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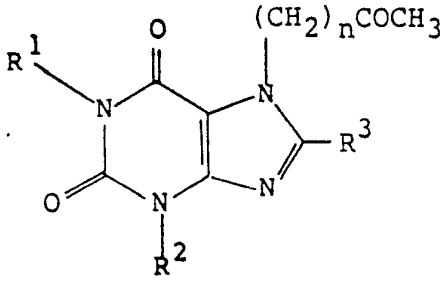

(I)

(57) Abstract

A compound of formula (I), wherein R^1 and R^2 each independently represent a C_{2-6} alkyl group, R^3 represents a moiety $-(CH_2)_mCHOHCH_3$; or a carboxyl group or a salt, ester or amide thereof, and n and m each independently represent an integer 1, 2 or 3; a process for preparing such a compound, a pharmaceutical composition containing such a compound and the use of such a compound and composition in medicine.

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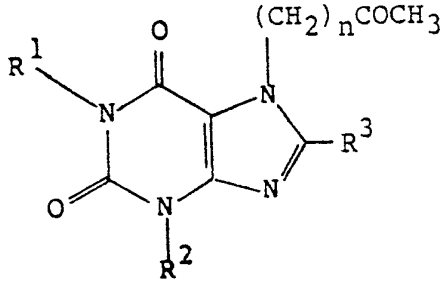
XANTHINE COMPOUNDS

This invention relates to a group of 8-substituted xanthines, to compositions containing such compounds and to their use in medicine.

European Patent Application, publication number 0,195,496 discloses certain xanthines and their use in the treatment of proliferate skin disease.

It has now surprisingly been discovered that certain 8-substituted xanthines are active as phosphodiesterase inhibitors and that they also elevate cyclic AMP levels; they are therefore potentially useful in the treatment of proliferate skin disease. These compounds are also potentially useful in the treatment and/or prophylaxis of peripheral vascular disease, such as intermittant claudication and/or cerebrovascular disorders and/or disorders associated with cerebral senility.

Accordingly, the present invention provides a compound of formula (I):



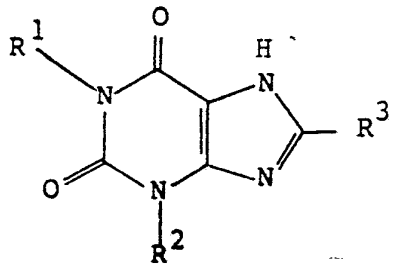
(I)

wherein,

R^1 and R^2 each independently represent a C_{2-6} alkyl group,

R^3 represents a moiety $-(CH_2)_mCHOHCH_3$; or a carboxyl group or a salt ester or amide thereof; and n and m each independently represent an integer 1, 2 or 3.
Suitably, R^1 represents a butyl group, preferably n-butyl.
Suitably, R^2 represents a butyl group, preferably n-butyl.
Suitably, n represents 1 or 2.
Suitably, when R^3 represents a moiety $-(CH_2)_m-CHOHCH_3$, m represents 1.
Suitably, R^3 represents a C_{1-6} alkyl ester of a carboxyl group, for example an ethyl ester.

The present invention also provides a process for the preparation of the hereinbefore defined compound of formula (I), which process comprises reacting a compound of formula (II):



(II)

wherein R^1, R^2 and R^3 are as defined in relation to formula (I), with:

(a) a compound of formula (III):

$$X-(CH_2)_n-CO.CH_3 \qquad \text{(III)}$$

wherein n is as defined in relation to formula (I) and X represents a leaving group preferably a chlorine atom, or

(b) for compounds of formula (I) wherein n represents 2 or 3, a compound of formula (IV):

$$CH_2=CH-(CH_2)_p-CO-CH_3 \qquad (IV)$$

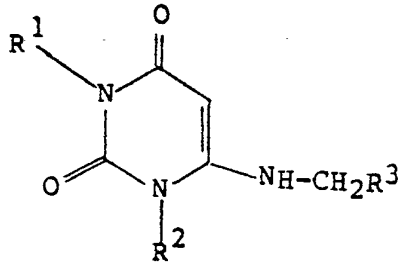
wherein p represents zero or 1.

Suitably, in the reaction between the compounds of formula (II) and (III), the compound of formula (II) is provided in the form of a metallic salt, preferably a sodium salt.

The compounds of formula (II) are novel intermediates and as such form a further aspect of the present invention.

The compounds of formula (I) may be isolated and purified by any conventional method.

The compounds of formula (II) may be prepared by reacting a compound of formula (V):



(V)

wherein R^1, R^2 and R^3 are as defined in relation to formula (I); with a source of nitrite anions, for example sodium nitrite.

The uracils of formula (V) are either known compounds or may be prepared by methods analogous to those used to prepare known compounds.

The reaction between the compounds of formulae (II) and (III) may be carried out under any convenient conditions, for example by reaction of the sodium salt of the compound of formula (II) with a compound of formula (III) in ethanol under reflux.

The reaction between the compounds of formulae (II) and (IV) may be carried out in any convenient solvent, for example methanol, at ambient to elevated temperatures, for example 45°C, preferably in the presence of triethylamine.

As indicated above the compounds of formula (I) have useful pharmaceutical properties.

Accordingly, the present invention provides a compound of formula (I) for use as an active therapeutic substance.

In one aspect the present invention provides a compound of formula (I) for use in the treatment of proliferate skin disease.

In a further aspect of the present invention there is provided a pharmaceutical composition which comprises a compound of formula (I) and a pharmaceutically acceptable carrier therefor.

The present invention also provides the use of a compound of formula (I) for the manufacture of a medicament for treating proliferative skin disease in human or non-human mammals.

As used herein the expression 'proliferative skin diseases' means benign and malignant proliferative skin diseases which are characterized by accelerated cell division in the epidermis, dermis or appendages thereto, associated with incomplete tissue differentiation. Such diseases include: psoriasis, atopic dermatitis, non-specific dermatitis, primary irritant contact dermatitis, allergic contact dermatitis, basal and squamous cell carcinomas of the skin, lamellar ichthyosis, epidermolytic hyperkeratosis, premalignant sun induced keratosis, non-malignant keratosis, acne, and seborrheic dermatitis in humans and atopic dermatitis and mange in domesticated animals.

The compounds of formula (I) are also effective in increasing oxygen tension and contractility in ischaemic skeletal muscle and are therefore of potential use in the treatment of peripheral vascular disease, such as intermittant claudication.

The compounds of formula (I) also have a protective effect against the consequences of cerebral metabolic inhibition and/or enhance cognition in animals and are therefore of potential use in the treatment of cerebrovascular disorders and disorders associated with cerebral senility in humans and non-human mammals.

Accordingly, the present invention provides a compound of formula (I), for use in the treatment and/or prophylaxis of; peripheral vascular disease, such as intermittant claudication and/or cerebrovascular disorders and/or disorders associated with cerebral senility.

The present invention also provides a method for the treatment and/or prophylaxis of, peripheral vascular disease, such as intermittant clavdication and/or cerebrovascular disorders and/or disorders associated with cerebral senility in humans or non-human mammals,which treatment comprises the administration to the human or non-human mammal in need of such treatment an effective and/or prophylactic amount of a compound of formula (I).

The present invention also provides the use of a compound of formula (I) for the manufacture of a medicament for the treatment and/or prophylaxis of; peripheral vascular disease, such as intermittant claudication and/or cerebrovascular disorders and/or disorders associated with cerebral senility.

The administration to the human or non-human mammal may be by way of oral administration, parenteral administration or, in the case of proliferate skin disease, topical administration.

An amount effective to treat proliferative skin disease depends on the usual factors such as the nature and severity of the problem and the weight of the human or non-human mammal. However, a unit dose will normally contain 5 to 500 mg for example 20 to 200 mg, of compound (I). Unit doses will normally be administered once or more than once a day, for example 2, 3, 4, 5 or 6 times a day, more usually 2 to 4 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 5 to 1000 mg, for example 50 to 600 mg, that is in the range of approximately 0.07 to 15 mg/kg/day, more usually 1 to 10 mg/kg/day, for example 2 to 5 mg/kg/day.

An amount effective to treat peripheral vascular disease, such as intermittant claudication, and/or cerebrovascular disorders and/or disorders associated with cerebral senility depends on the usual factors such as the nature and severity of the disorders being treated and the weight of the human or non-human mammal. However, a unit dose will normally contain 1 to 100 mg for example 2 to 50 mg, of the compound of the invention. Unit doses will normally be administered once or more than once a day, for example 2, 3, 4, 5 or 6 times a day, more usually 2 to 4 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 0.1 to 250 mg, for example 50 to 150 mg, that is in the range of approximately 0.002 to 3.5 mg/kg/day, more usually 1 to 3 mg/kg/day, for example 0.7 to 2 mg/kg/day.

Suitably, a compound of formula (I) is administered in the form of a unit-dose composition, such as a unit dose oral or parenteral composition.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting

agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.
These solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid unit dose forms are prepared containing a compound of formula (I) and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

In the treatment of proliferate skin disease, the compounds of formula (I) may also be administered as a topical formulation in combination with conventional topical excipients.

Topical formulations may be presented as, for instance, ointments, creams or lotions, impregnated dressings gels, gel sticks, spray and aerosols, and may contain appropriate conventional additives such as

preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions.

Suitable cream, lotion, gel, stick, ointment, spray, or aerosol formulations that may be used for compounds of formula (I) are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics and cosmetics, such as Harry's Cosmeticology published by Leonard Hill Books, Remington's Pharmaceutical Sciences, and the British and US Pharmacopoeias.

Suitably, the compound of formula (I) will comprise from about 0.5 to 20% by weight of the formulation, favourably from about 1 to 10% for example 2 to 5%.

No adverse toxicological effects are indicated in any of the above mentioned dosage ranges.

The invention will now be illustrated by reference to the following Examples which do not limit it in any way.

Example 1

Preparation of 1,3-dibutyl-7-(-3'-oxobutyl)-8-(2-hydroxypropyl)-xanthine

1,3-di-n-butyl-8-(2-hydroxypropyl)xanthine(2.4g), methylvinyl ketone (0.6g) and triethylamine (0.3ml) were dissolved in methanol (8ml) and the mixture was slowly heated with stirring at 45°C for seven hours, then cooled to room temperature and continued stirring overnight to complete tne reaction.

The reaction mixture was treated with water and then extracted with chloroform several times, the chloroform phase washed with IN NaOH and water, dried with sodium sulphate, filtered and the chloroform remained in vacuo to yield a solid which, on crystallisation in petroether (40°/80°C), gave 1,3 di-butyl-7-(3'-oxobutyl)-8-(2-hydroxypropyl)xanthine as a white powder.
Melting point: 82°C
Yield: 1.3g

	Elemental analysis Calculated (%)	Found (%)
C	61.20	61.14
H	8.22	8.16
N	14.21	14.28
O	16.31	16.48

Example 2

Preparation of 1,3-di-n-butyl-7-(2'-oxopropyl)-8-carbethoxy-xanthine

1,3-di-n-butyl-8-carbethoxy-xathine (1.7g) was treated with sodium (0.12g) in absolute ethanol (5ml) to give the 1,3 di-n-butyl-8-carbethoxy sodium salt by heating under reflux for one hour. 1-chloropropan-2-one (0.92g) dissolved in ethanol (10ml) was added dropwise and the reaction mixture heated under reflux for a further 6 hours. The reaction was then complete (as inidcated by thin layer of chromatography (tlc)).

After standing overnight, the precipitated sodium chloride was filtered off under suction.

The filtrate was diluted with water and the precipitated 1,3-di-n-butyl-7-(2'-oxopropyl)-8-carbethoxy-xanthine raw material filtered off under suction, washed with water, dried and recrystallised several times from acetone/water (80%:20%)diethylether and finally methanol/water (90%:10%) to give a white powder.
Melting point: 108°C.
Yield: 0.3g

	Elemental analysis Calculated (%)	Found (%)
C	58.15	58.19
H	7.19	6.81
N	14.28	14.19
O	20.38	20.81

Preparation 1

Preparation of 1,3-dibutyl-8-(2-hydroxypropyl)xanthine

To a suspension of sodium nitrite (2.4g) in methanol (36ml) 1,3-di-n-butyl-4-(-3-hydroxybutyl)aminouracil (9.6g) was added at about -5°C. At this temperature concentrated hydrochloric acid (3.5ml) was slowly added to give a pH of 3.

The reaction was completed, as indicated by tlc, by stirring for a further 30 minutes. The reaction mixture was poured into ice-water and extracted with chloroform several times, the chloroform washed with water.

The chloroform phase was dried with sodium-sulphate, filtered and the chloroform removed in vacuo to yield an oil which was dissolved in toluene (200ml) and heated to reflux for 3 hours to remove the reaction water with a water separator.

Then the reaction mixture was cooled to room temperature. After several hours a pale solid precipitated which was first recrystallised from methanol/water (80%:20%) and then twice more from ethylacetate to yield 1,3-di-n-butyl-8-(2-hydroxy-propyl)-xanthine.
Melting point: 171°C.
Yield: 3,9g.

	Elemental analysis Calculated (%)	Found (%)
C	59.60	59.73
H	8.13	8.03
N	17.38	17.30
O	14.89	14.98

Preparation 2

Preparation of 1,3-di-n-butyl-8-carbethoxy-xanthine

To a suspension of sodium nitrite (1.45g) in methanol (22ml) 1,3-di-n-butyl-4-(carbethoxymethyl)-aminouracil (5.9g) was added at about -5°C. At this temperature concentrated hydrochloric acid (2.7ml) was dropwise added with stirring, then stirring continued until the reaction is complete (as indicated by tlc). The reaction mixture was then poured into water, extracted with chloroform several times and the chloroform phase washed with water. Then the chloroform phase was dried with sodium sulphate, filtered and the chloroform removed in vacuo to yield an oil and a solid, which was dissolved in toluene and heater to reflux for several hours with a water separator.

Then the toluene was removed in vacuo, the residue dissolved in methanol and treated with charcoal to remove the colour of the solution. The precipitated compound was recrystallised twice from methanol/water (90%:10%) to yield the 1,3-d-n-butyl-8-carbethoxy-xanthine as a white powder.
Melting point: 184°C
Yield: 1,3g

	Elemental analysis Calculated (%)	Found (%)
C	57.13	58.14
H	7.19	7.07
N	16.66	16.95
O	19.02	18.02

Pharmacological Data

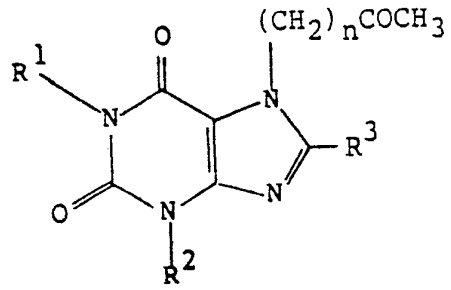
The activity of cyclic AMP phosphodierterase in homogenates of rat gastocnemius muscle was measured in the presence of various concentrations of compounds of formulae (I) using 0.31 µM cyclic AMP as substration. The reciprocal of the reaction rate was plotted on the y axis against the concentration of each compound on the x axis (Dixon plot). The apparent Ki value was estimated by extrapolating the steeper linear portion of the Dixon plot to the x axis and obtaining the negative intercept on the x axis.

Compounds of formula (I)

R^1	R^2	R^3	n	Apparent Ki value. (µ Molar)
C_4H_9	C_4H_9	$CH_2CHOHCH_3$	2	18
C_4H_9	C_4H_9	$COOC_2H_5$	1	28.8

Claims

1. A compound of formula (I):



(I)

wherein,
R^1 and R^2 each independently represent a C_{2-6} alkyl group;
R^3 represents a moiety $-(CH_2)_mCHOHCH_3$; or a carboxyl group or a salt ester or amide thereof; and n and m each independently represent an integer 1, 2 or 3.

2. A compound according to claim 1, wherein R^1 represents a butyl group.

3. A compound according to claim 1 or claim 2, wherein R^2 represents a butyl group.

4. A compound according to any one of claims 1 to 3, wherein R^3 represents a C_{1-6} alkyl ester of a carboxyl group.

5. A compound according to any one of claims 1 to 4, wherein when R^3 represents a moiety $-(CH_2)_m-CHOHCH_3$, m represents 1.

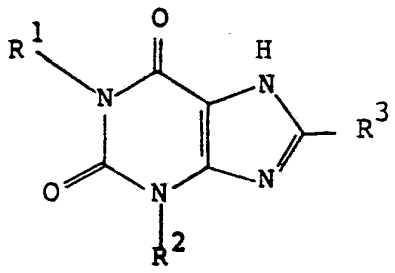
6. A compound according to any one of claims 1 to 5, wherein when n represents 1 or 2.

7. A compound according to claims 1, selected from:

1,3-dibutyl-7-(-3'-oxobutyl)-8-(2-hydroxypropyl)-xanthine; and

1,3-di-n-butyl-7-(2'-oxopropyl)-8-carbethoxy- xanthine.

8. A process for the preparation of a compound of formula (I) as claimed in claim 1, which process comprises reacting a compound of formula (II):



(II)

wherein R^1, R^2 and R^3 are as defined in relation to formula (I), with:

(a) a compound of formula (III):

$$X\text{-}(CH_2)_n\text{-}CO.CH_3 \qquad \text{(III)}$$

wherein n is as defined in relation to formula (I) and X represents a leaving group preferably a chlorine atom; or

(b) for compounds of formula (I) wherein n represents 2 or 3, a compound of formula (IV):

$$CH_2=CH-(CH_2)_p-CO-CH_3 \qquad (IV)$$

wherein p represents zero or 1.

9. A process according to claim 8, wherein the compound of formula (II) is provided in the form of a metallic salt.

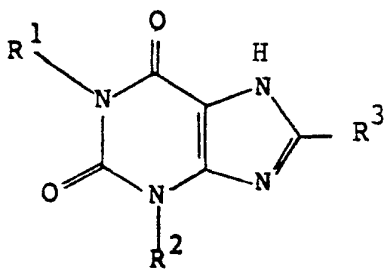
10. A pharmaceutical composition which comprises a compound of formula (I), according to claim, and a pharmaceutically acceptable carrier therefor.

11. A compound of formula (I), according to claim 1, for use as an active therapeutic substance.

12. A compound of formula (I), according to claim 1, for use in the treatment and/or prophylaxis of; peripheral vascular disease, such as intermittant claudication and/or cerebrovascular disorders and/or disorders associated with cerebral senility.

13. The use of a compound of formula (I), according to claim 1, for the manufacture of a medicament for treating proliferative skin disease in human or non-human mammals.

14 A compound of formula (I),



(II)

wherein R^1, R^2 and R^3 are as defined in relation to formula (I), useful as an intermediate.