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COMPLETE SPECIFICATION

Barbituric Acid Derivatives

We, TAKEDA CHEMICAL INDUSTRIES LTD. of 27 Doshomachi 2 chome, Higashi-ku, Osaka, Japan a corporation organized under the laws of Japan, 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:—

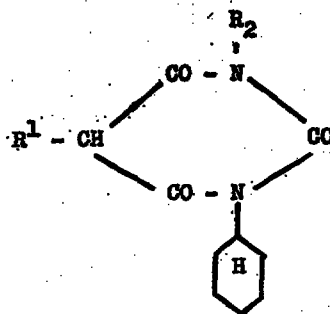
This invention relates to barbituric acid derivatives which are particularly useful as anti-inflammatory agents.

Inflammation is one of the most common symptoms observed in clinical medicine and, although it is known that many diseases originate therefrom, physicians have often met with difficulties in removing this symptom during the therapy of various diseases. To eliminate such a harmful symptom as soon as possible or to prevent the symptom from occurring is very important for the purpose of shortening the term of a disease and relieving patients from pain as quickly as possible.

The known anti-inflammatory agents can be divided into two groups; one of which comprises steroidal anti-inflammatory agents, i.e. adrenocortical hormones such as prednisolone or triamcinolone, and the other comprising non-steroidal anti-inflammatory agents which consists mainly of pyrazolidine derivatives such as phenylbutazone, oxyphenbutazone or 1,4-diphenyl-3,5-dioxypyrazolidine. However, those of the former group provoke hypofunction of the anterior pituitary gland and atrophy of the adrenal cortex when they are used for a long period and those of the latter group often disturb the normal functions of the kidney, liver and heart, so that both need to be carefully administered to patients, especially those who are suffering from a hormonal or metabolic mechanism or function of their viscera such as kidney, liver or heart. Therefore, there is a need for a general anti-inflammatory agent which can be safely administered to patients.

We have found a series of novel barbituric acid derivatives which are not only very effective in anti-inflammatory activity but have far fewer side-effects than those observed in known anti-inflammatory agents.

The present invention provides compounds of the general formula:



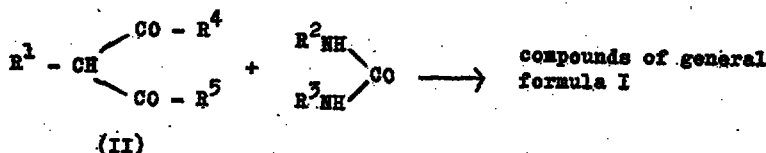
and pharmaceutically acceptable salts (preferably alkali metal and alkaline earth metal salts) thereof, in which formula R^1 is a hydrocarbon radical containing from one to six carbon atoms and R^2 is a hydrogen atom or a cyclohexyl radical, with the proviso that when R^2 is a cyclohexyl group, R^1 is not an *n*-butyl group.

It is to be understood that the term "alkaline earth metal" as used herein, includes magnesium.

Preferred compounds are: 1-cyclohexyl-5-methylbarbituric acid and pharmaceutically acceptable salts thereof, 1-cyclohexyl-5-ethylbarbituric acid and pharmaceutically acceptable salts thereof, 1-cyclohexyl-5-propylbarbituric acid and pharmaceutically acceptable salts thereof, 1-cyclohexyl-5-allylbarbituric acid and pharmaceutically acceptable salts thereof, 1-cyclohexyl-5-butylbarbituric acid and pharmaceutically acceptable salts thereof, 1-cyclohexyl-5-*sec*-butylbarbituric acid and pharmaceutically acceptable salts thereof, 1-cyclohexyl-5-pentylbarbituric acid and pharmaceutically acceptable salts thereof, 1-cyclohexyl-5-*sec* pentyl barbituric acid and pharmaceutically acceptable salts thereof, 1,5-dicyclohexylbarbituric acid and pharmaceutically acceptable salts thereof, 1-cyclohexyl-5-phenylbarbituric acid and pharmaceutically acceptable salts thereof, 1,3-dicyclohexyl-5-methylbarbituric acid and pharmaceutically acceptable salts thereof, 1,3-dicyclohexyl-5-ethylbarbituric acid and pharmaceutically acceptable salts thereof, 1,3-dicyclohexyl-5-propylbarbituric acid and pharmaceutically acceptable salts thereof, 1,3-dicyclohexyl-5-allylbarbituric acid and pharmaceutically acceptable salts thereof, 1,3-dicyclohexyl-5-*isopropyl*barbituric acid and pharmaceutically acceptable salts thereof, 1,3-dicyclohexyl-5-*iso*-butylbarbituric acid and pharmaceutically acceptable salts thereof, 1,3-dicyclohexyl-5-*sec*-butylbarbituric acid and pharmaceutically acceptable salts thereof, 1,3-dicyclohexyl-5-pentylbarbituric acid and pharmaceutically acceptable salts thereof, 1,3-dicyclohexyl-5-*sec*-pentylbarbituric acid and pharmaceutically acceptable salts thereof, 1,3,5-tricyclohexylbarbituric acid and pharmaceutically acceptable salts thereof, 1,3-dicyclohexyl-5-phenylbarbituric acid and pharmaceutically acceptable salts thereof.

The compounds of the above general formula can be prepared by any of the following methods A—H.

(A) The reaction of a malonic acid derivative of the general formula (II)



with cyclohexylurea or 1,3-dicyclohexylurea, in which R^1 and R^2 have the same meaning as in the formula I and R^3 is a hydrogen atom or a cyclohexyl radical with the proviso that R^2 and R^3 are not both hydrogen atoms, and R^4 and R^5 each is a hydroxyl, an alkoxy, an aryloxy or an aralkyloxy group or a halogen atom.

The α -substituted malonic acid derivative used can be, for example, methylmalonic acid, ethylmalonic acid, propylmalonic acid, isopropylmalonic acid, propenylmalonic acid, isopropenylmalonic acid, butylmalonic acid, *sec*-butylmalonic acid, *iso*-butylmalonic acid, but-2-enylmalonic acid, but-3-enylmalonic acid, amylmalonic acid, *iso*-amylmalonic acid, hexylmalonic acid, cyclohexylmalonic acid, cyclohex-1 (or 2 or 3)-enylmalonic acid, cyclohexa-1,3-(or -1,4- or -2,4-)dienylmalonic acid, phenylmalonic acid, cyclopentylmalonic acid, cyclopent-1 (or 2 or 3)-enylmalonic acid or cyclopent-1,3-(or -2,4-)dienylmalonic acid, or an ester of said α -substituted malonic acids as a methyl ester, an ethyl ester, a propyl ester, a hexyl ester, a decyl ester, a myristyl ester, a stearyl ester, phenyl ester, a toluyl ester, a benzyl ester or a phenethyl ester as well as an acid halide or semi-ester of said α -substituted malonic acids for example an acid chloride, an acid bromide or an acid iodide.

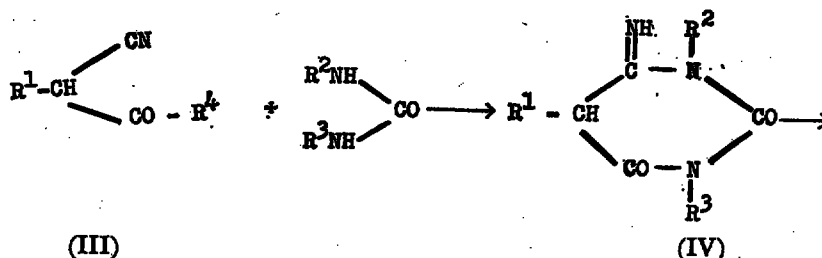
When a malonic acid ester derivative is used as a starting material, the reaction is preferably carried out in the presence of an alkaline condensation catalyst, for example an alkali metal alcoholate (such as sodium methylate, potassium methylate, sodium ethylate or potassium ethylate), a magnesium alcoholate (such as magnesium methylate or magnesium ethylate), an alkali metal (such as sodium or potassium) or magnesium. The reaction is usually accelerated by heating. The solvent for the reaction is usually a lower aliphatic alcohol such as methanol, ethanol, propanol or butanol, but other solvents can be employed so long as they do not disturb the reaction. It is desirable that

the solvent is as anhydrous as possible. After the reaction, the solvent used is removed from the reaction mixture and the residue, after being washed with water if required, is dissolved in water at an alkaline pH. The alkaline solution can be acidified to precipitate the desired compound. Preferred malonic acid ester derivatives which can be used are the lower alkyl esters such as a methyl ester, an ethyl ester or a propyl ester but a phenyl ester, benzyl ester or a higher alkyl ester may, of course, be employed, if desired.

When the malonic acid derivative is the free carboxylic acid, (i.e. R^4 and R^5 are both hydroxyl radicals), the reaction can be accelerated by heating a mixture of both starting materials in the presence of a dehydrating agent such as phosphorus pentachloride, phosphorus pentoxide, phosphoryl chloride, polyphosphoric acid (a mixture of phosphoric acid and phosphorus pentoxide), thionyl chloride or concentrated sulphuric acid to assist condensation. This reaction may be carried out without using solvent. However, if desired, an anhydrous organic solvent such as chloroform, acetone, benzene, or toluene or a mixture thereof may be used so long as it does not disturb the reaction. After the reaction, distillable substances are removed by distillation under reduced pressure and the residue is washed with water. The water-insoluble residue is dissolved in an aqueous alkali solution and the solution is acidified to precipitate the desired compound.

When the malonic acid derivative is an acid halide, (i.e. R^4 and R^5 are both halogen atoms) the reaction takes place with the generation of the hydrogen halide. However, it is generally preferable to accelerate the reaction by heating. A solvent is usually unnecessary for this reaction, but, if desired, an anhydrous organic solvent such as acetone, benzene or toluene may be used. Moreover, the reaction may be accelerated by adding an acid acceptor such as an inorganic base, for example an alkali metal hydroxide (e.g. calcium hydroxide or potassium hydroxide), an alkaline earth metal hydroxide (e.g. calcium hydroxide or magnesium hydroxide) or an alkali metal carbonate (e.g. sodium carbonate, potassium carbonate or sodium hydrogen carbonate,) or an organic base such as pyridine, quinoline, dimethylaniline, diethylaniline or any other tertiary amine.

(B) The reaction of cyclohexylurea or 1,3-dicyclohexylurea with a cyanoacetic acid derivative of the general formula III to give an imide of a barbituric acid of the general formula IV which gives the desired barbituric acid derivative on hydrolysis,



compounds of general formula I.

in which R^1 , R^2 and R^3 have the same meaning as in method A and R^4 is a halogen atom, a hydroxyl, an alkoxy, an aryloxy or an aralkoxy radical.

Examples of cyanoacetic acid derivatives which can be used are α -cyanocarboxylic acids, such as α -cyanopropionic acid, α -cyanobutyric acid, α -cyanovaleric acid, α -cyanoisovaleric acid, 2-cyanobut-3-enoic acid, 2-cyanopent-3(or 4)-enoic acid, 2-cyano-3-methylbut-3-enoic acid, α -cyanocaproic acid, 2-cyano-3(or 4)-methylpentanoic acid, 2-cyano-3,3-dimethylbutanoic acid, 2-cyanohex-3(or 4) (or 5)-enoic acid, α -cyanoenanthic acid, 2-cyano-3 (or 4 or 5)-methylhexanoic acid, α -cyanocaprylic acid, α -cyano- α -cyclohexylacetic acid, α -cyano- α -cyclohex-1(or 2 or 3)enylacetic acid, α -cyano- α -cyclohexa-1,3-(or 1-, 4- or -2,4-)dienylacetic acid, α -cyano- α -phenylacetic acid, α -cyano- α -cyclopent-1(or 2 or 3)-enylacetic acid, α -cyano- α -cyclopenta-1,3-(or -2,4-)dienylacetic acid, or an ester of said α -cyanocarboxylic acids (for example the methyl ester, ethyl ester, propyl ester, hexyl ester, decyl ester, myristyl ester, stearyl ester, phenyl ester, toluyl ester, benzyl ester or phenethyl ester); or an acid halide of said α -cyanocarboxylic acids (for example the acid chloride, acid bromide or acid iodide). A lower alkyl ester such as the methyl or ethyl ester is preferred.

The reaction can be carried out substantially in the same manner as in method (A). In method (B), the initial product is an imino compound (IV) while the course (A)

yields the desired barbituric acid derivative (I) directly.

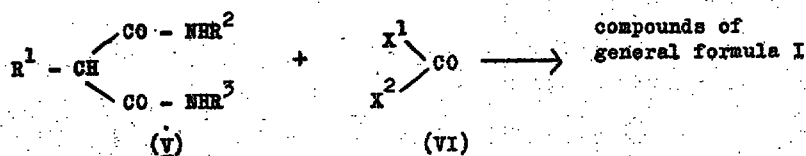
When a cyanoacetic acid ester derivative is used as starting material, the reaction is preferably carried out in the presence of an alkaline condensation catalyst, for example an alkali metal alcoholate (such as sodium methylate, potassium methylate or sodium ethylate), a magnesium alcoholate (such as magnesium methylate or magnesium ethylate), an alkali metal (such as sodium or potassium) or magnesium. The reaction is usually accelerated by heating. The solvent for the reaction is usually a lower aliphatic alcohol such as methanol, ethanol, propanol or butanol, but other solvents can be employed so long as they do not disturb the reaction. It is desirable that the solvent be as anhydrous as possible. After the reaction, the solvent used is removed from the reaction mixture and the residue, after being washed with water if desired, is dissolved in water at an alkaline pH. The alkaline solution is acidified to precipitate the desired compound. The cyanoacetic acid ester derivative advantageously is a lower alkyl ester such as the methyl ester, ethyl ester or propyl ester but the phenyl ester, benzyl ester or a higher alkyl ester may, of course, be employed, if desired.

When the cyanoacetic acid derivative is a free carboxylic acid (i.e. R^4 is a hydroxyl group) the reaction is accelerated by heating a mixture of both starting materials in the presence of a dehydrating agent to assist the condensation. Examples of dehydrating agents are phosphorus pentachloride, phosphorus pentoxide, phosphoryl chloride, polyphosphoric acid (a mixture of phosphoric acid and phosphorus oxide), thionyl chloride or concentrated sulphuric acid. This reaction may be carried out without using a solvent. However, if desired, an anhydrous organic solvent such as chloroform, acetone, benzene or toluene or a mixture thereof may be used so long as it does not disturb the reaction. After the reaction, distillable substances are removed by distillation under reduced pressure and the residue is washed with water. The water-insoluble residue is dissolved in an aqueous solution and the solution is acidified to precipitate the desired compound.

When the cyanoacetic acid derivative is an acid halide (i.e. R^4 is a halogen atom such as chlorine or bromine) the reaction takes place with generation of the hydrogen halide. However, it is generally preferable to accelerate the reaction by heating. A solvent is usually unnecessary for this reaction but, if desired, an anhydrous organic solvent such as acetone, benzene or toluene may be used. Moreover, the reaction may be accelerated by adding an acid acceptor such as an inorganic base, for example an alkali metal hydroxide (e.g. sodium hydroxide or potassium hydroxide), an alkaline earth metal hydroxide (e.g. calcium hydroxide or magnesium hydroxide) or an alkali metal carbonate (e.g. sodium carbonate, potassium carbonate or sodium hydrogen carbonate) or such an organic base as pyridine, quinoline, dimethylaniline, diethylaniline or any other tertiary amine.

The imide obtained is then hydrolysed. The reaction can be carried out by heating the imide in an aqueous medium containing an acid catalyst such as hydrochloric acid, hydrobromic acid or sulphuric acid. If desired, the hydrolysis can be effected by using a strongly acid cation exchange resin for the same purpose.

(C) The reaction of a malonic acid amide derivative of the general formula V with a carbonic acid derivative of the general formula VI,

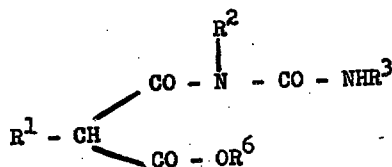


in which R^1 , R^2 and R^3 have the same meaning as in method A, and X^1 and X^2 each is a halogen atom such as chlorine or bromine or an alkoxy radical containing up to 4 carbon atoms such as methoxy, ethoxy, propoxy or butoxy.

The reaction can take place without heating. However, it is generally desirable to accelerate the reaction by heating. A solvent may be unnecessary for this reaction but, if desired, an anhydrous organic solvent such as acetone, benzene or toluene, or a mixture thereof may be used. Moreover, the reaction may be accelerated by the addition of an acid acceptor, which may be an inorganic base such as an alkali metal hydroxide (e.g. sodium hydroxide or potassium hydroxide), an alkaline earth metal hydroxide (e.g. calcium hydroxide or magnesium hydroxide) or an alkali metal carbonate (e.g. sodium carbonate, potassium carbonate or sodium hydrogen carbonate), or an organic base such

as pyridine, quinoline, dimethylaniline, diethylaniline or any other tertiary amine. In addition, when the carbonic acid derivative used is a halocarbonic acid ester or a carbonic acid diester, an alkali metal alcoholate such as sodium methylate, potassium methylate, calcium methylate, magnesium methylate, sodium ethylate, potassium ethylate, sodium propylate or sodium butylate may be used.

(D) The reaction of a malonic acid derivative of the general formula VII with an alkaline agent to form the desired compound I by intramolecular ring-closure:

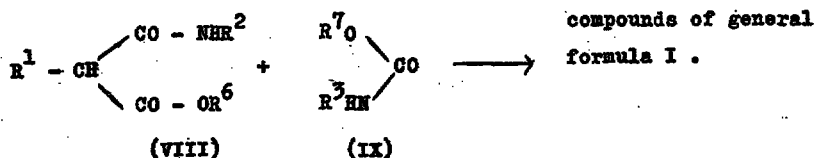


(VII)

in which R^1 , R^2 and R^3 have the same meaning as in method A and R^6 is a hydrocarbon radical such as an alkyl (e.g. methyl, ethyl, propyl, butyl, decyl or myristyl), an aryl (e.g. phenyl or tolyl), or an aralkyl (e.g. benzyl or phenethyl) radical. The reaction is accelerated in the presence of the alkaline agent such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, barium hydroxide, trisodium phosphate, sodium methylate, sodium ethylate, and the reaction may take place at room temperature, but is accelerated by heating.

As the alkaline agent is usually employed in the form of an aqueous solution, it is not necessary to employ any other solvent for the reaction, but a solvent which does not disturb the reaction may be used. After the reaction, the reaction mixture is made weakly acid with, for example, hydrochloric acid, hydrobromic acid, sulphuric acid or acetic acid, cooling if desired, and then the desired compound can be separated out from the solution.

(E) The reaction of a malonic acid monoamide of the general formula VIII with a carbamic acid derivative of the general formula IX:

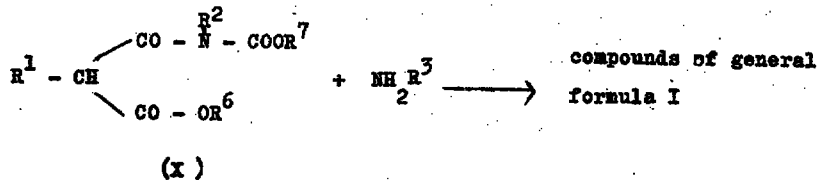


where R^1 , R^2 and R^3 have the same meaning as in method A and R^6 and R^7 each is a hydrocarbon radical such as an alkyl (e.g. methyl, ethyl, propyl, butyl, decyl or myristyl), an aryl (e.g. phenyl or tolyl), or an aralkyl (e.g. benzyl or phenethyl) radical.

It is desirable to use an amide of a malonic ester, especially that of the lower alkyl ester, though amides of the higher alkyl esters, of the aryl esters or of the aralkyl esters can of course be used for the same purpose. The reaction is accelerated in the presence of an alkaline agent such as sodium methylate, sodium ethylate, potassium methylate, potassium ethylate, sodium amide, metallic sodium or metallic potassium. Usually, heating is desirable to allow the reaction to take place smoothly.

Alcohols such as methanol, ethanol, propanol and butanol are usually employed as solvent for the reaction but any organic solvent can be employed so long as it does not disturb the reaction.

(F) The reaction of ammonia or cyclohexylamine with an ester of a malonic acid N-cyclohexyl amide derivative or an ester of a malonic acid amide derivative, both esters being of the general formula X, whereby the following reaction takes place:



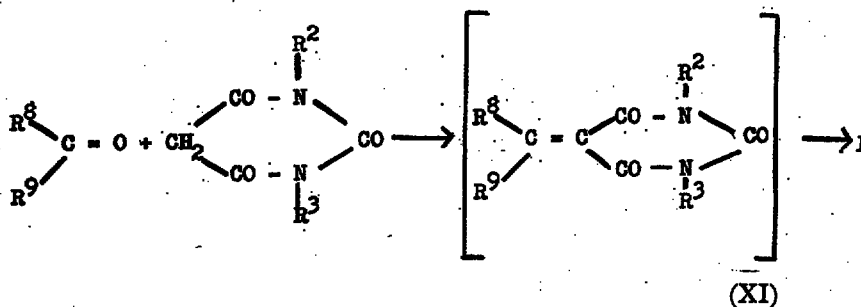
in which R¹, R² and R³ have the same meaning as in method A, and R⁶ and R⁷ each is a hydrocarbon radical such as a lower alkyl, an aryl or an aralkyl radical.

The group —COOR⁷ is an ester radical, and the formula X therefore shows that the starting material can also be regarded as a carbamic acid derivative as well as a malonic acid imide derivative. As the starting material, it is generally preferable to use those compounds in which the group R⁷ is a lower alkyl radical such as methyl, ethyl or propyl, although those having as the group R⁷ any other hydrocarbon group such as a higher alkyl (e.g. hexyl, decyl, myristyl or stearyl), an aryl (e.g. phenyl or tolyl), or an aralkyl (e.g. benzyl or phenethyl) radical can also be employed for the reaction.

The reaction is generally accelerated by heating. Furthermore, the presence of an alkali metal alcoholate such as sodium methylate, sodium ethylate, potassium methylate or potassium ethylate, can also accelerate the reaction. Any solvent can be employed so long as it does not disturb the reaction.

The starting material of formula X can be prepared by reacting an alkyl, aryl or aralkyl haloformate with the corresponding ester of malonic acid amide with elimination of the hydrohalic acid.

(G) The reaction of an aldehyde or a ketone, both having up to six carbon atoms, with 1-cyclohexylbarbituric acid or with 1,3-dicyclohexylbarbituric acid to form a 5-alkylidene-1-(or 1,3-di-) cyclohexylbarbituric acid of the general formula XI, and reducing this intermediate to give the desired compound I:



in which R² and R³ have the same meaning as in method A and R⁸ and R⁹ each is a hydrogen atom or a hydrocarbon radical or together are a hydrocarbon radical, and the total of carbon atoms of R⁸ and R⁹ being not more than five and when R² is cyclohexyl, R⁸ and R⁹ are not *n*-butyl groups.

1-Cyclohexylbarbituric acid or 1,3-dicyclohexylbarbituric acid can be prepared, for example, (1) by reaction between malonic acid or a reactive derivative thereof (e.g. acid chloride, acid bromide, methyl ester or ethyl ester) and cyclohexylurea or 1,3-dicyclohexylurea, (2) by reaction between an ester of malonic acid N-mono-cyclohexyl diamide or an ester of malonic acid N,N'-dicyclohexyl-diamide and phosgene or carbonyl bromide, or by other means similar to the process for producing known barbituric acids.

Examples of aldehydes which can be used as the starting material are formaldehyde, acetaldehyde, propylaldehyde, acrolein, butylaldehyde, 2-methylpropanal, amylaldehyde, 2(or 3)-methylpentanal, 2,2-dimethylpropanal, hexylaldehyde, 2(or 3 or 4)-methylpentanal, 2,2(or 3,3)-dimethylbutanal and (2 or 3)-ethylpropanal. Examples of ketones are acetone, methyl ethyl ketone, diethyl ketone, vinyl ethyl ketone, ethyl propyl ketone, ethyl isopropenyl ketone, cyclohexanone, cyclopentanone, cyclohex-2(or 3)-enone and cyclopent-2(or 3)-enone.

As stated above, this method for the production of the desired compounds of general formula I comprises condensation and hydrogenation (or reduction) reactions. These reactions can be carried out simultaneously or by performing the reduction after the condensation.

When it is intended to carry out both reactions simultaneously, the aldehyde or ketone is allowed to react with 1-cyclohexylbarbituric acid or with 1,3-dicyclohexylbarbituric acid under reducing conditions, for example by adding a reducing agent to the reaction system or by introducing hydrogen gas to the reaction medium in the presence of a suitable catalyst.

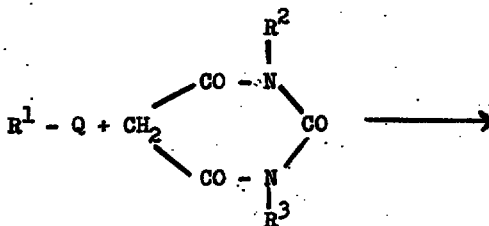
The reducing agent can, for example, be a metal and an acid (e.g. the metal being tin, iron or zinc-amalgam, and the acid being hydrochloric acid, acetic acid or sulphuric acid), a metal and an alcohol (e.g. the metal being sodium, lithium, aluminium, magnesium-amalgam or zinc, and the alcohol being methanol or ethanol), a metal such as sodium, sodium-amalgam, magnesium, magnesium-amalgam, aluminium-amalgam, zinc or iron, a metal and an alkali (e.g. the metal being aluminium or zinc, and the alkali being sodium hydroxide or potassium hydroxide) as well as stannous chloride, ferrous chloride or a complex metal hydride.

The catalyst for catalytic reduction can be, for example, one of those of the platinum series (e.g. platinum sponge, platinum black, platinum plate, platinum oxide or colloidal platinum), one of those of the palladium series (e.g. colloidal palladium, palladium sponge or palladium black), one of those of nickel series (e.g. reduced nickel, nickel oxide, Raney nickel or Urushibara nickel, and other metals or reducing compounds of cobalt, copper, iron, molybdenum, tungsten or zinc, those consisting of two or more of the above-mentioned metals and/or metal compounds (i.e. binary catalysts, multiple catalysts or alloy catalysts) and those of the above-mentioned catalysts supported on a carrier such as diatomaceous earth, clay, active carbon, silica, alumina or asbestos. Although, theoretically one mole of hydrogen is absorbed per mole of the starting barbituric acid derivative during the reaction, an excess of hydrogen may be conducted into the reaction system.

A solvent can be used for the reaction, for example alcohols (such as methanol or ethanol), ethers (such as diethyl ether, dioxane or tetrahydrofuran) or carboxylic acid esters (such as methyl acetate or ethyl acetate) but any other solvent may be employed so long as it does not disturb the reaction. The reaction may be carried out at room temperature or by heating. The reaction can be carried out at atmospheric pressure, but it may be carried out at an elevated pressure, if desired. Moreover, the reaction, especially the condensation, may be accelerated by the addition of a catalytic amount of piperidine acetate—acetic acid or ammonium acetate—acetic acid to the reaction system.

When it is desired to form the intermediate and then reduce the intermediate it may, if desired, be separated from the reaction mixture of the condensation reaction. The condensation is usually effected in a solvent such as methanol, ethanol, propanol, ether, dioxane, tetrahydrofuran or glacial acetic acid at room or at an elevated temperature, and under atmospheric pressure or at an elevated pressure. The hydrogenation can be carried out using the same procedure as mentioned above.

(H) The reaction of 1-cyclohexylbarbituric acid or 1,3-dicyclohexylbarbituric acid with an R^1 -halide, -sulphate or -sulphonate, such as an alkyl halide, an alkyl sulphate, an alkyl benzene sulphonate or an alkyl toluene sulphonate, the moiety R^1 of which is to be introduced to the 5-position of the barbituric acid derivative. Thus, the reaction proceeds as follows:



compounds of general formula I.

in which R^1 , R^2 and R^3 stand for the same meaning as in method A and Q is a halogen

atom such as chlorine, bromine and iodine, an equivalent of SO_3 or a sulphonyloxy radical such as benzenesulphonyloxy, toluenesulphonyloxy or methanesulphonyloxy radical.

It should be understood that the above process is a reaction to introduce a hydrocarbon radical having up to six carbon atoms into the position 5 of the 1-(or 1,3-di)-cyclohexylbarbituric acid and includes the case in which a cycloalkyl radical such as cyclohexyl or cyclopentyl, an alkenyl radical such as propenyl, vinyl, but-2(or 3)-enyl or pent-2(or 3 or 4)-enyl, an alkynyl radical such as but-2-ynyl or a cycloalkenyl radical such as cyclohex-1(or 2 or 3)-enyl or cyclopent-1(or 2 or 3)-enyl is introduced into the 5-position of the barbituric acid derivative.

The reaction is preferably carried out in the presence of a base, for example an alkali metal (e.g. sodium or potassium), an alkali metal alcoholate (e.g. sodium methylate, potassium methylate or sodium ethylate), an alkali metal hydroxide (e.g. sodium hydroxide or potassium hydroxide), an alkaline earth metal oxide (e.g. calcium oxide or magnesium oxide), an alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, sodium hydrogen carbonate or potassium hydrogen carbonate), an alkali metal acylate (e.g. sodium acetate or potassium acetate) or an organic base such as pyridine, quinoline, dimethylaniline or dimethylformamide.

It is preferable that the reaction is carried out in a solvent. Any solvent can be used so long as it does not disturb the reaction, for example, alcohols such as methanol or ethanol, aromatic hydrocarbons such as benzene, toluene or xylene, or ethers such as diethyl ether, dioxane, or tetrahydrofuran. When an organic base is employed to assist the reaction, the base can act as a solvent, and it is not necessary to use any other solvent.

In general, the reaction is carried out by heating under reflux at the boiling point of the solvent used. When an alkylating agent of low boiling point such as methyl iodide or ethyl bromide is used, the reaction preferably is effected in a sealed vessel and is accelerated by heating under pressure. The alkylation usually ends after about 5—8 hours.

The barbituric acid derivatives of the general formula I may be isolated as the free acid form or in the form of salt with for example sodium, potassium, ammonium, calcium or magnesium. Of course, one form is easily convertible to the other. For example, the free acid can be converted into a salt thereof by adding to an alcoholic or aqueous medium containing an approximately equivalent amount of the base, the salt of which is desired and by concentrating the mixture and/or allowing the same to cool on standing. On the contrary, a salt can be changed into the free acid in a manner known *per se*, i.e. by neutralising with an acid such as hydrochloric acid, hydrobromic acid or sulphuric acid or by heating with cation-exchange resins. Commercially available cation-exchange resins which can be used include, for example, Amberlite IR-120 (Rohm & Haas Co., Inc., U.S.A.), Dowex 50 (Dow Chemical Co., Inc., U.S.A.), Permutit Co., Inc., U.S.A.) and Diaion SK #1 (Mitsubishi Chemical Industries, Ltd., Japan). (The words "Amberlite", "Dowex" and "Permutit" are Registered Trade Marks.)

Further examples of compounds according to the invention are given in Table A below:

TABLE A

1-cyclohexyl-5-vinylbarbituric acid;
1-cyclohexyl-5-ethynylbarbituric acid;
1-cyclohexyl-5-(prop-1-enyl)barbituric acid;
1-cyclohexyl-5-isopropylbarbituric acid;
1-cyclohexyl-5-isopropenylbarbituric acid;
1-cyclohexyl-5-(but-1-enyl)barbituric acid;
1-cyclohexyl-5-(but-2-enyl)barbituric acid;
1-cyclohexyl-5-(but-3-enyl)barbituric acid;
1-cyclohexyl-5-(but-2-ynyl)barbituric acid;
1-cyclohexyl-5-(buta-1,3-dienyl)barbituric acid;
1-cyclohexyl-5-(but-1-en-3-ynyl)barbituric acid;
1-cyclohexyl-5-(1-methylprop-1-enyl)barbituric acid;
1-cyclohexyl-5-(1-methylprop-2-enyl)barbituric acid;
1-cyclohexyl-5-*iso*-butylbarbituric acid;
1-cyclohexyl-5-(2-methylprop-1-enyl)barbituric acid;
1-cyclohexyl-5-(2-methylprop-2-enyl)barbituric acid;
1-cyclohexyl-5-*tert*-butylbarbituric acid;

	1-cyclohexyl-5-(pent-1-enyl)barbituric acid;	
	1-cyclohexyl-5-(pent-2-enyl)barbituric acid;	
	1-cyclohexyl-5-(pent-3-enyl)barbituric acid;	
	1-cyclohexyl-5-(pent-4-enyl)barbituric acid;	
5	1-cyclohexyl-5-(1-methylbutyl)barbituric acid;	5
	1-cyclohexyl-5-(2-methylbutyl)barbituric acid;	
	1-cyclohexyl-5-(3-methylbutyl)barbituric acid;	
	1-cyclohexyl-5-(1-ethylpropyl)barbituric acid;	
10	1-cyclohexyl-5-(1,2-dimethylpropyl)barbituric acid;	10
	1-cyclohexyl-5-hexylbarbituric acid;	
	1-cyclohexyl-5-(1-methylpentyl)barbituric acid;	
	1-cyclohexyl-5-(2-methylpentyl)barbituric acid;	
	1-cyclohexyl-5-(3-methylpentyl)barbituric acid;	
15	1-cyclohexyl-5-(4-methylpentyl)barbituric acid;	15
	1-cyclohexyl-5-(1-ethylbutyl)barbituric acid;	
	1-cyclohexyl-5-(2-ethylbutyl)barbituric acid;	
	1-cyclohexyl-5-(1,2-dimethylbutyl)barbituric acid;	
	1-cyclohexyl-5-(1,3-dimethylbutyl)barbituric acid;	
20	1-cyclohexyl-5-(1,1-dimethylbutyl)barbituric acid;	20
	1-cyclohexyl-5-(2,2-dimethylbutyl)barbituric acid;	
	1-cyclohexyl-5-(3,3-dimethylbutyl)barbituric acid;	
	1-cyclohexyl-5-(1-ethyl-2-methylpropyl)barbituric acid;	
	1-cyclohexyl-5-(cyclohex-1-enyl)barbituric acid;	
25	1-cyclohexyl-5-(cyclohex-2-enyl)barbituric acid;	25
	1-cyclohexyl-5-(cyclohex-3-enyl)barbituric acid;	
	1-cyclohexyl-5-(cyclohexa-1,3-dienyl)barbituric acid;	
	1-cyclohexyl-5-(cyclohexa-1,4-dienyl)barbituric acid;	
	1-cyclohexyl-5-(cyclohexa-2,4-dienyl)barbituric acid;	
30	1-cyclohexyl-5-cyclopentylbarbituric acid;	30
	1-cyclohexyl-5-(cyclopent-1-enyl)barbituric acid;	
	1-cyclohexyl-5-(cyclopent-2-enyl)barbituric acid;	
	1-cyclohexyl-5-(cyclopent-3-enyl)barbituric acid;	
	1-cyclohexyl-5-(cyclopenta-1,3-dienyl)barbituric acid;	
35	1-cyclohexyl-5-(cyclopenta-1,4-dienyl)barbituric acid;	35
	1-cyclohexyl-5-(cyclopenta-2,4-dienyl)barbituric acid;	
	1,3-dicyclohexyl-5-vinylbarbituric acid;	
	1,3-dicyclohexyl-5-ethynylbarbituric acid;	
	1,3-dicyclohexyl-5-(prop-1-enyl)barbituric acid;	
40	1,3-dicyclohexyl-5-(prop-1-ynyl)barbituric acid;	40
	1,3-dicyclohexyl-5-isopropenylbarbituric acid;	
	1,3-dicyclohexyl-5-(but-1-enyl)barbituric acid;	
	1,3-dicyclohexyl-5-(but-2-enyl)barbituric acid;	
	1,3-dicyclohexyl-5-(but-3-enyl)barbituric acid;	
	1,3-dicyclohexyl-5-(but-2-ynyl)barbituric acid;	
45	1,3-dicyclohexyl-5-(buta-1,3-dienyl)barbituric acid;	45
	1,3-dicyclohexyl-5-(but-1-en-3-ynyl)barbituric acid;	
	1,3-dicyclohexyl-5-(1-methylprop-1-enyl)barbituric acid;	
	1,3-dicyclohexyl-5-(1-methylprop-2-enyl)barbituric acid;	
	1,3-dicyclohexyl-5-(2-methylprop-1-enyl)barbituric acid;	
50	1,3-dicyclohexyl-5-(2-methylprop-2-enyl)barbituric acid;	50
	1,3-dicyclohexyl-5- <i>tert</i> -butylbarbituric acid;	
	1,3-dicyclohexyl-5-(pent-1-enyl)barbituric acid;	
	1,3-dicyclohexyl-5-(pent-2-enyl)barbituric acid;	
	1,3-dicyclohexyl-5-(pent-3-enyl)barbituric acid;	
55	1,3-dicyclohexyl-5-(pent-4-enyl)barbituric acid;	55
	1,3-dicyclohexyl-5-(1-methylbutyl)barbituric acid;	
	1,3-dicyclohexyl-5-(2-methylbutyl)barbituric acid;	
	1,3-dicyclohexyl-5-(3-methylbutyl)barbituric acid;	
	1,3-dicyclohexyl-5-(1-ethylpropyl)barbituric acid;	
60	1,3-dicyclohexyl-5-(1,2-dimethylpropyl)barbituric acid;	60
	1,3-dicyclohexyl-5-hexylbarbituric acid;	
	1,3-dicyclohexyl-5-(1-methylpentyl)barbituric acid;	
	1,3-dicyclohexyl-5-(2-methylpentyl)barbituric acid;	
	1,3-dicyclohexyl-5-(3-methylpentyl)barbituric acid;	

	1,3-dicyclohexyl-5-(4-methylpentyl)barbituric acid;	
	1,3-dicyclohexyl-5-(1-ethylbutyl)barbituric acid;	
	1,3-dicyclohexyl-5-(2-ethylbutyl)barbituric acid;	
5	1,3-dicyclohexyl-5-(1,2-dimethylbutyl)barbituric acid;	5
	1,3-dicyclohexyl-5-(1,3-dimethylbutyl)barbituric acid;	
	1,3-dicyclohexyl-5-(1,1-dimethylbutyl)barbituric acid;	
	1,3-dicyclohexyl-5-(2,2-dimethylbutyl)barbituric acid;	
	1,3-dicyclohexyl-5-(3,3-dimethylbutyl)barbituric acid;	
10	1,3-dicyclohexyl-5-(1-ethyl-2-methylpropyl)barbituric acid;	10
	1,3-dicyclohexyl-5-(cyclohex-1-enyl)barbituric acid;	
	1,3-dicyclohexyl-5-(cyclohex-2-enyl)barbituric acid;	
	1,3-dicyclohexyl-5-(cyclohex-3-enyl)barbituric acid;	
	1,3-dicyclohexyl-5-(cyclohexa-1,3-dienyl)barbituric acid;	
15	1,3-dicyclohexyl-5-(cyclohexa-1,4-dienyl)barbituric acid;	15
	1,3-dicyclohexyl-5-(cyclohexa-2,4-dienyl)barbituric acid;	
	1,3-dicyclohexyl-5-cyclopentylbarbituric acid;	
	1,3-dicyclohexyl-5-(cyclopent-1-enyl)barbituric acid;	
	1,3-dicyclohexyl-5-(cyclopent-2-enyl)barbituric acid;	
20	1,3-dicyclohexyl-5-(cyclopent-3-enyl)barbituric acid;	20
	1,3-dicyclohexyl-5-(cyclopenta-1,3-dienyl)barbituric acid;	
	1,4-dicyclohexyl-5-(cyclopenta-1,4-dienyl)barbituric acid and	
	1,3-dicyclohexyl-5-(cyclopenta-2,4-dienyl)-barbituric acid	
	as well as their salts with bases especially such bases as to form pharmaceutically acceptable salts, such as the sodium, potassium, calcium or magnesium salts.	
25	The novel barbituric acid derivatives have interesting physiological and physico-chemical properties.	25
	(1) One of the characteristics of the compounds of the general formula I is their low toxicity as is shown in the following experiments.	
30	A tragacanth emulsion of each test compound was administered intraperitoneally or orally to mice (dd-strain) weighing 14 to 15 grams, and LD ₅₀ and 95%-confidence limits were calculated by the Litchfield-Wilcoxon method on the basis of the number of mice that died during 24 hours after the administration. The result shown in Table 1, from which it can be concluded that the compounds of this invention are significantly less toxic than phenylbutazone or aminopyrine.	30

TABLE 1

Test Compound	LD ₅₀ (95%—C.L.) mg/10 g. in mice	
	Intraperitoneally	Orally
1-Cyclohexyl-5-methylbarbituric acid	6.16 (5.40—7.02)	—
1-Cyclohexyl-5-ethylbarbituric acid	2.41 (2.19—2.65)	—
1-Cyclohexyl-5-propylbarbituric acid	3.36 (2.80—4.04)	—
1-Cyclohexyl-5-isopropylbarbituric acid	4.10 (3.45—4.88)	—
1-Cyclohexyl-5-allylbarbituric acid	3.88 (3.53—4.26)	5.60 (3.99—7.90)
1-Cyclohexyl-5-butylbarbituric acid	3.31 (2.88—3.81)	6.80 (5.91—7.82)
1-Cyclohexyl-5-sec-butylbarbituric acid	3.29 (3.02—3.60)	—
1-Cyclohexyl-5-pentylbarbituric acid	3.25 (3.04—3.46)	—
1-Cyclohexyl-5-(1-methylbutyl)barbituric acid	2.90 (2.63—3.19)	—
1,5-Dicyclohexylbarbituric acid	2.90 (2.52—3.34)	18.60 (14.9—23.2)
1-Cyclohexyl-5-phenylbarbituric acid	2.70 (2.37—3.08)	—
1,3-Dicyclohexyl-5-methylbarbituric acid	2.90 (2.44—3.45)	12.5 (10.6—14.8)
1,3-Dicyclohexyl-5-ethylbarbituric acid	10.1 (8.79—11.6)	Ca 70
1,3-Dicyclohexyl-5-propylbarbituric acid	12.5 (11.6—13.5)	—
1,3-Dicyclohexyl-5-isopropylbarbituric acid	12.0 (11.0—13.1)	—
1,3-Dicyclohexyl-5-allylbarbituric acid	4.61 (4.22—5.05)	—
1,3-Dicyclohexyl-5-sec-butylbarbituric acid	16.4 (15.0—18.0)	—
1,3-Dicyclohexyl-5-iso-butylbarbituric acid	8.50 (7.59—9.53)	—
1,3-Dicyclohexyl-5-pentylbarbituric acid	9.75 (8.63—11.0)	—
1,3-Dicyclohexyl-5-phenylbarbituric acid	3.70 (3.42—4.02)	—
1,3,5-Tricyclohexylbarbituric acid	6.8 (5.76—8.03)	70
Phenylbutazone	2.20 (1.94—2.49)	3.90 (3.34—4.57)
Aminopyrine	—	4.38 (4.14—4.64)

LD₅₀ and 95%-confidence limits were further measured on some typical representatives of the novel compounds to show that the toxicity of the same is weaker than that of phenylbutazone or aminopyrine in any cases of oral administration, subcutaneous or intravenous injection as well as intraperitoneal injection.

TABLE 2

Test Compound	LD ₅₀ (95%—C.L.) mg/10 g. in mice		
	Intraperitoneally	Orally	Subcutaneously
1-Cyclohexyl-5-methylbarbituric acid	5.05 (3.66—6.98)	14.3 (12.8—14.1)	—
1-Cyclohexyl-5-allylbarbituric acid	3.88 (3.53—4.26)	5.60 (3.99—7.90)	—
1-Cyclohexyl-5-butylbarbituric acid	3.38 (2.58—4.36)	9.20 (8.35—10.3)	—
Phenylbutazone	2.20 (1.94—2.49)	3.90 (3.34—4.57)	—
Aminopyrine	2.40 (2.26—2.53)	4.38 (4.14—4.64)	3.15 (2.97—3.34)
Intravenously			
Sodium 1-cyclohexyl-5-methylbarbiturate	7.59 (6.97—8.27)	5.41 (4.82—6.05)	—
Sodium 1-cyclohexyl-5-allylbarbiturate	3.71 (3.17—4.34)	3.95 (3.69—4.23)	3.71 (3.47—4.03)
Sodium 1-cyclohexyl-5-butylbarbiturate	4.61 (4.08—5.20)	3.71 (3.44—4.01)	3.80 (3.33—4.33)
Sodium salt of phenylbutazone	2.28 (2.06—2.63)	1.38 (1.29—1.48)	2.57 (2.24—2.96)
Aminopyrine	—	1.53 (1.35—1.76)	—

Another experiment was carried out to investigate the influences of successive administration on animal growth. The compounds, 1-cyclohexyl-5-allylbarbituric acid, 1-cyclohexyl-5-butylbarbituric acid and 1-cyclohexyl-5-methylbarbituric acid as well as phenylbutazone and aminopyrine as controls, were administered intraperitoneally to separate young rats once a day in an amount of 100 milligrams per kilogram for 15 days, during which the body weight of each rat was measured. The growth of the rats to which the compounds of this invention were administered was slightly inhibited in comparison with normal rats to which no test compound was administered, but the degree of the inhibition was not more than that in the case of aminopyrine. On the other hand, the growth of the rats to which phenylbutazone was administered was greatly inhibited and the rats not only could not gain a substantial increase of body weight but also two of five rats used died during the experiment.

(2) It was also found by the present inventors that the compounds of the general formula I have an outstanding anti-inflammatory effect.

100 milligrams per kilogram of test compound was enjected intraperitoneally to male rats (Wister-strain) weighing 130 to 180 grams. 30 minutes after the injection, these rats as well as those for control were injected subcutaneously through a hind paw with 0.05 cc. of 6% aqueous dextran solution or 0.1 c.c. of 10% aqueous egg white solution as substances to provoke inflammatory edema, and the percentages of the maximum inhibition of the edema relative to the control were measured with regard to each test compound. The results is shown in Table 3, from which it is observed that most of the compounds of the present invention show an anti-inflammatory action

superior to phenylbutazone and even those having a poor activity of the compounds of general formula I show an inhibitory action not less than that of phenylbutazone.

TABLE 3

Test Compound	Dextran	Egg White
1-Cyclohexyl-5-methylbarbituric acid	+3	+4
1-Cyclohexyl-5-ethylbarbituric acid	+2	+3
1-Cyclohexyl-5-propylbarbituric acid	+4, +2	+4, +3
1-Cyclohexyl-5- <i>iso</i> -propylbarbituric acid	+2	—
1-Cyclohexyl-5-allylbarbituric acid	+4	+2
1-Cyclohexyl-5-butylbarbituric acid	+3, +3	+4, +3
1-Cyclohexyl-5- <i>sec</i> -butylbarbituric acid	±	+3
1-Cyclohexyl-5-pentylbarbituric acid	+2, +1	+3, +3
1-Cyclohexyl-5-(1-methylbutyl) barbituric acid	+2	+3
1-Cyclohexyl-5-phenylbarbituric acid	+2, +2	+1, +1
1,5-Dicyclohexylbarbituric acid	+2, +2	+3, +3
1,3-Dicyclohexyl-5-methylbarbituric acid	+2, +3	+4, +4
1,3-Dicyclohexyl-5-ethylbarbituric acid	+2	+3
1,3-Dicyclohexyl-5-propylbarbituric acid	+2, +4	+3, +3
1,3-Dicyclohexyl-5- <i>iso</i> -propylbarbituric acid	+2	+2
1,3-Dicyclohexyl-5-allylbarbituric acid	+3, +3	+3, +2
1,3-Dicyclohexyl-5- <i>sec</i> -butylbarbituric acid	+2	+3
1,3-Dicyclohexyl-5- <i>iso</i> -butylbarbituric acid	+2	+3
1,3-Dicyclohexyl-5-pentylbarbituric acid	+2	+3
1,3-Dicyclohexyl-5-phenylbarbituric acid	+1, +2	+2, +2
1,3,5-Tricyclohexylbarbituric acid	+2, +2	+3, +3
Phenylbutazone	+1, +2	+1, +2
Aminopyrine	+1	+3

Remarks: — : Not tested.

± : Inhibition lower than 15%

+1 : 15—25% inhibition.

+2 : 26—50% inhibition.

+3 : 51—65% inhibition.

+4 : Inhibition higher than 65%.

Further examinations were made with some typical representatives of the compounds of the general formula I.

One such examination was carried out to follow changes of the inhibitory effect as the progress of time after the administration.

After 30 minutes from the time when 100 mg/kg each of the test compounds was administered intraperitoneally to rats, 0.1 c.c. of 10% aqueous egg white solution was injected to the rats as well as those rats as a control to which no test compound was administered. The inhibitory activity to inflammatory edema provoked by the injection of egg white is shown in Table 4, from which it is clearly shown that the inhibitory effects of the compounds of the present invention are far superior to that of phenylbutazone.

TABLE 4

Test Compound	Inhibition to swelling (%)					
	0	1	2	3	4	5 (hours)
1-Cyclohexyl-5-methylbarbituric acid	0	60	69	69	70	84
1-Cyclohexyl-5-allylbarbituric acid	0	64	76	80	90	96
1-Cyclohexyl-5-butylbarbituric acid	0	39	58	58	68	71
Aminopyrine	0	33	48	48	54	58
Phenylbutazone	0	4	7	8	21	28
Control	0	-1	-7	-10	-12	-4

A similar experiment was carried out by using 0.05 c.c. of 6% aqueous dextran solution in place of egg white solution in the above mentioned experiment to give the result as shown in Table 5, from which the same conclusion as above is deduced.

A further experiment was carried out, where ovalbumin was used as an irritant and the observation was continued for 20 hours. The result is shown in Table 6, from which it can be seen that the compounds of this invention are not only superior to phenylbutazone in their inhibitory activity to swelling, but also their activity appears immediately after the administration, while that of phenylbutazone does not appear immediately but after some time-lag.

TABLE 5

Test compound	Inhibition to swelling (%)						
	0	0.5	1	2	3	4	5 (hrs)
1-Cyclohexyl-5-allylbarbituric acid	0	74	85	90	93	91	95
1-Cyclohexyl-5-butylbarbituric acid	0	61	64	77	68	72	69
Aminopyrine	0	64	68	61	59	57	57
Phenylbutazone	0	12	16	15	17	22	23
Control	0	-10	-2	-18	-31	-23	-20

TABLE 6

Test compound	Inhibition to swelling (%)							(hours)		
	0	0.5	1	2	3	5	7	10	15	20
1-Cyclohexyl-5-methylbarbituric acid	0	39	53	48	50	48	48	41	42	51
1-Cyclohexyl-5-allylbarbituric acid	0	64	70	72	72	72	71	68	53	69
1-Cyclohexyl-5-butylbarbituric acid	0	32	59	64	70	73	73	71	67	67
Aminopyrine	0	45	47	50	49	40	49	45	45	31
Phenylbutazone	0	-5	20	24	24	24	30	34	38	23
Control	0	-1	-5	-7	-14	-9	-9	-2	-1	-3

The next experiment was directed to examining the anti-inflammatory effect of test compounds on the sustained edema provoked by the injection of mustard powder. Mustard powder was suspended in 1% aqueous tragacanth solution to make 0.5% mustard powder suspension, and 0.1 millilitre of the suspension was injected subcutaneously to hind paw of rats. For 3 days from 24 hours after the injection of mustard powder, 50 milligrams per kilogram each of test compounds (with the exception that the dose of prednisolone was 5 mg/kg and that of dexamethasone was 1 mg/kg) was repeatedly administered intraperitoneally every six hours to the rats. The degree of swelling in per cent are shown in Table 7. In addition to the observation on swelling the body weight of rats was measured and the result is shown in Table 8. From these observations, it is shown that the compounds of the present invention have a strong activity in inhibiting the swelling, and that the anti-inflammatory activity lasts for as long a time as a week or more, while aminopyrine action is not lasting. The compounds of the invention which were tested are superior to aminopyrine in this activity. All rats to which phenylbutazone was administered died within 48 hours after the start of administering the test compound, thus suggesting how phenylbutazone is toxic to animal bodies, especially when it is successively administered. Although the dose (50 mg/kg) of 1-cyclohexyl-5-allylbarbituric acid corresponds to about 1 mg/kg of dexamethasone in view of their activity to inhibiting swelling *per se*, the rats to which dexamethasone was administered induced a significant decrease of their body weight. Thus, the compounds of the present invention are very suitable for the treatment of inflammation compared with the known steroidal and non-steroidal anti-inflammatory agents.

TABLE 7

Test Compound	Swelling (%)							
	0	1	2	3	4	6	8	10 (days)
1-Cyclohexyl-5-methyl-barbituric acid	0	60	24	19	18	31	34	26
1-Cyclohexyl-5-allyl-barbituric acid	0	62	17	8	-2	5	5	15
1-Cyclohexyl-5-butyl-barbituric acid	0	63	26	14	10	20	30	37
Aminopyrine	0	60	21	30	36	40	41	52
Phenylbutazone	0	61	19	. . . all rats died.				
Prednisolone	0	65	31	26	25	44	39	44
Dexamethasone	0	69	28	7	+3	12	16	14
Control	0	63	48	63	42	39	39	41

TABLE 8

Test compound	Body weight (grams)						8 10 (days)
	1	2	3	4	6		
1-Cyclohexyl-5-methyl-barbituric acid	135	136	142	137	143	147	154
1-Cyclohexyl-5-allyl-barbituric acid	140	140	148	139	141	146	153
1-Cyclohexyl-5-butyl-barbituric acid	137	135	134	134	136	145	154
Aminopyrine	138	139	142	138	144	150	155
Phenylbutazone	143	146	. . . all rats died				
Prednisolone	142	141	145	146	147	153	162
Dexamethasone	141	139	134	125	119	110	124
Control	140	142	148	147	149	157	163

Similar experiments with some other irritants such as hyaluronidase or 5-hydroxytryptamine gave the same conclusion as mentioned above.

(3) It is an interesting property of the compounds of the present invention that a synergistic effect is observed between aminopyrine and the compounds of the present invention, as is seen from Table 9. Thus, prior to the injection of irritant, 100 mg/kg of a mixture consisting of a compound of this invention and the same amount of aminopyrine was administered intraperitoneally to rats, and, after 30 minutes, 0.05 c.c. of 6% aqueous dextran solution was injected to hind paw of the rats. The observation was made in the same manner as in the experiment shown in Tables 4 and 5.

TABLE 9

Test compound	Dose (mg/kg)	Inhibition (%)					
		0	1	2	3	4	5 (hours)
{ Aminopyrine 1-Cyclohexyl-5-allyl- barbituric acid	{ 50 50 }	0	52	59	60	61	61
{ Aminopyrine 1-Cyclohexyl-5-butyl- barbituric acid	{ 50 50 }	0	57	78	76	69	73
{ Aminopyrine Phenylbutazone	{ 50 50 }	0	29	28	28	21	12
Aminopyrine	100	0	45	58	56	57	57
Control	0	0	1	7	2	-5	-3

The equal amount of a mixture of aminopyrine and a compound of the invention shows a lower toxicity than that of aminopyrine and phenylbutazone. Each of test compounds including phenylbutazone was mixed with the same amount of aminopyrine, and the mixture was dissolved in water to prepare a 30% aqueous solution of the mixtures. LD₅₀ and 95%-confidence limits were measured to give the result as shown in Table 10.

TABLE 10

Test Compound	LD ₅₀ (95%—C.L.) mg/10 g. in mice	
	Intraperitoneally	Orally
Aminopyrine and 1-cyclohexyl-5-allylbarbituric acid	4.20 (3.75—4.71)	6.05 (5.40—6.78)
Aminopyrine and 1-cyclohexyl-5-butylbarbituric acid	4.26 (4.02—4.52)	7.20 (6.37—8.14)
Aminopyrine and phenylbutazone	3.05 (2.85—3.26)	4.80 (4.53—5.09)
Aminopyrine	—	4.49 (3.93—5.12)
	Subcutaneously	Intravenously
Aminopyrine and sodium 1-cyclohexyl-5-methylbarbiturate	—	3.28 (2.98—3.16)
Aminopyrine and sodium 1-cyclohexyl-5-allylbarbiturate	6.45 (6.20—6.72)	3.92 (3.75—4.18)
Aminopyrine and sodium 1-cyclohexyl-5-butylbarbiturate	6.15 (5.54—6.76)	3.78 (3.40—4.20)
Aminopyrine and sodium salt of phenylbutazone	3.76 (3.26—4.29)	2.24 (2.10—2.39)

The alkali metal salts such as the sodium or potassium salts of the novel compounds are very stable. Aqueous solutions in which the given amount (weight per volume per cent) of the compound or compounds is dissolved show the pHs illustrated at 22°C.

- (1) Sodium 1-cyclohexyl-5-methylbarbiturate (15%) Ph 8.19
- (2) Sodium 1-cyclohexyl-5-allylbarbiturate (15%) pH 8.1
- (3) Sodium 1-cyclohexyl-5-butylbarbiturate (15%) pH 8.0
- (4) Sodium 1-cyclohexyl-5-methylbarbiturate (15%) and
aminopyrine (15%) pH 8.25
- (5) Sodium 1-cyclohexyl-5-allylbarbiturate (15%) and aminopyrine (15%) pH 8.5
- (6) Sodium 1-cyclohexyl-5-butylbarbiturate (15%) and aminopyrine (15%) pH 8.4
- (7) Sodium salt of phenylbutazone (15%) and aminopyrine (15%)
(for control) pH 9.8

The data show that aqueous solutions of the compounds of the present invention are more neutral than that of phenylbutazone even in admixture with aminopyrine. The neutral pH of the aqueous solutions favours a non-irritating injection of the same.

The most interesting property of alkali metal salts of the barbituric acid derivatives is that the salt can act in water as a solubilising agent for aminopyrine, which is well known to be rather insoluble in water. Therefore, an aqueous composition consisting of aminopyrine, a compound of the present invention and pharmaceutically acceptable carrier is very suitable as an injectible composition which is stable and non-irritating as well as very effective owing to the synergy between both therapeutic components.

(4) A synergism in the anti-inflammatory activity was also observed between the compounds of this invention and known steroidal anti-inflammatory agents such as

prednisolone, dexamethasone and triamcinolone. It was also found that the almost threshold dose of the steroidal anti-inflammatory agents is sufficient to exhibit the desirable synergy. From this, it has become possible to lessen the dose of steroidal anti-inflammatory agents. As mentioned above, steroidal anti-inflammatory agents generally have a serious shortcoming that they induce hypofunction of the anterior pituitary gland or atrophy of adrenal cortex and disturb an animal body's hormonal and metabolic balances, although their anti-inflammatory activity is strong. Thus, a pharmaceutical composition consisting of one or more of the novel barbituric acid derivatives of this invention and one or more of steroidal anti-inflammatory agents and any pharmaceutically acceptable carrier is very suitable as an anti-inflammatory composition.

Test compounds were intraperitoneally administered to male rats weighing 130 to 150 grams. After 30 minutes from the administration, 0.05 millilitre of 6% aqueous dextran solution was injected to hind paw of the rats. The result of the measurement is shown in Table 11.

TABLE 11

Test compounds	Dose (mg/kg)	Inhibition (%)						Sum of percentages
		0	1	2	3	4	5 (hrs.)	
Dexamethasone	0.2	0	42	43	43	40	40	208...(a)
1-Cyclohexyl-5-butyl-barbituric acid	50							
Prednisolone	1.0	0	16	31	34	34	31	146...(b)
1-cyclohexyl-5-butyl-barbituric acid	50							
1-Cyclohexyl-5-butyl-barbituric acid	50	0	18	21	29	20	20	108...(c)
Dexamethasone	0.2	0	5	11	13	2	-2	29...(d)
Prednisolone	1.0	0	11	6	-3	-4	-5	5...(e)
Control	—	0	-14	-1	-4	-10	-8	-37

(c) + (d) = 108 + 29 = 137 : less than (a) i.e. 208 by 71.

(c) + (e) = 108 + 5 = 113 : less than (b) i.e. 146 by 33.

The active compounds of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers preferably in unit dosage form or may be administered, as mentioned above, together with aminopyrine or a steroidal anti-inflammatory agent with or without any other pharmaceutically acceptable carriers. The compounds may be administerable as powders, tablets, solutions or emulsions for oral administration or as injections or suppositories for non-oral administration. The choice of the carrier is determined by the preferred route of administration, the solubility of the compound and standard pharmaceutical practice. In general, the dosage of these compounds of the invention is approximately a maximum of 50 milligrams to 1 gram per day for an adult man. Because of their great anti-inflammatory activity and their low toxicity it is sometimes possible to use dosages of these compounds less than 50 milligrams or more than 1-gram. Especially when these compounds are used together with other anti-inflammatory agents as mentioned above, the dosage may be decreased in accordance with the magnitude of the synergistic effect between them.

The following Examples illustrate the invention. In the Examples, the temperatures are all uncorrected. The products of the Examples have been confirmed by means of elementary analyses.

EXAMPLE 1

A mixture of 7.2 g. of allylmalonic acid and 22.9 g. of phosphorus pentachloride was heated on water bath for 1.5 hours before the reaction mixture was allowed to stand to cool. About 50 cc. of chloroform and 11.2 g. of dicyclohexylurea were added to the cooled mixture and the resultant mixture was refluxed for 4 hours. After the reaction, chloroform and phosphoryl chloride were distilled off. The residue was washed with cold water and dissolved in about 200 cc. of 10% aqueous sodium hydroxide solution while stirring, followed by the addition of about 1 litre of water. The diluted solution was treated with active carbon at room temperature and filtered. The filtrate was treated with concentrated hydrochloric acid to make the pH weakly acid, whereupon precipitates separated, were collected by filtration, washed with water and recrystallised from methanol to give 1,3-dicyclohexyl-5-allylbarbituric acid as white prisms melting at 84°C. Yield 5.2g.

EXAMPLE 2.

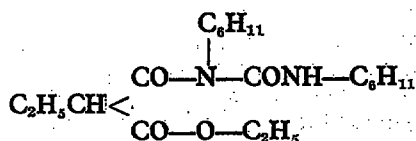
4.6 G of metallic sodium were dissolved in 200 cc. of absolute alcohol and 43 g. of diethyl butylmalonate and 28.4g. of cyclohexylurea were added to the sodium ethylate solution. The mixture was refluxed for 7 hours. After the reaction, ethanol was distilled off and the residue was dissolved in 200 cc. of water. The aqueous solution was treated with active carbon at room temperature and filtered. The filtrate was acidified with hydrochloric acid to give precipitates, which were collected by filtration and recrystallised from methanol to give 1-cyclohexyl-5-butylbarbituric acid as white prisms melting at 84°C. Yield 30g.

EXAMPLE 3.

To an ethanolic sodium ethylate solution, which was prepared by dissolving 1.2 g. of metallic sodium in 60 cc. of absolute ethanol, there were added 8.5 g. of ethyl α -cyanocapronate and 7.1 g. of cyclohexylurea, and the mixture was heated under reflux on water bath for 8 hours. 30% Acetic acid was added to the reaction mixture to adjust the mixture to a weakly acid pH and the solvent was evaporated to leave crude intermediate. 50 ccs. of 30% sulphuric acid were added to the residue and the mixture was heated under reflux for 3 hours and was allowed to stand to separate crystals. The crystals filtered, washed and dissolved in an ethanolic sodium ethylate solution prepared from 1.6 g. of metallic sodium and 60 cc. of ethanol. The solution was concentrated under reduced pressure to remove ethanol to leave a residue. The residue was dissolved in 150 cc. of water and, after the treatment with active charcoal, was filtered to obtain a filtrate which was acidified with hydrochloric acid to give crystals of 1-cyclohexyl-5-butylbarbituric acid. The crystals were recrystallised from methanol to give 6.8 g. of colourless needles melting at 84°C.

EXAMPLE 4.

A mixture of 8.9 g. of ethylmalonic acid chloride ethyl ester, 11.4 g. of 1,3-dicyclohexylurea and 50 cc. of chloroform was heated under reflux on water bath for 4 hours. After the reaction, chloroform was distilled off and the residue was extracted with 300 cc. of hot benzene. The residue comprised the compound



The benzene extract was washed with 5% aqueous sodium hydrogen carbonate solution and with water, and dried over anhydrous potassium carbonate. The benzene solution was concentrated to dryness and an ethanolic sodium ethylate solution prepared from 1.2 g. of metallic sodium and 60 cc. of absolute ethanol was added to the residue. The mixture was heated under reflux for 8 hours to cause ring closure (i.e. reaction D). After the reaction, the ethanol was distilled off and the residue was dissolved in 150 cc. of water. The aqueous solution was treated with active carbon at room temperature and acidified with hydrochloric acid to give crystals, which were filtered and recrystallised from methanol to obtain 2.1 g. of 1,3-dicyclohexyl-5-ethylbarbituric acid as white needles melting at 107°C.

EXAMPLE 5

Hydrogen was introduced into a solution of 5.9 g. of 1,3-dicyclohexyl-barbituric acid, 1.3 g. of acrolein and a few drops of pyridine in 100 cc. of glacial acetic acid in



white



ethylmalonic

the presence of 10% palladium-carbon while shaking. The theoretical amount of hydrogen was consumed in about 2 hours. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was washed with water and recrystallised from methanol to give 1,3-dicyclohexyl-5-allylbarbituric acid as white prisms melting at 84°C. Yield 3.0 g.

EXAMPLE 6

In 100 cc. of glacial acetic acid there were dissolved 4.2 g. of 1-cyclohexylbarbituric acid and 1.6 g. of butyl aldehyde and the solution was reacted in the same way as in Example 5, in the presence of Raney nickel to obtain 1-cyclohexyl-5-butylbarbituric acid as white needles melting at 84°C. Yield 2.5 g.

EXAMPLE 7

After a mixture of 5.8 g. of 1,3-dicyclohexylbarbituric acid and 1.3 g. of acrolein was allowed to stand for 2 hours at room temperature, a mixture of 100 cc. of concentrated hydrochloric acid and 100 cc. of acetone was added to the mixture, followed by the addition of about 30 g. of stannous chloride. The whole mixture was heated for 3 hours and the acetone was distilled off. The residue was diluted with water and the aqueous solution was adjusted to a weakly acid pH with aqueous sodium hydroxide solution while cooling and stirring. The thus adjusted solution was extracted with chloroform. The chloroform extract was washed with water and the chloroform was distilled off. The residue was recrystallised from methanol to obtain 2.8 g. of 1,3-dicyclohexyl-5-allylbarbituric acid as white prisms melting at 84°C.

EXAMPLE 8

15.7 g. of 1-cyclohexylbarbituric acid was dissolved in a mixture of 60 cc. of water and 60 cc. of ethanol while warming. To the solution were added 10.2 g. of sodium acetate and a mixture of 10.7 g. of butyl bromide, 38 cc. of water and 90 cc. of ethanol, and the resulting mixture was refluxed on water bath for 8 hours. After the reaction, the reaction mixture was concentrated under reduced pressure. The residue was washed with water and extracted with hot ligroin. The ligroin extract was allowed to stand for cooling and filtered. The filtrate was concentrated and the residue was distilled under reduced pressure to give 4.1 g. of pale yellow viscous liquid boiling at 180—185°C/0.5 mm Hg. The viscous substance was recrystallised twice from petroleum ether to obtain 1-cyclohexyl-5-butylbarbituric acid as colourless grains melting at 84°C. Yield 3.1 g.

This product was dissolved under warming in a sodium ethylate solution prepared by dissolving the calculated amount of metallic sodium in ethanol in as small an amount as possible. Acetone was added to the resulting solution in a quantity about 5 times as much as the solution, and the mixture was allowed to stand to separate the sodium salt of the product as fine prisms melting at a temperature higher than 235°C.

The sodium salt of the product was dissolved in water and an aqueous calcium chloride solution was added to the sodium salt solution to separate the calcium salt of the product as fine crystals which did not melt even at 300°C.

EXAMPLE 9

1.2 G. of sodium was dissolved in 100 cc. of butanol and then 10.5 g. of 1-cyclohexylbarbituric acid were added. The mixture was warmed to dissolve the starting material, and to the solution was added 6.1 g. of allyl bromide. The mixture was refluxed for 5 hours. After the reaction, butanol was distilled off, and the residue was washed with water and dissolved in hot ligroin. The ligroin solution was allowed to stand, filtered and concentrated. The residue was distilled *in vacuo* to give 3.2 g. of pale yellow viscous liquid boiling at 190—195°C/0.5 mm Hg. The viscous liquid was dissolved in petroleum ether and the solution was allowed to stand to give 1-cyclohexyl-5-allylbarbituric acid as colourless prisms melting at 98°C. Yield 1.5 g.

This product was dissolved, while warming, in a sodium ethylate solution prepared from the calculated amount of metallic sodium and as small an amount of ethanol as possible. Acetone was added to the resulting solution in a quantity about 5 times as much as the solution, and the mixture was allowed to stand to separate the sodium salt of the product as fine crystals melting at a temperature higher than 244°C.

EXAMPLE 10

To a solution of 1.6 g. of 1,3-dicyclohexylbarbituric acid in a mixture of 200 cc. of methanol and 10 cc. of water, there were added 2.5 g. of finely pulverised calcium oxide and 5 g. of dimethyl sulphate, and the resultant mixture was refluxed in water

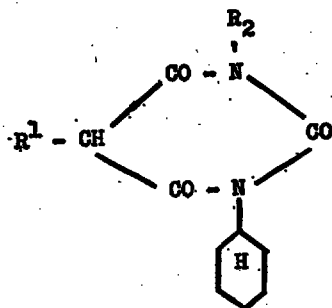
bath for 8 hours. After the reaction, methanol was distilled off, and the residue was treated with diluted hydrochloric acid and extracted with hot ligroin. The ligroin extract was treated with active carbon, concentrated to some extent and allowed to stand to separate crystals, which were recrystallised from ligroin and methanol to give 1,3-dicyclohexyl-5-methylbarbituric acid as colourless prisms melting at 99.5°C. Yield 2.2 g.

EXAMPLE 11

11.6 G. of 1,3-dicyclohexylbarbituric acid was dissolved in a solution of 2 g. of sodium hydroxide in 100 cc. of water. A mixture of 5 g. of allyl bromide and 20 cc. of methanol was gradually dropped into the solution. After reaction for 3 hours at room temperature, the reaction mixture was heated at about 60°C. for an additional 3 hours, and was extracted with chloroform. The chloroform extract was washed with water, concentrated under reduced pressure to leave a residue, which was repeatedly recrystallised from methanol to give 1,3-dicyclohexyl-5-allylbarbituric acid as colourless prisms melting at 84°C. Yield 1.9 g.

EXAMPLE 12

The same procedure as in the preceding Examples were repeated to obtain the compounds listed below, which are all novel and useful and fall within the scope of the general formula I.



R ¹	R ²	Crystal form when recrystallised from methanol	Melting Point (°C.) Unless otherwise noted	The methods by which the compound was produced
CH ₃	H	Needles	121 (The sodium salt melts above 223°C.)	A, B, H
CH ₃ -CH ₂ -	H	Prisms	115	A, B, H
CH ₃ -(CH ₂) ₂ -	H	Needles	103	A, B
CN ₂ =CH-CH ₂ -	H	Prisms	98 Boiling point 190—195°C./0.5 mm Hg.	B
CH ₃ -CH(CH ₃)-	H	"	108	A, B
CH ₃ -(CH ₂) ₃ -	H	Needles	84 Boiling Point 185—187°C./0.8 mm. Hg.	C
CH ₃ -CH ₂ -CH(CH ₃)-	H	"	106	A, B
CH ₃ -(CH ₂) ₄ -	H	"	96	A, B
CH ₃ -(CH ₂) ₃ -CH(CH ₃)-	H	Leaflets	81	A, C
Cyclohexyl	H	Needles	160—161	A, C
Phenyl	H	"	167	A, C

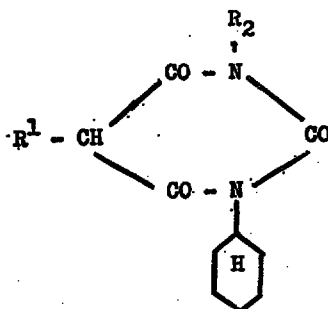
CH₂

R ¹	R ²	Crystal form when recrystallised from methanol	Melting Point (°C.) Unless otherwise noted	The methods by which the compound was produced
CH ₃ —	Cyclohexyl	Needles	99.5	A, B
CH ₃ —CH ₂ —	"	"	107	A, B, G
CH ₃ —(CH ₂)—	"	"	57	A, B, D, G
CH ₂ =CH—CH ₂ —	"	Prisms	84	A
CH ₃ —CH(CH ₃)—	"	"	108	A, B, G
CH ₃ —CH(CH ₃)—CH ₂ —	"	"	90	A, C
CH ₃ —CH ₂ —CH(CH ₃)—	"	Needles	89	A, G
CH ₃ —(CH ₂) ₄ —	"	Prisms	63	A
			Boiling Point, 180°C./1 mm. Hg.	
CH ₃ —(CH ₂) ₃ —CH(CH ₃)—	"	—	Boiling point 195°C./0.4 mm. Hg.	A
Cyclohexyl	"	Prisms	153	A, C, G
Phenyl	"	Plates	167	A, C



WHAT WE CLAIM IS:—

1. Compounds of the general formula:



- | | | |
|----|---|----|
| 5 | and pharmaceutically acceptable salts, preferably alkali metal and alkaline earth metal salts thereof, in which formula R ¹ is a hydrocarbon radical containing from one to six carbon atoms and R ² is a hydrogen atom or a cyclohexyl group with the proviso that when R ² is a cyclohexyl group R ¹ is not an <i>n</i> -butyl group. | 5 |
| 10 | 2. The compounds listed in Table A herein and pharmaceutically acceptable salts, preferably alkali metal or alkaline earth metal salts, of said compounds. | 10 |
| 15 | 3. 1-Cyclohexyl-5-methylbarbituric acid and pharmaceutically acceptable salts thereof. | 15 |
| 20 | 4. 1-Cyclohexyl-5-ethylbarbituric acid and pharmaceutically acceptable salts thereof. | 20 |
| 25 | 5. 1-Cyclohexyl-5-propylbarbituric acid and pharmaceutically acceptable salts thereof. | 25 |
| 30 | 6. 1-Cyclohexyl-5-allylbarbituric acid and pharmaceutically acceptable salts thereof. | 30 |
| 35 | 7. 1-Cyclohexyl-5-butylbarbituric acid and pharmaceutically acceptable salts thereof. | 35 |
| 40 | 8. 1-Cyclohexyl-5- <i>sec</i> -butylbarbituric acid and pharmaceutically acceptable salts thereof. | 40 |
| 45 | 9. 1-Cyclohexyl-5-pentylbarbituric acid and pharmaceutically acceptable salts thereof. | 45 |
| | 10. 1-Cyclohexyl-5- <i>sec</i> -pentylbarbituric acid and pharmaceutically acceptable salts thereof. | |
| | 11. 1,5-Dicyclohexylbarbituric acid and pharmaceutically acceptable salts thereof. | |
| | 12. 1-Cyclohexyl-5-phenylbarbituric acid and pharmaceutically acceptable salts thereof. | |
| | 13. 1,3-Dicyclohexyl-5-methylbarbituric acid and pharmaceutically acceptable salts thereof. | |
| | 14. 1,3-Dicyclohexyl-5-ethylbarbituric acid and pharmaceutically acceptable salts thereof. | |
| | 15. 1,3-Dicyclohexyl-5-propylbarbituric acid and pharmaceutically acceptable salts thereof. | |
| | 16. 1,3-Dicyclohexyl-5-allylbarbituric acid and pharmaceutically acceptable salts thereof. | |
| | 17. 1,3-Dicyclohexyl-5- <i>isopropyl</i> barbituric acid and pharmaceutically acceptable salts thereof. | |
| | 18. 1,3-Dicyclohexyl-5- <i>iso</i> -butylbarbituric acid and pharmaceutically acceptable salts thereof. | |
| | 19. 1,3-Dicyclohexyl-5- <i>sec</i> -butylbarbituric acid and pharmaceutically acceptable salts thereof. | |
| | 20. 1,3-Dicyclohexyl-5-pentylbarbituric acid and pharmaceutically acceptable salts thereof. | |
| | 21. 1,3-Dicyclohexyl-5- <i>sec</i> -pentylbarbituric acid and pharmaceutically acceptable salts thereof. | |
| | 22. 1,3,5-Tricyclohexylbarbituric acid and pharmaceutically acceptable salts thereof. | |



23. 1,3-Dicyclohexyl-5-phenylbarbituric acid and pharmaceutically acceptable salts thereof.

24. A pharmaceutical composition which comprises a therapeutically effective amount of at least one compound as claimed in any of claims 1 to 23 and an inert carrier.

25. An anti-inflammatory composition, which comprises aminopyrine, at least one compound as claimed in any of claims 1 to 23 and an inert carrier.

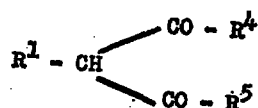
26. An anti-inflammatory composition, which comprises a steroidal anti-inflammatory agent, at least one compound as claimed in any of claims 1 to 23 and an inert carrier.

27. An anti-inflammatory composition as claimed in claim 26 wherein the steroidal anti-inflammatory agent is prednisolone, dexamethasone or triamcinolone.

28. An injectible anti-inflammatory composition, which comprises aminopyrine and a sterile solution of at least one alkali metal salt of a compound as claimed in any of claims 1 to 23.

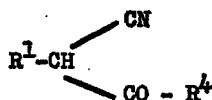
29. An anti-inflammatory composition as claimed in any of claims 25, 26 and 27, wherein the composition is in unit dosage form.

30. A process for the production of the compounds claimed in claim 1, which comprises reacting cyclohexylurea or 1,3-dicyclohexylurea with a malonic acid derivative of the general formula



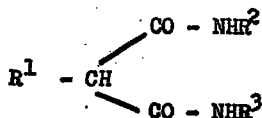
in which R^1 is a hydrocarbon radical containing from one to six carbon atoms with the proviso that, when 1,3-dicyclohexyl urea is used, R^1 is not an *n*-butyl group and R^4 and R^5 are each a hydroxyl, an alkoxy, an aryloxy or an aralkyloxy radical or a halogen atom.

31. A process for the production of the compounds claimed in claim 1, which comprises reacting cyclohexylurea or 1,3-dicyclohexyl-urea with a cyanoacetic acid derivative of the general formula:



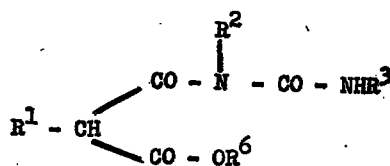
in which R^1 is a hydrocarbon radical containing from 1 to 6 carbon atoms with the proviso that, when 1,3-dicyclohexyl urea is used R^1 is not an *n*-butyl group and R^4 is a hydroxyl, alkoxy, aralkoxy or aryloxy radical or a halogen atom, and hydrolysing the product obtained.

32. A process for the production of the compounds claimed in claim 1, which comprises reacting a compound of the general formula



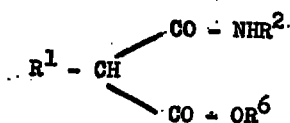
in which R^1 and R^2 have the meaning given in claim 1 and R^3 is a hydrogen atom or a cyclohexyl radical with the proviso that R^2 and R^3 cannot both be hydrogen atoms, with a carbonic acid derivative of the general formula $\text{X}^1 - \text{CO} - \text{X}^2$ in which X^1 and X^2 each is a halogen atom or an alkoxy radical having 1 to 4 carbon atoms.

33. A process for the production of the compounds claimed in claim 1, which comprises intramolecularly condensing, in the presence of an alkaline agent, a compound of the general formula:



in which R¹, R² and R³ have the meaning given in claim 32 and R⁶ is a hydrocarbon radical.

34. A process for the production of the compounds claimed in claim 1, which comprises reacting a compound of the general formula:

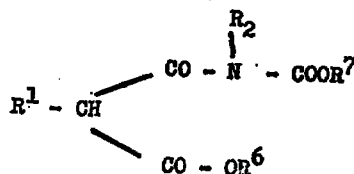


with a carbamate derivative of the general formula,



in which R¹, R², R³ and R⁶ have the meaning given in claim 33 and R⁷ is a hydrocarbon radical.

35. A process for the production of the compounds claimed in claim 1, which comprises reacting ammonia or cyclohexylamine with a compound of the general formula



in which R¹ and R² have the meaning given in claim 1, and R⁶ and R⁷ each is a hydrocarbon radical.

36. A process for the production of the compounds claimed in claim 1, which comprises the steps of (i) reacting an aldehyde or ketone, said aldehyde or ketone containing up to six carbon atoms with either 1-cyclohexylbarbituric acid or 1,3-dicyclohexylbarbituric acid, with the proviso that, when 1,3-dicyclohexyl barbituric acid is used, the aldehyde or ketone does not contain an *n*-butyl group and (ii) reducing the product obtained.

37. A process for the production of the compounds claimed in claim 1, which comprises reacting 1-cyclohexylbarbituric acid or 1,3-dicyclohexylbarbituric acid with a compound of the general formula



where R¹ is a hydrocarbon radical containing 1 to 6 carbon atoms with the proviso that, when 1,3-dicyclobarbituric acid is used, R¹ is not an *n*-butyl group, and Q is a sulphate radical.

38. A process for the production of the compounds claimed in claim 1, which comprises reacting 1-cyclohexylbarbituric acid or 1,3-dicyclohexylbarbituric acid with a compound of the general formula





in which R^1 has the meaning given in claim 37 and Q^1 is a halogen atom or a sulphonyloxy radical.

39. A process as claimed in any of claims 30, 31 or 34, wherein the reaction is carried out in the presence of an alkaline condensation catalyst.

40. A process as claimed in any of claims 30, 31, 34, 37 or 38, wherein the reaction is carried out in the presence of an alkali metal alcoholate.

41. A process for the production of the compounds claimed in claim 1, substantially as described with reference to any of the Examples.

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