) in 100 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 42,9 g (not dried). (XI). The amide (XI) was refluxed in 100 ml of 2 N NaOH for 2 hours and then neutralized with 5 N HCl. The crystals were filtered off and washed with ethanol. Yield 28.4 g (74%) (XII), NMR.

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Example 3

Preparation of 3,7-dihydro-3-(2-methylpropyl)-1H-purine-2,6-dione (XVIII)

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

To a solution of 47 g (0.55 mol) cyanoacetic acid and 100 ml of acetic anhydride was added 58 g (0.5 mol) of 2-methylpropylurea. The solution was stirred at 60—70°C for 2 hour. After cooling white crystals were filtered off and washed with ethanol. Yield 64.8 g (71%) (XIII). This was stirred in 500 ml of hot water and 20 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 44.7 g (70%) (XIV), NMR.

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

To 44,7 g (0.24 mol) of 6-amino-1-)2-methylpropyl)-2,4-(1H,3H)-pyrimidinedione (XIV), dissolved in 2 l hot water, was added 50 ml of 5 N HCl and 17 g of $NaNO_2$ (0.25 mol) which was dissolved in water. After cooling the red crystals were filtered off and washed with water. Yield 44.6 g (95%) (XV), NMR.

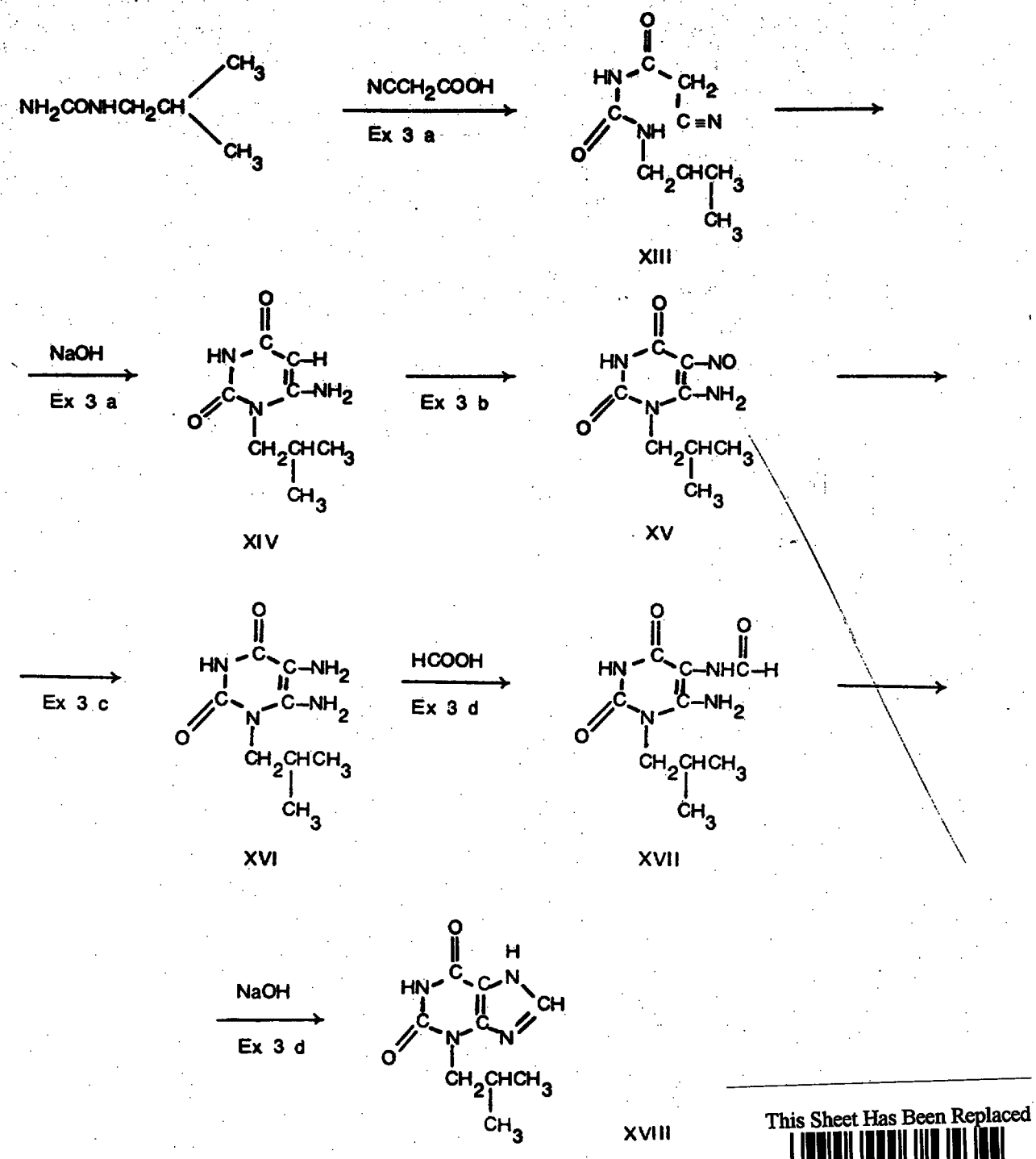
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c/ Preparation of 5,6-diamino-1-(methylpropyl)-2,4-(1H,3H)-pyrimidinedione (XVI)

40 g of 6-amino-1-2-(methylpropyl)-5-nitroso-2,4-(1H,3H)-pyrimidinedione (XV) slurried in 1 l of water and 175 ml of 2 N HCl was added. This was catalytically hydrogenated in the presence of 0.1 g PtO_2 for 4 hours and at room temperature and at pressure of 200 KPa. The catalyst was filtered off and the filtrate was neutralized with 175 ml of 2 N NaOH. The crystals were filtered off and washed with water. Yield 24.2 (61%) (XVI), NMR.

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

A solution of 24,2 g of 5,6-diamino-1-(2-methylpropyl)-2,4-(1H,3H)-pyrimidinedione (XVI) in 60 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 17.8 g (XVII). The amide (XVII) was refluxed in 50 ml of 2 N NaOH for 2 hours and then neutralized with 5 N HCl. The crystals were filtered off and recrystallized from ethanol. Yield 11.6 g (46%), NMR.



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

Example 4
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. "Myglyol" denotes a triglyceride of saturated vegetable oils. Or a pulver aerosol where the active substance is mixed with lactose.

Example 5
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
	350.0 mg

Example 6
Suppositories

Each suppository contains

Active substance		50.0 mg
Ascorbyl palmitate		1.0 mg
Suppository base (Imhausen H)	ad	2000.0 mg

Example 7
Injection solution

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

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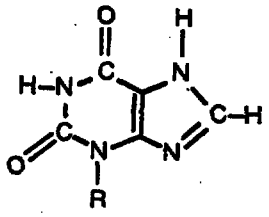
Example 8
Sublingual tablets

Each tablet contains

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

Claims

1. A pharmaceutical preparation for use in the treatment of chronic obstructive airway disease or cardiac disease comprising as active ingredient an effective amount of a compound of the formula

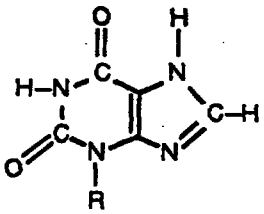


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or a therapeutically acceptable salt thereof, wherein R is $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$ or $-CH_2CH(CH_3)_2$ in association with a pharmaceutically acceptable carrier.

2. A pharmaceutical preparation according to claim 1 wherein the active ingredient is a compound of formula I wherein R is $-CH_2CH_2CH_3$.

3. A compound of the formula



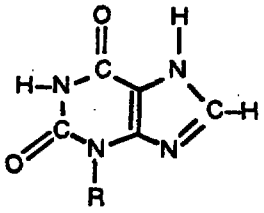
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or a therapeutically acceptable salt thereof, wherein R is $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$ or $-CH_2CH(CH_3)_2$ for use in the treatment of chronic obstructive airway disease or cardiac disease.

4. A compound of the formula I according to claim 3, wherein R is $-CH_2CH_2CH_3$.

Patentansprüche

1. Pharmazeutisches Präparat zur Verwendung bei der Behandlung von chronischer obstruktiver Erkrankung der Luftwege oder von Herzleiden umfassend als aktives Ingredienz eine wirksame Menge einer Verbindung der Formel



(I)

oder eines therapeutisch akzeptablen Salzes derselben, worin R $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$ oder $-CH_2CH(CH_3)_2$ bedeutet, in Verbindung mit einem pharmazeutisch akzeptablen Träger.

2. Pharmazeutisches Präparat nach Anspruch 1, worin das aktive Ingredienz eine Verbindung der Formel I ist, worin R $-CH_2CH_2CH_3$ bedeutet.

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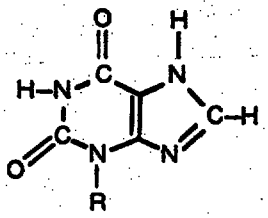
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Sublingual tablets

Each tablet contains

Active substance	20.0 mg
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Claims

1. A pharmaceutical preparation for use in the treatment of chronic obstructive airway disease or cardiac disease comprising as active ingredient an effective amount of a compound of the formula

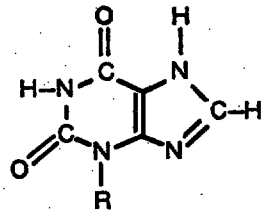


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or a therapeutically acceptable salt thereof, wherein R is $—CH_2CH_2CH_3$, $—CH_2CH_2CH_2CH_3$ or $—CH_2CH(CH_3)_2$ in association with a pharmaceutically acceptable carrier.

2. A pharmaceutical preparation according to claim 1 wherein the active ingredient is a compound of formula I wherein R is $—CH_2CH_2CH_3$.

3. A compound of the formula



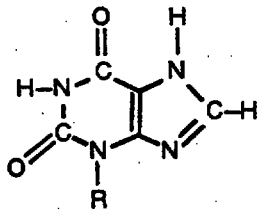
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or a therapeutically acceptable salt thereof, wherein R is $—CH_2CH_2CH_3$, $—CH_2CH_2CH_2CH_3$ or $—CH_2CH(CH_3)_2$ for use in the treatment of chronic obstructive airway disease or cardiac disease.

4. A compound of the formula I according to claim 3, wherein R is $—CH_2CH_2CH_3$.

Patentansprüche

1. Pharmazeutisches Präparat zur Verwendung bei der Behandlung von chronischer obstruktiver Erkrankung der Luftwege oder von Herzleiden umfassend als aktives Ingredienz eine wirksame Menge einer Verbindung der Formel

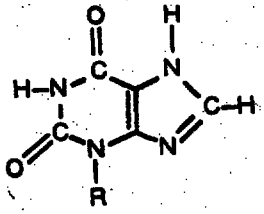


(I)

oder eines therapeutisch akzeptablen Salzes derselben, worin R $—CH_2CH_2CH_3$, $—CH_2CH_2CH_2CH_3$ oder $—CH_2CH(CH_3)_2$ bedeutet, in Verbindung mit einem pharmazeutisch akzeptablen Träger.

2. Pharmazeutisches Präparat nach Anspruch 1, worin das aktive Ingredienz eine Verbindung der Formel I ist, worin R $—CH_2CH_2CH_3$ bedeutet.

3. Verbindung der Formel



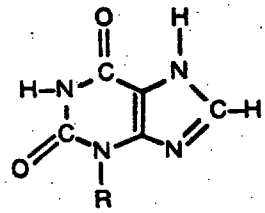
(I)

oder ein therapeutisch akzeptables Salz derselben, worin R $—CH_2CH_2CH_3$, $—CH_2CH_2CH_2CH_3$ oder $—CH_2CH(CH_3)_2$ bedeutet, zur Verwendung bei der Behandlung von chronischer obstruktiver Erkrankung der Luftwege oder von Herzleiden.

4. Verbindung der Formel I nach Anspruch 3, worin R $—CH_2CH_2CH_3$ bedeutet.

Revendications

1. Préparation pharmaceutique destinée à servir au traitement des obstructions chroniques des voies aériennes ou des maladies cardiaques, caractérisée en ce qu'elle comprend comme ingrédient actif une quantité efficace d'un composé de formule:

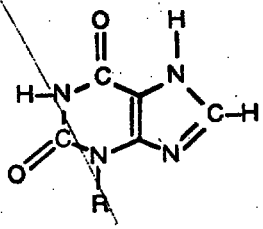


(I)

[dans laquelle R représente $—CH_2CH_2CH_3$, $—CH_2CH_2CH_2CH_3$ ou $—CH_2CH(CH_3)_2$], ou bien un sel thérapeutiquement acceptable de ce composé, en association avec un excipient ou véhicule pharmaceutiquement acceptable.

2. Préparation pharmaceutique selon la revendication 1, dans laquelle l'ingrédient actif est un composé de formule (I) dans laquelle R représente $—CH_2CH_2CH_3$.

3. Composé de formule:



(I)

(dans laquelle R représente $—CH_2CH_2CH_3$, $——CH_2CH_2CH_2CH_3$ ou $—CH_2CH(CH_3)_2$), ou sels pharmaceutiquement acceptables de ce composé, destinés à servir au traitement d'une maladie d'obstruction chronique des voies aériennes ou d'une maladie cardiaque.

4. Composé de formule (I) selon la revendication 3, dans laquelle R représente $—CH_2CH_2CH_3$.

This Sheet Has Been Replaced