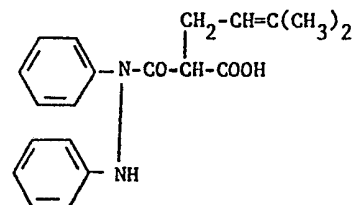


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(54) **N,N'-Diphenylhydrazine derivative**

(57) 2-(3-methyl-2-butenyl)-N,N'-diphenylmalonomonohydrazide of formula I,



and salts thereof of use as analgesic, anti-inflammatory and antipyretic agents.

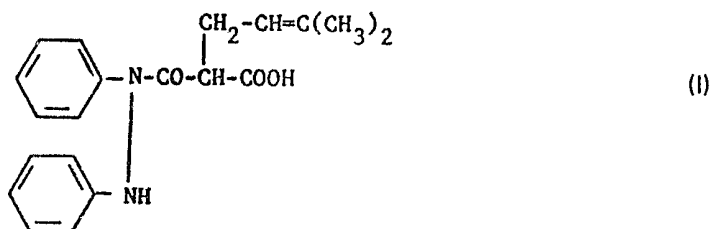
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SPECIFICATION

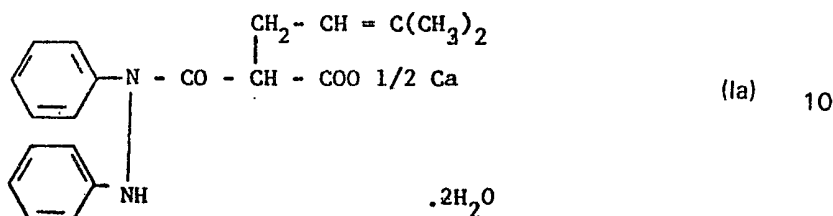
N,N'-Diphenylhydrazine derivative

This invention relates to a new N,N'-diphenylhydrazine derivative and its salts, to processes for their preparation and to pharmaceutical compositions containing them.

According to one feature of the present invention we provide 2-(3-methyl-2-butenyl)-N,N'-diphenylmalonomonohydrazide of formula I,



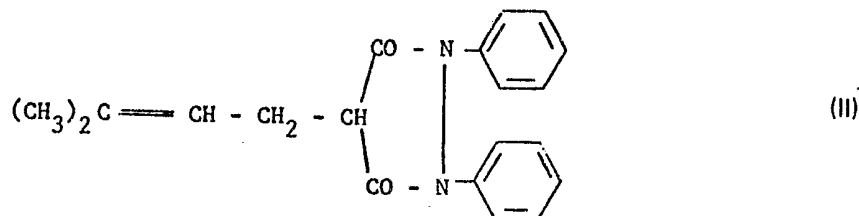
and salts thereof, especially the alkali metal and alkaline earth metal salts. A particular preferred salt is the calcium salt (in the form of a dihydrate) corresponding to the formula Ia,



The compounds according to the invention possess interesting pharmacological properties and in particular analgesic, anti-inflammatory and antipyretic activity. It will be appreciated that, for pharmaceutical use, the salt referred to above will be physiologically compatible but other salts may find use, for example in the preparation of the compound of formula I and its physiologically compatible salts.

The compounds according to the invention may, for example, be prepared by the following processes, which processes constitute further features of the present invention:

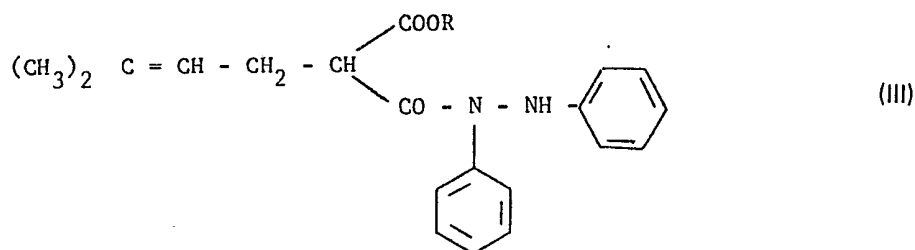
A. Hydrolysis of 4-(3-methyl-2-butenyl)-1,2-diphenyl-3,5-dioxypyrazolidine of formula II,



with an alkali and subsequently, if required, converting the compound of formula I thus obtained into a salt thereof.

The hydrolysis is conveniently carried out by dissolving the starting material of formula II in a dilute alkali metal hydroxide, preferably sodium hydroxide and by heating the solution thus obtained for a long time (for example from 5 to 40 hours). The addition of an inorganic sodium salt, for example, sodium chloride, disodium hydrogen phosphate, sodium acetate (preferably disodium hydrogen phosphate) to the hydrolysis medium is of advantage in order to improve yields. The reaction product may be precipitated by adding an inorganic acid to the reaction medium. The precipitated acid may then be converted if desired in conventional manner to a corresponding salt. Thus, for example the calcium salt of formula Ia may be obtained by dissolving the acid monohydrazide of formula I in ammonium hydroxide and precipitating the desired salt by addition of a calcium salt (for example calcium chloride).

B. Hydrolysis of an ester of formula III,



(wherein R represents a lower alkyl group, preferably an ethyl group) with an alkali and subsequently, if required, converting the compound of formula I thus obtained into a salt thereof. The ester saponification is conveniently performed by heating the compound of formula III with an alkali metal hydroxide solution, preferably sodium hydroxide solution. The acid monohydrazide may be precipitated from the reaction mixture by acidification with an inorganic acid. The conversion into a salt e.g. the calcium salt, where required, may be performed in conventional manner, for example by dissolving the acid monohydrazide in an alkali metal hydroxide, for example sodium hydroxide and then precipitating the desired salt. Thus, for example, the calcium salt of formula Ia can be precipitated by adding an inorganic soluble calcium salt such as e.g. calcium chloride.

The compound of formula I and its physiologically compatible salts particularly the calcium salt of formula Ia, show an excellent analgesic, anti-inflammatory and antipyretic activity. This activity is even higher than that of bumadizon-calcium which is structurally analogous (see *Arzneimittel-Forschung* 23 (9), pages 1215—1225, 1973). Furthermore, these compounds are characterised by their low toxicity and in particular for a lack of gastrolesive effects and thus they may usefully be employed in the treatment of rheumatic and other inflammatory complaints.

According to a further feature of the present invention there are provided pharmaceutical compositions comprising, as active ingredient, the compound of formula I as hereinbefore defined or a physiologically salt thereof, preferably the calcium salt of formula Ia, in association with a pharmaceutical carrier or excipient. If desired, these compositions may contain one or more further therapeutically active substances.

These compositions may be formulated in conventional manner, most preferably in a form suitable for oral or rectal administration. For oral administration the compositions are preferably formulated in solid form, e.g. as tablets or hard gelatine capsules, using conventional excipient such as, for example, magnesium stearate, starch and talc. The compositions for rectal administration may be formulated as suppositories, e.g. with a conventional suppository base such as cocoa butter or glycerides of fatty acids.

Advantageously the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Suitable dosage units for adults contain from 20—1000 mg, preferably from 50—500 mg of active ingredient.

The pharmacology of the active ingredient of formula Ia according to the invention may be illustrated as follows.

Pharmacology

The compound of formula Ia (hereinafter referred to as DA—3715) exhibits an anti-inflammatory (Table I), analgesic-anti-inflammatory (Table IV) and antipyretic activity (Table V) which is higher than that of the known compound bumadizon-calcium. It should be noted that antipyretic activity is observed at a dosage which is substantially free from a statistically significant hypothermic effect (Table VI).

The analgesic activity of DA—3715 investigated according to the hot plate test is higher, occurs more rapidly and lasts longer than that of bumadizon-calcium.

The activity on arthritis induced in rats by Freund's adjuvant is similar for both active ingredients.

DA—3715 is less toxic (Table VII) and less ulcerogenic (Table VIII) than the comparison compound. In summary the properties of DA—3715 as compared with those of bumadizon-calcium represent on the whole, a substantial therapeutic advance. The above properties of the new salt are illustrated by the results of the following experiments.

Methods

In the present study DA—3715 was administered by gavage as an aqueous suspension in 5% acacia gum in a constant volume of 10 ml/kg to male Swiss mice and male Sprague-Dawley rats. Control rats and mice were given a corresponding volume of the aqueous suspending medium.

Bumadizon was used as a comparison active ingredient. The results were statistically evaluated by Dunnett's test (C.V. Dunnett.: J.A. Stat. Ass., 40, 1096, 1955).

Anti-inflammatory activity

Anti-inflammatory activity was determined in the carrageenin oedema test according to the method described by Winter *et al.*, (see C.A. Winter, E.A. Risley, G.W. Muss: J. Pharm. Exp. Ther. 141, 369, 1963).

- 5 The oedema was provoked in rats by a subplantar injection into the right hind paw of 0.1 ml of a 1% carrageenin suspension in sterile saline solution. 5

Rats were treated orally with the active ingredient (DA—3715 or bumadizon-calcium) 60 minutes before the injection of carrageenin. The volume of the foot was measured with a mercury differential volume-meter immediately before injection of the carrageenin and 3 and 5 hours thereafter.

- 10 Anti-inflammatory activity was evaluated as percent oedema inhibition of treated rats in comparison with the controls, according to the following formula: 10

$$\frac{\text{oedema volume (control rats)} - \text{oedema volume (treated rats)}}{\text{oedema volume (control rats)}} \cdot 100$$

Activity on arthritis induced in rats by Freund's adjuvant

- 15 Arthritis was induced in rats by an intradermal injection of 0.1 ml of a heavy oil suspension containing 5 mg/ml of heat-killed *Mycobacteria tuberculosis* into the right hind foot pad. The following Mycobacteria strains were used: PN, DT and C. 15

- Severity of arthritis was evaluated by measuring the oedema of the left paw (secondary lesion) by means of a mercury differential volume-meter. Animals showing at least 40% oedema of left hind paw on the 16th day were given orally 40, 80 or 160 mg/kg of each active ingredient (DA—3715 or bumadizon-calcium) from the 16th to the 20th day. 20

Paw oedema was measured on the day of injection of Freund's adjuvant and on days 16 and 20.

Anti-inflammatory activity was evaluated as percent inhibition of oedema in the treated rats in comparison with the controls, according to the following formula:

$$\frac{\text{Oedema volume (control rats)} - \text{oedema volume (treated rats)}}{\text{oedema volume (control rats)}} \cdot 100$$

25 25

Analgesic activity

- 30 Analgesic activity was evaluated in mice in the hot plate test according to Janssen and Jageneau (J. Pharm. Pharmac., 9, 381, 1957). 30

Plate temperature was kept constant at 55°C; reaction time was determined before and 30, 60, 90 and 120 minutes after oral administration of the active ingredients. Average values after administration of the active ingredients were compared with those obtained before treatment.

Analgesic-anti-inflammatory activity

- 35 Analgesic-anti-inflammatory activity was evaluated in rats according to Randall and Selitto (Arch. Int. Pharmacodyn., 111, 409, 1957), using an analgesymeter to measure the minimum load that must be used to a rat's hind paw to elicit a painful stimulus. 35

Both controls and experimental rats were injected in the right hand paw with 0.1 ml of 20% brewer's yeast in sterile saline immediately before the administration of the active ingredient.

- 40 The volume of the inflamed right hind paws was measured 1, 2 and 4 hours after the administration of the active ingredients. 40

Analgesic-anti-inflammatory activity was evaluated using an "analgesic index" expressed as a ratio between the sum of the average weights (grams) necessary to provoke painful stimulus at different times in treated and control animals.

- 45 *Antipyretic activity* 45

Antipyretic activity was investigated in rats according to Niemegeers *et al* (see Arzneim. Forsch. 25, 1519, 1975).

Rectal temperature was measured immediately before and 4 hours after the subcutaneous injection of 1 ml/100 g body weight of a 15% brewer's yeast suspension in 1% acacia gum.

- 50 DA—3715 and bumadizon-calcium were administered orally to groups of 5 different rats for each dose, 4 hours after the yeast injection. The rectal temperature was measured 0.5, 1, 1.5, 2, 2.5, 3 and 19 hours after treatment. 50

Average values of the temperatures obtained in the treated rats were compared with those of control rats.

Activity on normal temperature of rats

Rectal temperature was measured at 30 minute intervals before and after the administration of active ingredient (that is to -15, -1, -0.5, 0.5, 1, 1.5 and 2 hours) using groups of 10 rats each for each dose level.

- 5 Average values of the temperatures obtained in the treated rats were compared with those of control rats. 5

Acute toxicity

Acute toxicity was investigated in groups of 10 rats receiving 500, 1,000, 1,500 and 2,000 mg/kg of DA—3715 or bumadizon-calcium by gavage.

- 10 The number of deaths was recorded over 7 days after administration of active ingredient and LD₅₀ values were calculated according to Litchfield and Wilcoxon (J. Pharm. and Exp. Ther., 96, 99, 1949). 10

Ulcerogenic effect

The ulcerogenic effect was investigated in rats according to Niemegeers *et al* (Arzneimittel Forschung 25, 1537, 1975).

- 15 DA—3715 and bumadizon-calcium were given in a single oral dose to groups of 15 rats fasted 9 hours before treatment and kept fasting throughout the whole experimental period. 15

The animals were sacrificed 16 hours after treatment; the severity of lesions were scored according to an arbitrary scale, going from + to +++++. For each group of rats, the ulcerogenic index was calculated according to Pauls *et al*, (Gastroenterology 8, 774, 1947).

- 20 The results are shown in the following tables: 20

TABLE I
Anti-inflammatory activity (carragenin-induced oedema)

Compound	Hours after carragenin	Oedema volume in mm ³ Mean ± standard deviation
Control	3	1.50 ± 0.48 (8)
	5	2.28 ± 0.60 (8)
DA 3715 40 mg/kg	3	^{**} 0.75 ± 0.32 (7) Δ
	5	^{**} 1.37 ± 0.51 (7) Δ
DA 3715 80 mg/kg	3	[*] 0.94 ± 0.48 (8)
	5	[*] 1.48 ± 0.63 (8)
DA 3715 160 mg/kg	3	^{**} 0.68 ± 0.16 (8)
	5	^{**} 0.75 ± 0.42 (8)
BUMADIZON — Ca 40 mg/kg	3	1.42 ± 0.27 (8)
	5	2.06 ± 0.42 (8)
BUMADIZON — Ca 80 mg/kg	3	[*] 0.96 ± 0.39 (8)
	5	^{**} 1.32 ± 0.60 (8)
BUMADIZON — Ca 160 mg/kg	3	^{**} 0.87 ± 0.32 (8)
	5	^{**} 1.26 ± 0.33 (8)

Δ 1 rat dead during the test.

* p<0.05 "Dunnett" — Test

** p<0.01

() = in parentheses the number of rats.

TABLE II
Activity on arthritis induced by Freund's adjuvant

Compound	days	Oedema volume in mm ³ Mean $\pm$ standard deviation	% Inhibition
Control	20	2.88 $\pm$ 0.32 (10)	
DA 3715 40 mg/kg	20	^{**} 1.89 $\pm$ 0.36 (8)	34%
DA 3715 80 mg/kg	20	^{**} 1.86 $\pm$ 0.35 (8)	35%
DA 3715 160 mg/kg	20	^{**} 1.37 $\pm$ 0.49 (8)	45%
BUMADIZON – Ca 40 mg/kg	20	[*] 2.00 $\pm$ 0.37 (8)	30%
BUMADIZON – Ca 80 mg/kg	20	^{**} 1.95 $\pm$ 0.65 (8)	32%
BUMADIZON – Ca 160 mg/kg	20	^{**} 1.68 $\pm$ 0.58 (8)	41.6%

* p<0.05 "Dunnett"-Test

** p<0.01

() = in parentheses the number of rats.

TABLE III
Analgesic activity (hot plate-Test): reaction time before and after administration of the active ingredients

Compound	Reaction time (sec.)				
	0	30'	60'	90'	120'
DA 3715 50 mg/kg	15.40 ± 2.76 (10)	16.70 ± 3.86	19.80 ± 3.36 ***	20.00 ± 4.22 **	20.00 ± 1.76 **
DA 3715 100 mg/kg	12.90 ± 3.21 (10)	16.30 ± 3.02	17.10 ± 5.26	16.90 ± 3.84	17.80 ± 4.26
DA 3715 200 mg/kg	14.40 ± 2.95 (10)	19.90 ± 5.45 *	21.30 ± 4.79 **	20.10 ± 3.51 **	20.40 ± 5.83 **
BUMADIZON-Ca 50 mg/kg	14.00 ± 3.80 (10)	16.50 ± 3.60	18.30 ± 3.06 *	19.30 ± 2.06 **	18.60 ± 4.12 *
BUMADIZON-Ca 100 mg/kg	14.30 ± 2.67 (10)	17.50 ± 3.37 *	17.50 ± 3.87	17.10 ± 4.48	16.10 ± 2.56
BUMADIZON-Ca 200 mg/kg	12.90 ± 2.92 (10)	16.89 ± 2.37 **	18.44 ± 2.51 **	17.22 ± 2.54 **	19.89 ± 3.14 **

* p<0.05

** p<0.01 "Dunnett"-Test

() = in parentheses the number of rats

TABLE IV

Analgesic-anti-inflammatory activity

Mean of the weights (in grams) eliciting painful stimulus at different times
and analgesic index

Compound	1 h.	2 h.	4 h.	Analg. Index
Control	116.2	87.6	78.8	1.0
DA 3715 40 mg/kg (8)	196.2	128.8	95.0	1.49
DA 3715 80 mg/kg (8)	192.6	147.6	146.2	1.72
DA 3715 160 mg/kg (8)	245.0	171.2	143.8	1.98
BUMADIZON—Ca 40 mg/kg (8)	145.0	108.8	105.0	1.27
BUMADIZON—Ca 80 mg/kg (8)	140	128.8	110.0	1.34
BUMADIZON—Ca 160 mg/kg (8)	142.8	161.2	140.0	1.57

() = in parentheses the number of rats

TABLE V
Activity of DA-3715 and Bumadizon-Ca on fever induced by brewer's yeast in rats

Compound	Rectal temperature (°C) measured at the different times (hours) Mean $\pm$ standard deviation								
	-4	0	1/2	1	1 1/2	2	2 1/2	3	19
Control	37.21 $\pm$ 0.32	38.16 $\pm$ 0.11	38.28 $\pm$ 0.37	38.22 $\pm$ 0.41	38.22 $\pm$ 0.44	38.13 $\pm$ 0.36	38.13 $\pm$ 0.10	38.03 $\pm$ 0.13	37.36 $\pm$ 0.39
DA 3715 40 mg/kg	37.00 $\pm$ 0.38	38.00 $\pm$ 0.31	37.51 $\pm$ 0.19	38.41 $\pm$ 0.55	38.24 $\pm$ 0.76	38.23 $\pm$ 0.74	38.28 $\pm$ 0.65	38.10 $\pm$ 0.57	37.51 $\pm$ 0.57
DA 3715 80 mg/kg	37.06 $\pm$ 0.38	38.14 $\pm$ 0.46	37.16 $\pm$ 0.30	37.47 $\pm$ 0.56	37.54 $\pm$ 0.24	37.57 $\pm$ 0.31	37.74 $\pm$ 0.25	37.47 $\pm$ 0.17	36.75 $\pm$ 0.34
DA 3715 160 mg/kg	36.46 $\pm$ 0.16	38.06 $\pm$ 0.25	37.14 $\pm$ 0.38	37.20 $\pm$ 0.37	37.62 $\pm$ 0.31	37.67 $\pm$ 0.28	37.58 $\pm$ 0.14	37.76 $\pm$ 0.20	36.86 $\pm$ 0.15
BUMADIZON-Ca 40 mg/kg	36.74 $\pm$ 0.33	38.08 $\pm$ 0.37	38.05 $\pm$ 0.04	38.20 $\pm$ 0.66	38.09 $\pm$ 0.69	38.17 $\pm$ 0.78	38.45 $\pm$ 0.57	38.01 $\pm$ 0.45	37.28 $\pm$ 0.59
BUMADIZON-Ca 80 mg/kg	36.96 $\pm$ 0.57	38.02 $\pm$ 0.47	37.10 $\pm$ 0.40	37.38 $\pm$ 0.30	37.48 $\pm$ 0.28	37.65 $\pm$ 0.80	37.96 $\pm$ 0.65	37.80 $\pm$ 0.71	37.44 $\pm$ 0.77
BUMADIZON-Ca 160 mg/kg	36.06 $\pm$ 0.66	38.52 $\pm$ 0.23	37.89 $\pm$ 0.65	37.81 $\pm$ 0.48	37.90 $\pm$ 0.63	37.34 $\pm$ 0.26	37.50 $\pm$ 0.22	37.41 $\pm$ 0.08	36.75 $\pm$ 0.22

* p<0.05

** p<0.01 "Dunnnett"-Test

TABLE VI
Activity of DA-3715 and Bumadizon-Ca on the normal temperature in rats

Compound	Rectal temperature (°C) at different times (hours)						
	Mean $\pm$ standard deviation						
	-1 1/2	-1	-1/2	1/2	1	1 1/2	2
Control	37.13 $\pm$ 0.37	36.73 $\pm$ 0.58	36.36 $\pm$ 0.51	36.33 $\pm$ 0.41	36.62 $\pm$ 0.60	36.68 $\pm$ 0.73	36.57 $\pm$ 0.69
DA 3715 40 mg/kg	36.81 $\pm$ 0.57	36.62 $\pm$ 0.76	36.20 $\pm$ 0.88	35.96 $\pm$ 0.77	36.28 $\pm$ 0.61	36.34 $\pm$ 0.50	36.54 $\pm$ 0.67
DA 3715 80 mg/kg	36.75 $\pm$ 0.66	36.42 $\pm$ 0.46	36.33 $\pm$ 0.64	36.25 $\pm$ 0.45	36.12 $\pm$ 0.57	36.14 $\pm$ 0.61	36.15 $\pm$ 0.63
DA 3715 160 mg/kg	37.01 $\pm$ 0.45	36.32 $\pm$ 0.76	36.22 $\pm$ 0.64	35.71 $\pm$ 0.27	35.85 $\pm$ 0.84	35.91 $\pm$ 0.37	35.86 $\pm$ 0.29
BUMADIZON-Ca 40 mg/kg	37.15 $\pm$ 0.40	36.62 $\pm$ 0.70	36.33 $\pm$ 0.84	36.02 $\pm$ 0.95	36.13 $\pm$ 0.90	36.10 $\pm$ 0.91	36.20 $\pm$ 0.71
BUMADIZON-Ca 80 mg/kg	36.69 $\pm$ 0.60	36.51 $\pm$ 0.57	36.34 $\pm$ 0.69	36.14 $\pm$ 0.72	36.27 $\pm$ 0.85	36.31 $\pm$ 0.64	36.47 $\pm$ 0.76
BUMADIZON-Ca 160 mg/kg	36.50 $\pm$ 0.27	36.52 $\pm$ 0.59	36.00 $\pm$ 0.59	35.62 $\pm$ 0.58	35.70 $\pm$ 0.52	35.92 $\pm$ 0.88	36.24 $\pm$ 0.88

* $p < 0.05$

** $p < 0.01$ "Dunnett"-Test

TABLE VII

LD₅₀ and confidential limits of DA-3715 and BUMADIZON-Ca according to Litchfield and Wilcoxon. The values are expressed in mg/kg.

DA 3715	BUMADIZON-Ca
1,057.54	796.34
721.30 – 1,550.51	537.75 – 1,179.28
n = 40	n = 40

n = number of rats

TABLE VIII

Gastric lesions observed in rats after administration of DA-3715 and BUMADIZON-Ca

Compound	no. of animals	Body weight in grams Mean ± Standard deviation	Mortality	% animals with gastric lesions	Ulcerogenic index
Control	15	191.67 ± 9.57	0	0	0
DA 3715 40 mg/kg	15	206.67 ± 9.00	0	0	0
DA 3715 80 mg/kg	15	205.33 ± 6.40	0	0	0
DA 3715 160 mg/kg	15	212.67 ± 12.23	0	0	0
DA 3715 320 mg/kg	15	218.67 ± 6.40	0	46.66	71.38
BUMADIZON-Ca 40 mg/kg	15	194.67 ± 7.43	0	0	0
BUMADIZON-Ca 80 mg/kg	15	190.67 ± 8.84	1	0	0
BUMADIZON-Ca 160 mg/kg	15	198.00 ± 11.46	0	6.66	0.47
BUMADIZON-Ca	15	186.67 ± 7.24	1	64.28	81.63

The following non-limiting Examples serve to illustrate the present invention.

A. Examples of preparation

5 EXAMPLE 1

64 g (0.2 mol) of 4-(3-methyl-2-butenyl)-1,2-diphenyl-3,5-dioxopyrazolidine are dissolved in a solution of sodium hydroxide (16 g (0.4 mol) of sodium hydroxide pellets in 640 ml of water). The solution obtained is heated for 7 hours then cooled to room temperature and washed twice with diethyl ether. The ethereal residue contains a little hydrazobenzene. The alkaline solution is then acidified with 10% hydrochloric acid (sufficient to turn congo red) and quickly extracted with diethyl ether. The organic layer is evaporated to dryness leaving an oily residue which is dissolved in ammonium hydroxide (obtained by diluting 40 ml of a 32% ammonium hydroxide solution with 600 ml of water). To this

5

10 10

solution is added a solution of 11 g of calcium chloride in 40 ml of water. The calcium salt of 2-(3-methyl-2-butenyl)-N,N'-diphenylmalonomonohydrazide thus precipitated under stirring is filtered off under suction and dried for 8 hours at 50°C and 15 Torr. The compound is obtained as a white solid (54.06 g, 72% yield, m.p. 166°C).

5 Analysis:

$C_{40}H_{46}CaN_4O_8$	calc.	C 63.98	H 6.17	Ca 5.33	N 7.46
	found	64.12	6.08	5.50	7.57

5

EXAMPLE 2

103.8 g (0.324 mol) of 4-(3-methyl-2-butenyl)-1,2-diphenyl-3,5-dioxypyrazolidine are dissolved in a solution of 12.96 g (0.324 mol) of sodium hydroxide pellets and 57.3 g (0.16 mol) of disodium hydrogen phosphate dodecahydrate in 400 ml of water. The resultant mixture is heated for 30 hours in an atmosphere of nitrogen, cooled, then diluted with 600 ml of water and filtered. The filtered solution is neutralised (pH 7 to 7.5) with 2N hydrochloric acid and extracted several times with chloroform. The crude 2-(3-methyl-2-butenyl)-N,N'-diphenylmalonomonohydrazide thus obtained is dissolved in 500 ml of 10% aqueous ammonium hydroxide. To this solution calcium chloride (17.9 g, 0.162 mol) dissolved in 50 ml of water is added under stirring.

The calcium salt of 2-(3-methyl-2-butenyl)-N,N'-diphenylmalonomonohydrazide is filtered off and dried for 8 hours at 50°C and 15 Torr.

This salt was obtained as a white solid (98.5 g, 81% yield) and has analytical and physico-chemical characteristics identical to the product of Example 1.

EXAMPLE 3

A suspension of 38.8 g (0.105 mol) of ethyl 2-(3-methyl-2-butenyl)-malonate, N,N'-diphenylhydrazide, in 130 ml of 3.5% aqueous sodium hydroxide solution is refluxed for 22 hours. The solution thus obtained is cooled, washed twice with diethyl ether and treated with decolourizing charcoal. The resultant solution is made acid (to congo paper) with 5% acetic acid and the oil which separates out is extracted with diethyl ether. The organic layer is washed until neutral with water, dried and evaporated to dryness to give 23.1 g of 2-(3-methyl-2-butenyl)-N,N'-diphenylmalonomonohydrazide as a colourless oil. This product is converted into its calcium salt by dissolving it in 300 ml of 0.5 N sodium hydroxide and adding to the solution obtained calcium chloride (3.78 g, 0.034 mol in 30 ml of water).

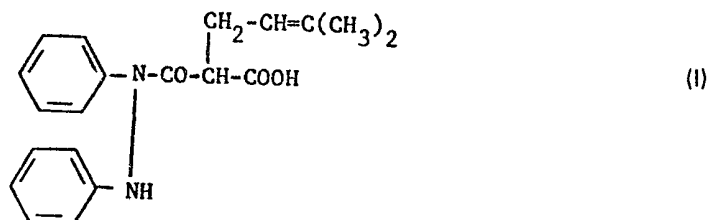
The calcium salt of 2-(3-methyl-2-butenyl)-N,N'-diphenylmalonomonohydrazide which precipitates is filtered off and dried for 8 hours at 50°C and 15 torr. This salt was obtained as a white solid (24 g, 61% overall yield) and had analytical and physico-chemical characteristics identical to those of the product of Example 1.

B. Examples of formulation

35	I <i>Tablets</i>	A	B	C	35
	2-(3-methyl-2-butenyl)-N,N'-diphenylmalonomonohydrazide, calcium salt	200 mg	300 mg	400 mg	
	microcrystalline cellulose	50 mg	50 mg	50 mg	
40	corn starch	77 mg	115 mg	115 mg	40
	talc and magnesium stearate	3 mg	5 mg	5 mg	
	II <i>Hard gelatine capsules</i>				
	Each capsule contains:	A	B	C	
45	2-(3-methyl-2-butenyl)-N,N'-diphenylmalonomonohydrazide, calcium salt	200 mg	300 mg	400 mg	45
	talc	5 mg	5 mg	5 mg	
	III <i>Suppositories</i>	A	B		
50	2-(3-methyl-2-butenyl)-N,N'-diphenylmalonomonohydrazide, calcium salt	300 mg	400 mg		50
	glycerides of fatty acids	2 g	2 g		

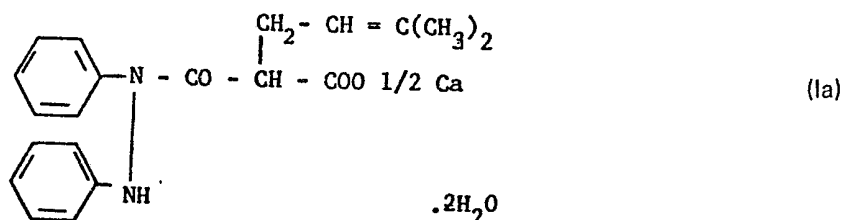
CLAIMS

1. 2-(3-methyl-2-butenyl)-N,N'-diphenylmalonomonohydrazide of formula I,

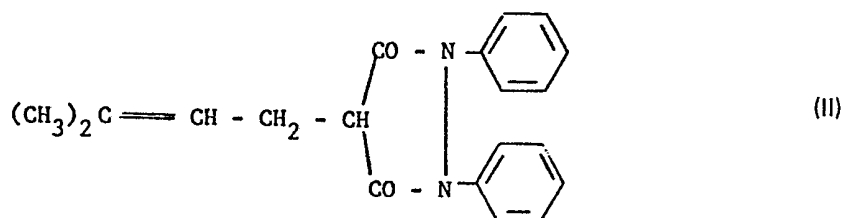


and salts thereof.

- 5 2. Physiologically compatible salts of the compound of formula I as defined in claim 1. 5
 3. Alkali metal and alkaline earth metal salts of the compound of formula I as defined in claim 1.
 4. The calcium salt of 2-(3-methyl-2-butenyl)-N,N'-diphenylmalonomonohydrazide, said salt having the formula Ia,

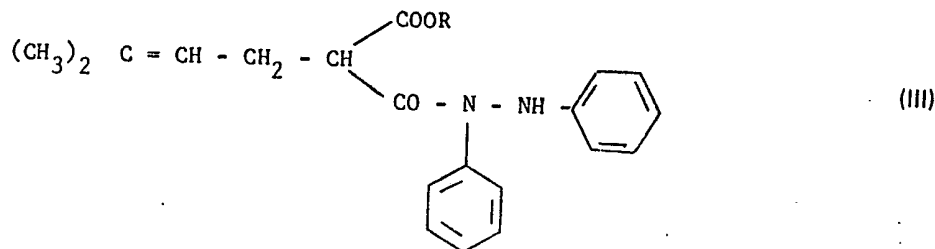


- 10 5. A process for the preparation of a compound as claimed in claim 1 which comprises hydrolysing 10
 4-(3-methyl-2-butenyl)-1,2 diphenyl-3,5-dioxypyrazolidine of formula II,



with an alkali and subsequently, if required, converting the compound of formula I thus obtained into a salt thereof.

- 15 6. A process as claimed in claim 5 wherein hydrolysis is effected by means of an alkali metal hydroxide. 15
 7. A process as claimed in claim 6, wherein hydrolysis is effected by means of sodium hydroxide and the hydrolysis is effected in the presence of an inorganic sodium salt.
 8. A process as claimed in claim 7 wherein the sodium salt is disodium hydrogen phosphate.
 20 9. A process as claimed in any one of claims 5 to 8 for the preparation of the compound of formula Ia wherein the compound of formula I obtained is reacted with an inorganic soluble calcium salt. 20
 10. A process as claimed in claim 9 wherein the compound of formula I is reacted with calcium chloride.
 11. A process for the preparation of a compound as claimed in claim 1 which comprises
 25 hydrolysing an ester of formula III, 25



(wherein R represents a lower alkyl group) with an alkali and subsequently, if required, converting the compound of formula I thus obtained into a salt thereof.

12. A process as claimed in claim 11 wherein hydrolysis is effected by means of an alkali metal hydroxide. 5
13. A process as claimed in claim 12 wherein the alkali metal hydroxide is sodium hydroxide. 5
14. A process as claimed in claim 11 or claim 12 wherein the hydrolysis is effected at elevated temperatures.
15. A process as claimed in any one of claims 11 to 14 wherein, in the compound of formula III, R represents an ethyl group. 10
16. A process for the preparation of a compound as claimed in claim 1 substantially as herein described. 10
17. A process for the preparation of a compound as claimed in claim 1 substantially as herein described in any one of Examples 1 to 3.
18. Compounds as claimed in claim 1 whenever prepared by a process as claimed in any one of claims 5 to 17. 15
19. Pharmaceutical compositions comprising, as active ingredient, the compound of formula I as defined in claim 1 and/or a physiologically compatible salt thereof, in association with a pharmaceutical carrier or excipient.
20. Compositions as claimed in claim 19 in a form suitable for oral or rectal administration. 20
21. Compositions as claimed in claim 19 or claim 20 in the form of tablets, gelatine capsules or suppositories.
22. Compositions as claimed in any one of claims 19 to 21 in the form of dosage units.
23. Compositions as claimed in claim 22 wherein each dosage unit contains from 20 to 1000 mg of active ingredient. 25
24. Compositions as claimed in claim 23 wherein each dosage unit contains from 50 to 500 mg of active ingredient.
25. Compositions as claimed in any one of claims 19 to 24 wherein the active ingredient comprises the compound claimed in claim 4.
26. Pharmaceutical compositions as claimed in claim 19 substantially as herein described. 30
27. Pharmaceutical compositions substantially as herein described in any one of Examples I to III.
28. The compound of formula I as defined in claim 1 and its physiologically compatible salts for use as analgesic, anti-inflammatory and antipyretic agents.
29. A method of treating patients suffering from inflammation or rheumatism which comprises administering to the said patient an effective amount of the compound of formula I as defined in claim 1 or a physiologically compatible salt thereof. 35
30. Each and every novel method, process, compound and composition herein disclosed.