

PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Novel Thiobarbituric Acid Derivatives and a process for the manufacture thereof

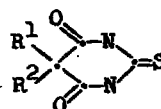
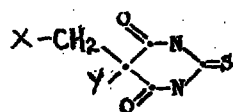
We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company, of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel thiobarbituric acid derivatives and a process for the manufacture thereof.

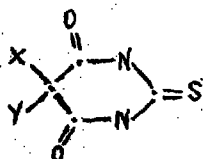
British Patent Specification No. 797,017 describes *inter alia* compounds of the formula

manufacture of same. According to the specification, these compounds have known therapeutically useful properties, some being hypnotics, sedatives and anaesthetics.

It has now been found in accordance with the present invention that compounds of the general formula



wherein X represents a tertiary alkyl group and Y represents an alkyl or alkenyl group, and salts thereof and a process for the preparation of same. According to the specification, these compounds are valuable as sedatives, hypnotics, soporifics and antiepileptics British Patent Specification No. 825,832 describes *inter alia* compounds of the formula



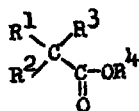
wherein X represents an alkyl group and Y represents an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, and alkali-metal and alkaline-earth-metal salts thereof and a process for the

wherein R¹ represents an alkyl radical containing from eleven to eighteen carbon atoms and R² represents an alkyl, alkenyl, alkynyl or halo-alkenyl group containing up to six carbon atoms or a cyclohexyl or cyclohexenyl group, and alkali-metal and alkaline-earth-metal salts thereof, none of which have been specifically disclosed in the prior specifications given earlier although in part falling within the general formulae given therein, are characterised in having valuable therapeutic and prophylactic properties against virus infections (against influenza viruses for example) while being unsuited for therapy normally associated with the administration of barbiturates.

The radicals, pentadecyl, myristyl, tridecyl and lauryl are preferred as values for R¹ in the foregoing formula. As to R², the radicals methyl, ethyl, propyl, isopropyl, butyl, isobutyl, hexyl, vinyl, allyl, β-methyl-allyl, γ,γ-dimethyl-allyl, propenyl, propargyl, β-bromo-allyl, cyclohexyl, cyclohexenyl (2) - yl are examples — allyl being preferred.

According to the process provided by the invention, the said derivatives are manufactured by condensing an ester of the general formula

[Price 4s. 6d.]



When using an ester starting material in which R^3 represents a cyano radical, it is necessary to transform the resulting 4-imino-thiobarbituric acid into the corresponding thiobarbituric acid by hydrolysis; for example, with a mineral acid such as hydrochloric acid (preferably in an amount equivalent to the 4-imino-thiobarbituric acid). The hydrolysis may be accomplished by heating the 4-imino-thiobarbituric acid with an equivalent amount of

The following examples are illustrative of the process of the invention:

16.3 g of sodium were dissolved in 162 ml of absolute methanol. To this solution were added 23.2 g of thiourea while stirring. After complete dissolution 80 g of allyl myristyl malonic acid diethyl ester were added. The reaction mixture was stirred at a bath temperature of 60°C until a sample was clearly soluble in water, which was the case after about 1 hour. The mixture was poured on to ice and acetic acid was added to a pH-value of 5. The thiobarbituric acid was extracted with ether, the ethereal layer was separated, washed with sodium bicarbonate solution and saturated sodium chloride solution, dried and concen-

trated. A viscous oily residue remained which was dissolved in petroleum ether (b.p. 60°—90°C) whilst heating. After filtration and cooling of the solution 5-allyl-5-myristyl-2-thiobarbituric acid of m.p. 78°—79°C crystallized out.

- By the same procedure as described above the following compounds can be prepared:
- 5-allyl - 5 - undecyl - 2 - thiobarbituric acid; m.p. 84°—86°C;
 - 5-allyl - 5 - lauryl - 2 - thiobarbituric acid; m.p. 68°—69°C;
 - 5-allyl - 5 - tridecyl - 2 - thiobarbituric acid; m.p. 68°—70°C;
 - 5-allyl - 5 - pentadecyl - 2 - thiobarbituric acid; m.p. 74°—75°C;
 - 5-allyl - 5 - cetyl - 2 - thiobarbituric acid; m.p. 69°—71°C;
 - 5-methyl - 5 - myristyl - 2 - thiobarbituric acid; m.p. 100°—104°C;
 - 5-butyl - 5 - myristyl - 2 - thiobarbituric acid; m.p. 41°—43°C;
 - 5-propyl - 5 - myristyl - 2 - thiobarbituric acid; m.p. 69°—71°C;
 - 5-iso-butyl - 5 - myristyl - 2 - thiobarbituric acid; m.p. 75°—77°C;
 - 5-(β -methyl - allyl) - 5-myristyl - 2 - thiobarbituric acid; m.p. 83°—85°C;
 - 5-propargyl - 5 - myristyl - 2 - thiobarbituric acid; m.p. 103°—105°C;
 - 5-cyclohexyl - 5 - myristyl - 2 - thiobarbituric acid; m.p. 58°—60°C;
 - 5-(β -bromo - allyl) - 5-myristyl - 2 - thiobarbituric acid; m.p. 90°—91°C;
 - 5-[cyclohexen - (2) - yl] - 5-myristyl - 2-thiobarbituric acid; m.p. 61°—64°C.

- The following disubstituted malonic acid diethyl esters were used as starting materials:
- allyl-myristyl-malonic acid diethyl ester; b.p. 170°C/0.025 mm;
 - allyl - undecyl - malonic acid diethyl ester; b.p. 170°C/0.15 mm;
 - allyl-lauryl-malonic acid diethyl ester; b.p. 157°C/0.15 mm;
 - allyl-tridecyl-malonic acid diethyl ester; b.p. 170°C/0.02 mm;
 - allyl-pentadecyl-malonic acid diethyl ester; b.p. 175°C/0.07 mm;
 - allyl-cetyl-malonic acid diethyl ester; b.p. 190°C/0.2 mm;
 - methyl-myristyl-malonic acid diethyl ester; b.p. 177°C/0.3 mm;
 - butyl-myristyl-malonic acid diethyl ester; b.p. 174°C/0.1 mm;
 - propyl-myristyl-malonic acid diethyl ester; b.p. 155°C/0.07 mm;
 - isobutyl-myristyl-malonic acid diethyl ester; b.p. 153°C/0.02 mm;
 - (β -methyl - allyl)-myristyl-malonic acid diethyl ester; b.p. 170°C/0.02 mm;
 - propargyl - myristyl - malonic acid diethyl ester; b.p. 186°C/0.25 mm;
 - cyclohexyl-myristyl - malonic acid diethyl ester; b.p. 200°C/0.4 mm;
 - (β -bromo - allyl) - myristyl-malonic acid diethyl ester; b.p. 190°C/0.07 mm;
 - [cyclohexen - (2) - yl] - myristyl-malonic acid diethyl ester; b.p. 195°C/0.04 mm.

EXAMPLE 2

- 4.6 g of sodium were dissolved in 100 ml of absolute ethanol. To this solution were added 8.4 g of thiourea at a temperature of 40°C, while stirring until the solution was complete. Thereafter 32.1 g of α -allyl- α -cyano-myristic acid ethyl ester (b.p. = 157°C/0.1 mm) were added. The stirring was continued over a period of 24 hours at a temperature of 60°—

80°C. After that time the mixture was poured on to ice, acidified with acetic acid and extracted with ether. The ethereal solution was washed with water, dried over sodium sulphate and concentrated. The residue was recrystallized from ethanol and represents 5-allyl-5-lauryl - 2 - thio - 4 - imino - barbituric acid of melting point 228°—230°C (decomposition).

2.35 g of 5 - allyl - 5 - lauryl - 2 - thio-4-imino-barbituric acid were heated under reflux during 48 hours in a mixture of 6.4 ml of water and 7.0 ml of 1-N hydrochloric acid. After cooling ether was added, the ethereal layer washed neutral with sodium bicarbonate solution, dried and concentrated. The residue was crystallized from petroleum ether (b.p. 60°—90°C). There was obtained in practically theoretical yield 5 - allyl - 5 - lauryl - 2 - thiobarbituric acid of melting point 68°—69°C. It is identical with the product prepared according to Example 1.

EXAMPLE 3

50 g of 5 - allyl - 5 - myristyl - 2 - thiobarbituric acid, 10 g of fumed silicon dioxide, 13.9 g of corn starch, 1 g of talc and 0.1 g of magnesium stearate were thoroughly mixed and the mass obtained was pressed to tablets of 750 mg.

EXAMPLE 4

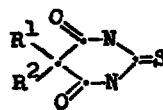
50 g of 5-allyl-5-pentadecyl-2-thiobarbituric acid, 10 g of fumed silicon dioxide, 13.9 g of corn starch, 1 g of talc and 0.1 g of magnesium stearate were thoroughly mixed and the mass obtained was pressed to tablets of 750 mg.

EXAMPLE 5

50 g of 5 - propyl - 5 - myristyl - 2 - thiobarbituric acid, 10 g of fumed silicon dioxide, 13.9 g of corn starch, 1 g of talc and 0.1 g of magnesium stearate were thoroughly mixed and the mass obtained was pressed to tablets of 750 mg.

WHAT WE CLAIM IS:—

- 1) Compounds of the general formula



wherein R¹ represents an alkyl radical containing from eleven to eighteen carbon atoms and R² represents an alkyl, alkenyl, alkynyl or halo-alkenyl group containing up to six carbon atoms or a cyclohexyl or cyclohexenyl group, and alkali-metal and alkaline-earth-metal salts thereof.

- 2) The sodium and calcium salts of the compounds formulated in claim 1.



trated. A viscous oily residue remained which was dissolved in petroleum ether (b.p. 60°—90°C) whilst heating. After filtration and cooling of the solution 5-allyl-5-myristyl-2-thio-barbituric acid of m.p. 78°—79°C crystallized out.

By the same procedure as described above the following compounds can be prepared: 5-allyl - 5 - undecyl - 2 - thiobarbituric acid; m.p. 84°—86°C; 5 - allyl - 5 - lauryl - 2 - thiobarbituric acid; m.p. 68°—69°C; 5 - allyl - 5 - tridecyl - 2 - thiobarbituric acid; m.p. 68°—70°C; 5 - allyl - 5 - pentadecyl - 2 - thiobarbituric acid; m.p. 74°—75°C; 5-allyl - 5 - cetyl - 2 - thiobarbituric acid; m.p. 69°—71°C; 5 - methyl - 5 - myristyl - 2 - thiobarbituric acid; m.p. 100°—104°C; 5-butyl - 5 - myristyl - 2 - thiobarbituric acid; m.p. 41°—43°C; 5 - propyl - 5 - myristyl - 2 - thiobarbituric acid; m.p. 69°—71°C; 5-*iso*-butyl - 5 - myristyl - 2 - thiobarbituric acid; m.p. 75°—77°C; 5 - (β - methyl - allyl) - 5 - myristyl - 2 - thiobarbituric acid; m.p. 83°—85°C; 5 - propargyl - 5 - myristyl - 2 - thiobarbituric acid; m.p. 103°—105°C; 5-*cyclo*-hexyl - 5 - myristyl - 2 - thiobarbituric acid; m.p. 58°—60°C; 5 - (β - bromo - allyl) - 5 - myristyl - 2 - thiobarbituric acid; m.p. 90°—91°C; 5 - [*cyclo*hexen - (2) - yl] - 5-myristyl - 2-thiobarbituric acid; m.p. 61°—64°C.

The following disubstituted malonic acid diethyl esters were used as starting materials: allyl-myristyl-malonic acid diethyl ester; b.p. 170°C/0.025 mm; allyl - undecyl - malonic acid diethyl ester; b.p. 170°C/0.15 mm; allyl-lauryl-malonic acid diethyl ester; b.p. 157°C/0.15 mm; allyl-tridecyl-malonic acid diethyl ester; b.p. 170°C/0.02 mm; allyl-pentadecyl-malonic acid diethyl ester; b.p. 175°C/0.07 mm; allyl-cetyl-malonic acid diethyl ester; b.p. 190°C/0.2 mm; methyl-myristyl-malonic acid diethyl ester; b.p. 177°C/0.3 mm; butyl-myristyl-malonic acid diethyl ester; b.p. 174°C/0.1 mm; propyl-myristyl-malonic acid diethyl ester; b.p. 155°C/0.07 mm; isobutyl-myristyl-malonic acid diethyl ester; b.p. 153°C/0.02 mm; (β - methyl - allyl)-myristyl-malonic acid diethyl ester; b.p. 170°C/0.02 mm; propargyl - myristyl - malonic acid diethyl ester; b.p. 186°C/0.25 mm; cyclohexyl-myristyl - malonic acid diethyl ester; b.p. 200°C/0.4 mm; (β - bromo - allyl) - myristyl-malonic acid diethyl ester; b.p. 190°C/0.07 mm; [cyclohexen - (2) - yl] - myristyl-malonic acid diethyl ester; b.p. 195°C/0.04 mm.

EXAMPLE 2

60 4.6 g of sodium were dissolved in 100 ml of absolute ethanol. To this solution were added 8.4 g of thiourea at a temperature of 40° C, while stirring until the solution was complete. Thereafter 32.1 g of α -allyl- α -cyano-*myristic acid ethyl ester* (b.p. = 157°C/0.1mm) were added. The stirring was continued over a period of 24 hours at a temperature of 60°—

80°C. After that time the mixture was poured on to ice, acidified with acetic acid and extracted with ether. The ethereal solution was washed with water, dried over sodium sulphate and concentrated. The residue was recrystallized from ethanol and represents 5-allyl-5-lauryl - 2 - thio - 4 - imino - barbituric acid of melting point 228°—230°C (decomposition).

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EXAMPLE 4

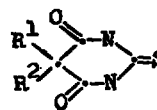
50 g of 5-allyl-5-pentadecyl-2-thiobarbituric acid, 10 g of fumed silicon dioxide, 13.9 g of corn starch, 1 g of talc and 0.1 g of magnesium stearate were thoroughly mixed and the mass obtained was pressed to tablets of 750 mg.

EXAMPLE 5

50 g of 5 - propyl - 5 - myristyl - 2 - thio-
barbituric acid, 10 g of fumed silicon dioxide,
13.9 g of corn starch, 1 g of talc and 0.1 g
of magnesium stearate were thoroughly mixed
and the mass obtained was pressed to tablets
of 750 mg.

WHAT WE CLAIM IS:—

1) Compounds of the general formula



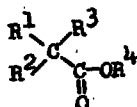
wherein R¹ represents an alkyl radical containing from eleven to eighteen carbon atoms and R² represents an alkyl, alkenyl, alkynyl or halo-alkenyl group containing up to six carbon atoms or a cyclohexyl or cyclohexenyl group, and alkali-metal and alkaline-earth-metal salts thereof.

2) The sodium and calcium salts of the compounds formulated in claim 1.



- 3) 5 - Allyl - 5 - pentadecyl - 2 - thio-
barbituric acid.
4) 5-Allyl-5-myristyl-2-thiobarbituric acid.
5) 5-Allyl-5-tridecyl-2-thiobarbituric acid.
5 6) 5-Allyl-5-lauryl-2-thiobarbituric acid.
7) 5 - Propyl - 5 - myristyl - 2 - thio-
barbituric acid.

- 8) A process for the manufacture of the
derivatives claimed in claim 1 hereof, which
10 process comprises condensing an ester of the
general formula



- wherein R^3 represents a cyano or carbalkoxy
radical, R^4 represents an alkyl group contain-
15 ing up to six carbon atoms and R^1 and R^2 have
the significance given in claim 1, with thio-
urea and, where the radical R^3 in said ester
represents a cyano group, hydrolyzing the
resulting 4 - imino - thio - barbituric acid and,
20 if desired, converting the condensation or
hydrolysis product into an alkali-metal or
alkaline-earth-metal salt.

- 9) A process in accordance with claim 8,
wherein the condensation product or hydrolysis

product as the case may be is converted into 25
an alkali-metal salt by treatment with an
alkali-metal alkoxide or hydroxide in a suit-
able alcohol, or into a calcium salt by effecting
said treatment using sodium hydroxide or
alkoxide and then treatment with calcium 30
chloride.

- 10) A process in accordance with claim 8 or
claim 9, wherein a starting material in which
 R^2 is allyl is used.

- 11) A process in accordance with claim 8, 35
claim 9 or claim 10, wherein an allyl-penta-
decyl-malonic acid dialkyl ester, allyl-myristyl-
malonic acid dialkyl ester, allyl-tridecyl-
malonic acid dialkyl ester or allyl-lauryl-
malonic acid dialkyl ester is used as the start- 40
ing material.

12. A process in accordance with claim 8 or
claim 9, wherein a propyl-myristyl-malonic
acid dialkyl ester is used as the starting 45
material.

- 13) A process for the manufacture of the
derivatives claimed in claim 1 hereof, sub-
stantially as described with reference to the
Examples 1 and 2.

- 14) An antiviral preparation comprising a 50
derivative as claimed in claim 1 hereof and a
compatible pharmaceutical excipient.

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