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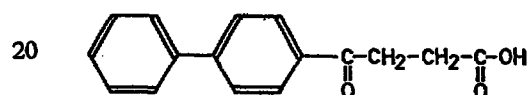
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(54) THERAPEUTIC COMPOSITIONS CONTAINING 3-(4-BIPHENYLCARBONYL)PROPIONIC ACID

(71) We, AMERICAN CYANAMID COMPANY, a corporation organised and existing under the laws of the State of Maine, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a therapeutic composition for use in meliorating inflammation and pain in warm-blooded animals, and to a method for preparing the therapeutic composition.

The present invention is based upon the unexpected discovery that 3 - (4 - biphenyl-carbonyl)propionic acid of the formula:



is highly active as an anti-inflammatory agent in meliorating inflammation and pain in warm-blooded animals, comparing very well with the therapeutic properties of chemically related biphenyl compounds disclosed in the patent literature.

The active propionic acid derivative used in accordance with this invention is formulated with a pharmaceutically acceptable carrier. The active compound may be used in the form of the free acid or in the form of a pharmaceutically acceptable salt, for example the sodium or calcium salts or an amine salt such as ethanalamine and tris-(hydroxymethyl) - methylamine salts. The active compound is useful in doses which range from 5 to 250 mg. per kilogram of body weight of warm-blooded animal per day. The

preferred daily dosage is usually from 5 to 50 mg. per kilogram of body weight.

The preparation of the active compound used in this invention is described in the chemical literature and in Example 1 hereinafter.

The active compound used in the present invention also shows immunological activity. For example, it is well known that if rabbit anti-serum to sheep erythrocytes is injected into the skin of a guinea pig, a haemorrhagic lesion results and should the injection be given intravenously, death from "heterophil shock" results. (Redfern W. W., Am. J. Hyg. 6, 276 (1926)). Both of these phenomena are complement-dependent as described by Glösky et al. J. immunol. 102, 1 (1969) and Becker et al., Textbook of Immunopathology, Miescher and Muller-Eberhard (Ed.), Grune and Stratton, New York, 1968 pp. 77. On the other hand, 3 - (4 - biphenylcarbonyl)-propionic acid when administered under appropriate conditions, protects guinea pigs from each of these challenges.

The active compound used in the present compositions is a nearly colorless crystalline solid only slightly soluble in water, but readily soluble in solvents such as methanol, ethanol and propylene glycol. The salts are soluble in water and in hydroxylic solvents.

For therapeutic administration the active compound is admixed with a pharmaceutically acceptable carrier and used, for example, in the form of tablets, dragees, capsules, suppositories, liquids, elixirs, emulsions, suspensions, syrups, chocolate, candy, wafers, chewing gum and solutions for parenteral administration. Such compositions will generally contain at least 0.1% by weight of the active 3 - (4 - biphenylcarbonyl)propionic acid or salt. The percentage in the compositions may, of course, be varied, and may often conveni-

ently be between 2% and 60% or more of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. This dosage can also be obtained by the use of sustained release preparations. Preferred compositions according to the present invention are prepared so that a dosage unit form contains from 1 to 250 milligrams of the active compound.

Tablets, pills and dragees, for example, may contain the following: a binder such as gum tragacanth, acacia, corn starch, or gelatin; a disintegrating agent such as corn starch, potato starch or alginic acid; a lubricant such as stearic acid, magnesium stearate or talc; a sweetening agent such as saccharin may be added, as well as a flavoring such as peppermint, an oil of wintergreen or cherry flavoring.

In determining the acute anti-inflammatory activity of the present compounds Royal Hart, Wistar strain rats ranging from 80 to 90 g. were used. The rats were fasted overnight prior to dosing but had free access to water.

The drugs in aqueous suspension were administered by gavage in a volume of 1.7 ml./50 g. rat (corresponds to hydration volume used by Winter et al., Proc. Soc. Exp. Biol. & Med. 111 544-547, 1962).

The phlogistic agent used was carrageenin prepared as a sterile 1% by weight suspension in 0.9% by weight sodium chloride for routine testing. A volume of .05 ml. was injected through a 26 international standard gauge needle into the plantar tissue of the right hind paw. Measurements were made 5 hours after drug administration (4 hours after carrageenin challenge) unless otherwise indicated.

Volumes of both the normal and carrageenin inflamed feet were determined. The difference between the two measurements was considered to be the increased oedema due to the carrageenin administration. Results were expressed as a C/T efficacy ratio (oedema of control animals/oedema of treated animals). The following Table I summarizes the results.

TABLE I

The effects of anti-inflammatory agents on carrageenin induced oedema of the rat paw* (pooled data)

Treatment	Dose** mg./kg.	No. Rats	Ratio control/ treated oedema
Controls	—	64	—
Aspirin	250	32	2.8
	83	32	1.4
	27	32	1.2
	9	32	.9
	3	32	1.0
Phenylbutazone	250	32	2.3
	83	32	2.4
	27	32	1.7
	9	32	1.3
	3	32	1.3
3-(4-biphenyl- carbonyl)propionic acid	250	24	1.8
	83	16	1.8
	27	16	1.6
	9	16	1.4

* — Rats fasted overnight prior to testing.

** — Measurements made 5 hours after oral administration.

The compound used in the present invention is an active analgesic when measured by the "writhing syndrome" test for analgesic activity as described by Siegmund, et al., Proceedings of the Society for Experimental Bio-

logy and Medicine, Vol. 95, p. 729, (1957), with modifications. This method is based upon the reduction of the number of writhes following the intraperitoneal injection of one mg./kg. of body weight of phenyl *p*-quinone in

male Swiss albino mice weighing 15—25 grams per mouse. The syndrome is characterized by intermittent contractions of the abdomen, twisting and turning of the trunk, and extension of the hind legs beginning 3 to 5 minutes after injection of the phenyl *p*-quinone. The test compound is administered orally to groups of two mice each 30 minutes before injection of the phenyl *p*-quinone. The total number of writhes exhibited by each group of mice is recorded for a 3 minute period commencing 15 minutes after injection of the phenyl *p*-quinone. A compound is considered active if it reduces the total number of writhes in two test mice from a control value of approximately 30 per pair to a value of 18 or less. The following Table II summarizes the relative activity of the present component as an active analgesic.

TABLE II

Compound	Oral Dosage mg./kg.	No. of Writhes per 3 minute period	
		Pair 1	Pair 2
3-(4-Biphenyl-carbonyl)-propionic acid	200	4	3
Controls	—	31	31

The following examples describe in detail the synthesis of the active compound used in the present invention, descriptions and results of tests using the percent components and formulations of various types of pharmaceutical preparations.

Example 1

Preparation of 3 - (4 - Biphenylcarbonyl)-propionic Acid

135 Grams of aluminum chloride is dissolved in 500 ml. of nitrobenzene, the solution being held below 10°C. by external cooling. A finely ground mixture of 50 g. of succinic anhydride and 75 g. of biphenyl is added to the stirred solution, the temperature being held below 10°C. It is then held at room temperature for four days. After pouring the reaction mixture into a solution of 150 ml. of concentrated hydrochloric acid in 1 liter of ice water, the nitrobenzene is removed by steam distillation. The solid is collected, dissolved in 4 liters of 3% hot sodium carbonate solution, clarified, and reprecipitated by the addition of excess 6N sulfuric acid solution. The crude product is col-

lected, dried, and recrystallized from ethanol to give the pure subject compound, melting point 185—187°C. Hey and Wilkinson, *J. Chem. Soc.* 1940, p. 1030 give a melting point of 185°C.

Example 2

The effect of the present compound on body temperature in yeast induced pyrexia was determined by the following procedure. Groups of three Wistar strain rats (Royal Hart) weighing 80±5 g. were injected subcutaneously in the nape of the neck with 0.6 ml. of a 40% suspension of dried brewers yeast in distilled water. Test compounds were suspended in a 1.5% buffered starch solution and administered at various doses by gavage 17 hours post challenge. Control rats were treated in a similar manner but were given only the buffered starch solution. At 19 hours post challenge the rectal temperature of each rat was measured with an electric thermometer. Each dose response experiment was replicated one or more times. The following Table III summarizes the results.

TABLE III

The effect of test drugs on the body temperature of normal and pyretic rats

Treatment	Oral dose mg./kg.	Normal Rats		Rats with yeast induced pyresis		Effective** Dose mg./kg.
		No.	Body Temp. °C.	No.	Body Temp. °C.	
Control	—	30	36.8	156	38.3	
Aspirin	250	4	37.0	15	36.8+	78
	83	4	37.1	15	37.1+	
	27	4	36.8	15	37.2+	
	9	4	37.0	15	37.5+	
	3	—	—	6	38.1+	
Phenylburazone	250	4	36.8	15	36.8+	90
	83	4	37.0	15	37.0+	
	27	4	36.9	15	37.2%	
	9	4	36.6	15	37.3+	
	3	—	—	15	37.7+	
3-(4-biphenyl-carbonyl)-propionic acid	250	8	36.3*	6	36.7+	135
	83	8	37.0	6	37.2+	
	27	8	36.9	6	37.6+	
	9	8	36.8	6	37.6+	
	3	8	—	6	37.7+	

*Significantly lower than normal control temperature. $p = < .05$ by t test.+ Significantly lower temperature than pyretic controls. $p = < .05$ by t test.

**Dose estimated to reduce temperature to 37°C.

Example 3

In order to test erythema in albino guinea pigs (Lederle breeding colony) they were depilated on their flanks, the evening before testing, with a standard mixture of barium sulfide and gum acacia. On the morning of testing, groups of four guinea pigs were dosed by gavage one hour prior to ultraviolet exposure (-1 hour). At 0-hour they were restrained in a plastic container which allows exposure of 3 circular spots. They were then

exposed to ultraviolet irradiation from a "Hanovia" Kromayer lamp model 10 for 60 seconds. At +1 and +4 hours the degree of erythema for each of the three sites was assessed according to the following scoring system: 0—no erythema, 0.5 incomplete circle or faint erythema and 1.0=complete circle of distinct erythema. Thus, the maximum score for each animal was 3.0. The following Table IV summarizes the results.

TABLE IV

The effect of anti-inflammatory agents on development of erythema in guinea pigs (pooled data)

Treatment	Dose mg./kg.	Score (avg.)		Dead G.P./ Total	Decision
		1 hr.	4 hr.		
Control	—	2.1	2.8	4/384	
Aspirin	250	.1	1.3	7/88	A
	125	.1	2.0	1/16	A
	62.5	.8	2.0	2/11	A
	31.3	1.2	2.3	0/12	A
Phenylbutazone	250	.0	.5	2/60	A
	125	.1	1.1	0/16	A
	62.5	.3	.9	1/12	A
	31.3	.4	1.7	1/12	A
	15.6	1.1	2.3	0/8	A
	7.8		2.9	0/8	—
3-(4-biphenyl- carbonyl)pro- pionic acid	250	0	1.8	0/8	A
	125	.1	1.3	0/8	A
	62.5	0	1.9	0/6	A
	31.3	0	2.2	0/8	A
	15.6	.1	2.3	0/8	A
	7.8	.9	2.3	0/8	A
	3.9	1.7	2.3	0/8	—

A — Active (discriminant function analysis)

* — Oral administration.

Example 4

Tests to show activity against chronic anti-inflammation in adjuvant arthritis were carried out. Groups of three Royal Hart Wistar strain rats, weighing 200 ± 10 g. each were injected intradermally in the right hind paw with Freund's adjuvant (dried human tubercle bacilli in a mineral oil vehicle) at a dose of 2 mg./kg. of body weight. Test compounds were administered orally in a 1.5% starch vehicle at the indicated dosage in mg./kg of body weight once daily on days 0 through 13 post-challenge. Control rats were treated in a similar manner, but given starch vehicle instead of the test compound. On the 14th and 21st day post-challenge the diameter of the injected paw (primary lesion) is measured

by micrometer caliper, the volumes of inflamed paws are estimated from these measurements, and the results are expressed as percent inhibition of swelling as compared to controls at the same time, the other inflamed sites, such as ears, paws and tail (secondary lesions) are observed and the rat graded as to degree of inflammation and swelling present. The grading is based on a scale of 0 to 24.0, where 0 represents a complete absence of induced arthritic nodules and 24.0 represents the maximum degree of inflammation. The mean grade for each treated group is calculated and the effects of each compound were expressed as percent inhibition of the control grade. The following Table V summarizes the results.

TABLE V

The effect of anti-inflammatory agents on adjuvant arthritis of rats (treatment day 0 to day 13)

Treatment	Oral dose mg./kg./day	Dead/treated at 21 days	Mean weight gain (gms.)		% Inhibition of swelling (primary lesion)		% Inhibition of score (secondary lesion)	
			Day 14	Day 21	14	21	14	21
Normal rats	—	4/51	69*	110*	—	—	—	—
Adjuvant controls	—	21/234	36	39	0	0	0	0
Phenylbutazone	150	0/18	45	50	80*	44	52*	31*
	75	2/18	57*	54	72*	23*	24*	11
	37.5	2/18	47	50	67*	19	12	14*
Aspirin	400	4/18	48	57	76*	68*	52*	48*
	200	1/18	31	27	51*	36*	14	18*
	100	7/18	42	49	40*	21**	19*	7
3-(4-biphenylcar- bonyl) propionic acid	50	8/24	19*	44	69*	55*	53*	39*
	25	2/12	32	56	76*	45*	44*	26*
	12.5	2/12	34	38	54*	23	13	1

*Significantly different from adjuvant controls ($p = < .05$ by t test).

Example 5
Experiments were conducted to determine analgesia by a modification of the method of Randall and Selitto (arch. int. Pharmacodyn 111 : 409—419, 1957). This method was used to measure the pain threshold of rats whose paws were made sensitive to pressure by injection of a 20% aqueous suspension (0.1 ml.) of brewers yeast into the plantar surface of the left hind paw. The pressure in mm. Hg. which, when applied to the inflamed paw, elicited a sudden struggle or vocalization was recorded. A maximum (cut-off) pressure of 300 in. Hg. was employed. Control rats respond at a pressure of about 100—120 mm. Hg. The following Table VI summarizes the results.

TABLE VI
Analgesic Potency and Efficacy in the Inflamed Rat Paw

Agent	Route	No. Rats Used (dose levels)	Post-Treatment/Pre-Treatment Ratio of Pressure to React			Rank Order* (overall)	
			1.5	2.0 mg./kg.	2.5	Potency	Efficacy
Aspirin	I.P.	40 (4)	50	200		6	2
	P.O.	48 (5)	100	>400		5 (5)	2 (3)
Phenyl- butazone	I.P.	50 (5)	20	40	>100	3 (4)	2 (2)
	P.O.	48 (5)	50	150	>400	4	1
3-(4-bi- phenylcar- bonyl)pro- pionic acid	I.P.	56 (5)	10	40	100	2 (2)	1 (1)
	P.O.	60 (4)	30	90	>200	3	1

Pre-treatment pressure thresholds were determined 2 hours after brewers' yeast. Post-treatment recordings were made 3 hours after the yeast (1 hour after agent). There was 8—10 rats at every dose level (3—6) for each agent studied. A ratio of post-pretreatment pressure threshold of >1.36 is significant at $p = 0.05$.

*Rank order for potency estimated from the doses required to attain a ratio of 1.5. Order for efficacy estimated from the highest ratio attainable. > indicates the highest dose tested at which the indicated ratio was not attained.

Using the procedure described in this example and determining the pressure-pain threshold ratio at periods from $\frac{1}{2}$ to 48 hours following the administration of 200 mg./kg. orally the following results were obtained.

TABLE VII

Ratio of Treated/Control
Pressure-Pain Threshold

Treatment (200 mg./kg. orally)

Hours After Treatment	Aspirin	Phenylbutazone	3-(4-biphenyl- carbonyl)- propionic acid
1/2	—	1.9	1.7
1	1.2	2.8	1.9
2	1.2	2.6	2.7
3	1.7	3.2	4.3
4	1.7	3.2	3.9
6	1.1	1.1	3.7
8	—	—	4.3
18	—	—	3.1
24	—	—	3.6
30	—	—	3.2
48	—	—	1.7

Analgesic Action* (Duration) in the Inflamed (Brewer's yeast) Raw Paw.

*Analgesia is considered to be present when the T/C ratio > 1.5. There were at least 8 rats tested for each time period.

The prolonged activity of the present compound over aspirin and phenylbutazone is shown in the above Table VII.

Example 6

Preparation of 50 mg. Tablets

Per Tablet		For 10,000 Tablets
0.050 g.	3-(4-biphenylcarbonyl) propionic acid	500. g.
0.080	Lactose	800.
0.010	Corn Starch (for mix)	100.
0.008	Corn Starch (for paste)	75.
0.148 g.		1475.
.002	Magnesium Stearate (1%)	15. g.
0.150 g.		1490. g.

The active ingredient, lactose and corn starch (for mix) are blended together. The corn starch (for paste) is suspended in 600 ml. of water, and heated with stirring, to form a paste. This paste is then used to granulate the mixed powders. Additional water is used, if necessary. The wet granules are passed through a No. 8 U.S. Standard hand screen

and dried at 120°F. The dry granules are then passed through a No. 16 U.S. Standard screen. The mixture is lubricated with 1% magnesium stearate and compressed into tablets in a suitable tableting machine.

Example 7

Preparation of Oral Syrup

Ingredient	Amount
Active ingredient:	
10 3 - (4 - biphenylcarbonyl)propionic acid	500 mg.
Sorbitol solution (70% N.F.)	40 ml.
Sodium benzoate	150 mg.
Saccharin	10 mg.
15 Red dye (F. D. & C. No. 2)	10 mg.
Cherry flavor	50 mg.
Distilled water, q.s. ad	100 mg.

The sorbitol solution is added to 40 ml. of distilled water and the active ingredient is suspended therein. The saccharin, sodium benzoate, flavor and dye are added and dissolved in the above solution. The volume is adjusted to 100 ml. with distilled water. Each ml. of syrup contains 5 mg. of drug.

Other ingredients may replace those listed in the above formulation. For example, a suspending agent such as bentonite magma, tragacanth, carboxymethylcellulose or methylcellulose may be used. Phosphates, citrates or tartrates may be added as buffers. Preservatives may include the parabens and sorbic acid and other flavors and dyes may be used in place of those listed above.

Example 8

Preparation of Parenteral Solution

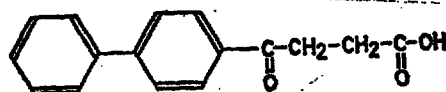
In a solution of 700 ml. of propylene glycol and 200 ml. of water for injection is dissolved 20.0 g. of 3 - (4 - biphenylcarbonyl)propionic acid with stirring. After dissolution is complete, a solution of 5 g. of 2-aminoethanol in 20 ml. of water for injection is then added to the formulation. The pH of this solution is then adjusted to 5.5 with hydrochloric acid and the volume is made up to 1000 ml. with distilled water. The formulation is filtered through a 0.22 micron sterilizing filter, filled into 5.0 ml. ampoules each containing 2.0 ml. (representing 40 mg. of drug) and sealed under nitrogen.

We make no claim herein to a composition which consists solely of 3-(4-biphenylcarbonyl)propionic acid, or a pharmaceutically acceptable salt thereof, and non-sterile water or pharmaceutically acceptable common organic solvent. Likewise we make no claim herein to a method of preparing such a composition by admixing 3 - (4 - biphenylcarbonyl)-

propionic acid, or a pharmaceutically acceptable salt thereof, with non-sterile water or a pharmaceutically acceptable common organic solvent.

Subject to the foregoing disclaimer, WHAT WE CLAIM IS:—

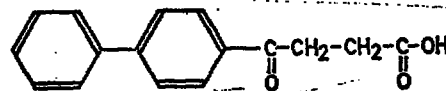
1. A therapeutic composition having anti-inflammatory and analgesic activity in warm-blooded animals, comprising 3 - (4 - biphenylcarbonyl)propionic acid of the formula:



or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

2. A composition according to Claim 1 in dosage unit form and containing from 1 to 250 milligrams of said propionic acid or salt thereof.

3. A method for the preparation of a therapeutic composition having anti-inflammatory and analgesic activity in warm-blooded animals, comprising admixing 3 - (4 - biphenylcarbonyl)propionic acid of the formula:



or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable carrier.

4. A method according to Claim 3, wherein said composition is prepared in a dosage unit form which contains from 1 to 250 milligrams of said propionic acid or salt thereof.

5. A method for the preparation of a therapeutic composition having anti-inflammatory and analgesic activity in warm-blooded animals, according to Claim 3 and substantially as hereinbefore described.

6. A therapeutic composition having anti-inflammatory and analgesic activity in warm-blooded animals, whenever prepared by a method according to any one of Claims 3—5.

7. A therapeutic composition having anti-inflammatory and analgesic activity in warm-blooded animals, according to Claim 1 and substantially as hereinbefore described.

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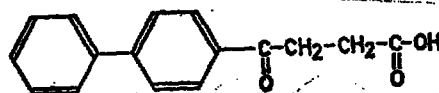
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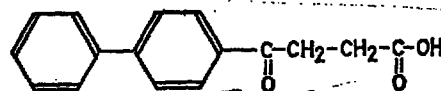
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or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

2. A composition according to Claim 1 in dosage unit form and containing from 1 to 250 milligrams of said propionic acid or salt thereof.

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4. A method according to Claim 3, wherein said composition is prepared in a dosage unit form which contains from 1 to 250 milligrams of said propionic acid or salt thereof.

5. A method for the preparation of a therapeutic composition having anti-inflammatory and analgesic activity in warm-blooded animals, according to Claim 3 and substantially as hereinbefore described.

6. A therapeutic composition having anti-inflammatory and analgesic activity in warm-blooded animals, whenever prepared by a method according to any one of Claims 3—5.

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