United States Patent Office

3,536,709
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3,536,709

2 - TRICHLOROMETHYL - 4 - MORPHOLINO-6-(SUCCINYLOXY ALKYL)AMINO - s - TRIAZINES AND LOWER ALKYL ESTERS THEREOF

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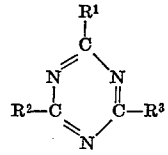
Claims priority, application Germany, May 21, 1966, D 50,171
Int. Cl. C07d 87/42
U.S. Cl. 260—247.2 4 Claims

ABSTRACT OF THE DISCLOSURE

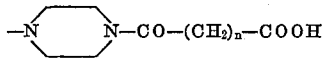
Dicarboxylic acid derivatives of s-triazine of the formula



in which R^1 and R^2 may be the same or different and signifying alkoxy or alkylthio of 1 to 4 carbon atoms, a straight or branched monoalkylamino or monoalkanolamino group of 1 to 4 carbon atoms, —CCl_3, —$CHCl_2$, —Cl, morpholino, piperazino or N-alkyl piperazino in which the alkyl is of 1 to 4 carbon atoms and R^3 signifies

—NH—Alk—O—CO—$(CH_2)_n$—COOH
—NH—Alk—NH—CO—$(CH_2)_n$—COOH

or



in which *n* is an integer of from 1 to 6 and Alk is a straight or branch chained alkylene of 1 to 4 carbon atoms and their pharmacologically acceptable salts, especially their alkali metal and alkaline earth metal salts, their addition salts with pharmacologically acceptable bases, as well as their alkyl esters wherein the alkyl is of 1 to 4 carbon atoms.

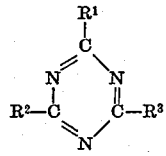
The compounds are useful as analgesics and as antiinflammatory agents.

Field of the invention

The invention relates to novel dicarboxylic acid derivatives of 2,4,6 substituted s-triazines which are useful as antiinflammatory agents and particularly as analgesics.

Summary of the invention

The invention concerns novel dicarboxylic acid derivatives of s-triazine of the formula

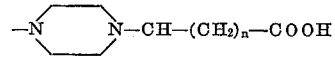


in which R^1 and R^2 may be the same or different and signifying alkoxy or alkylthio of 1 to 4 carbon atoms, a straight or branched monoalkylamino or monoalkanolamino group of 1 to 4 carbon atoms, —CCl_3, —$CHCl_2$,

—Cl, morpholino, piperazino or N-alkyl piperazino in which the alkyl is of 1 to 4 carbon atoms and R^3 signifies

—NH—Alk—O—CO—$(CH_2)_n$—COOH
—NH—Alk—NH—CO—$(CH_2)_n$—COOH

or

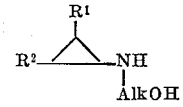


in which *n* is an integer of from 1 to 6 and Alk is a straight or branch chained alkylene of 1 to 4 carbon atoms and their pharmacologically acceptable salts, especially their alkali metal and alkaline earth metal salts, their addition salts with pharmacologically acceptable bases, as well as their alkyl esters wherein the alkyl is of 1 to 4 carbon atoms.

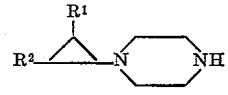
The compounds are useful as analgesics and as antiinflammatory agents.

Detailed description of the invention including the preferred embodiments

The novel compounds according to the invention which are as described under the summary of the invention can be produced by reacting a compound of the formula

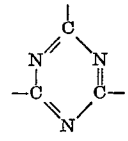


or



wherein

signifies



and Alk, R^1 and R^2 have the same significance as above in an organic solvent, preferably under exclusion of water with about equimolecular quantities of the corresponding dicarboxylic anhydride or dicarboxylic acid ester halide (a) by heating, if desired under reflux and if desired in the presence of a base or (b) in the presence of equimolecular quantities of a tertiary organic nitrogen base, if desired at an elevated temperature to produce the corresponding onium salt and recovering the desired product in a known manner.

It is advantageous to employ ethyl acetate or methylene chloride as the organic solvent, however, solvents such as acetone or halogenated hydrocarbons may be employed.

Aromatic, aliphatic or mixed aromatic-aliphatic tertiary organic nitrogen bases, such as, for instance, pyridine, collidine, trialkyl amines, preferably, triethyl amine, may be employed as the tertiary organic nitrogen bases.

When the process is carried out as under (a) the reaction mixture, for example, may be heated under reflux, if desired, and after cooling down the solution is shaken out with weakly alkaline water, slightly acidifying the aqueous phase whereupon the triazine compound precipitates out.

When the process is carried out under (b) it is expedient to employ temperatures between room temperature and about 60° C. If the onium salt precipitates out in crystalline form, it is expedient to isolate it and wash it. Thereafter it can be dissolved in water and be acidified with an acid to precipitate out the triazine compound. If the onium salt concerned does not precipitate out, the reaction solution can be shaken out with water and the triazine recovered from the aqueous solution by acidification.

The starting piperazino, morpholino or alkanol amino substituted triazines can be produced by the methods analogous to those disclosed in U.S. application Ser. No. 623,548, filed Mar. 16, 1967, by reacting trichloromethyl substituted triazines with alkanol amines, morpholine or piperazine.

As already indicated, the novel compounds according to the invention are useful as antiinflammatory antiphlogistic agents and particularly as analgesics.

The compounds, for example, upon oral administration to mice in doses of 300 to 400 mg./kg. have a strong analgesic action as determined by the mouse tail test according to Haffner and their acute toxicity (LD_{50}) between about 900 to 1700 mg./kg. The therapeutic index thereof is better than, for instance, that of phenacetin.

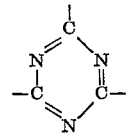
The application of the novel compounds may be enteral, for instance, in the form of pills, capsules, tablets, dragees, suppositories, oily or aqueous solutions or suspensions, or parenteral as injectable aqueous or oily solutions or suspensions.

The single dosage for relief of pain, depending upon the form of application, may be between 1 and 500 mg. and may be administered one or more times a day.

The following examples will serve to illustrate the novel compounds according to the invention with reference to a number of representative embodiments.

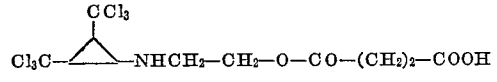
In the formulae given in the examples

represents the s-triazine nucleus



EXAMPLE 1

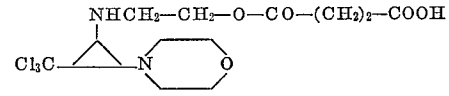
37.5 g. (0.1 mol) of 2,4-bis-trichloromethyl-6-ethanol amino-s-triazine were stirred with 10 g. (0.1 mol) of succinic acid anhydride in 60 ml. of ethyl acetate at 20° C. and 10.1 g. (0.1 mol) of triethyl amine slowly added thereto while cooling, whereupon solution occurred. After a short period of time the triethyl ammonium salt began to crystallize out. It was filtered off and washed. Its melting point was 99–103° C. The salt was dissolved in water and HCl added to provide a pH of 6 whereupon the 2,4-bis-trichloromethyl - 6 - (2-succinyloxyethyl)-amino-s-triazine:



precipitated out as free acid. Yield: 41 g. or 86% of theory. Melting point 112–118° C.

EXAMPLE 2

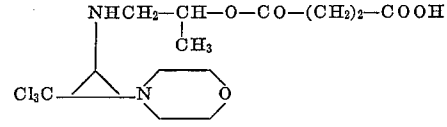
34.2 g. (0.1 mol) of 2-trichloromethyl-4-morpholino-6-ethanolamino-s-triazine were heated to 50° C. in 150 ml. of dried ethyl acetate together with 10.5 g. (0.105 mol) of succinic acid anhydride and 10.6 g. (0.105 mol) of triethylamine, whereupon solution occurred. After 30 minutes the reaction mixture was permitted to cool down and then shaken out with water whereupon the triethylamine salt went over into the aqeuous phase. Upon adjustment of the pH of the aqueous solution to 4 the 2-trichloromethyl-4-morpholino - 6 - (2 - succinyl-oxyethyl)-amino-s-triazine



is obtained in free acid form. After washing and drying the yield was 38 g. or 86% of theory (melting point 176–178° C.).

EXAMPLE 3

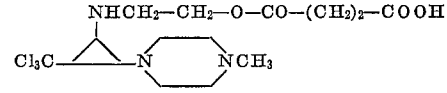
35.7 g. (0.1 mol) of 2-trichloromethyl-4-morpholino-6-(2-hydroxypropyl)-amino-s-triazine were heated under reflux for one hour in 150 ml. of ethyl acetate while stirring together with 10.5 g. (0.105 mol) of succinic acid anhydride and 10.6 g. (0.105 mol) of triethylamine. Solution occurred and after the reaction mixture had cooled down the salt was extracted with water and the free acid precipitated from the extract with the aid of HCl. 34 g. of 2 - trichloromethyl-4-morpholino-6-(2-succinyl-oxypropyl)-amino-s-trazine



were obtained. The melting point thereof was 160–161° C. and the yield was 74.5% of theory.

EXAMPLE 4

28.6 g. (0.08 mol) of 2-trichloromethyl-4-N'-methyl piperazino-6-ethanolamino-s-triazine were heated under reflux for 1 hour in 100 ml. of ethyl acetate together with 8.4 g. (0.084 mol) of succinic acid anhydride. Solution occurred and after cooling the reaction mixture was shaken out with aqueous sodium bicarbonate. The resulting aqueous phase was acidified to a pH of 6 by addition of HCl to precipitate the acid 2-trichloromethyl-4-N'-methyl-piperazino-6-(2-succinyloxyethylamino)-s-triazine

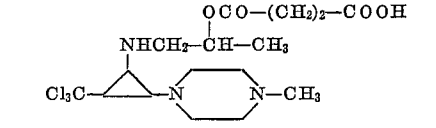


After filtering and washing with water the yield was 28 g. or 76% of theory. Its melting point was 156–161° C.

EXAMPLE 5

37.0 g. (0.1 mol) of 2-trichloromethyl-4-N'-methyl-piperazino - 6 - (2-hydroxypropyl)-amino-s-triazine were heated under reflux for 1 hour in 200 ml. of ethyl acetate together with 10 g. of succinic acid anhydride (0.1 mol) and 8.4 g. of $NaHCO_3$. After the reaction mixture cooled the salt formed was extracted with water and concentrated under vacuum. 49 g. (99% of theory) of the sodium salt were obtained.

The free 2-trichloromethyl-4-N'-methylpiperazino-6-(2-succinyloxypropyl)-amino-s-triazine

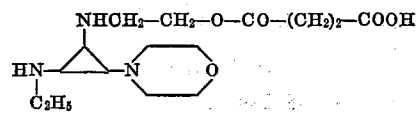


was obtained from the salt by treatment with HCl. The free acid had a melting point of 112–118° C.

EXAMPLE 6

26.8 g. of 2-ethylamino-4-morpholino-6-ethanolamino-s-triazine (0.1 mol) were stirred together with 10 g. of succinic acid anhydride chloride at room temperature whereupon the temperature rose to 38° C. and solution occurred. After standing overnight the methylene chloride solution was extracted with water. The resulting triethyl-

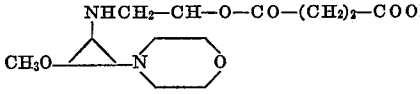
amine salt solution was adjusted to a pH of 6 by addition of HCl whereupon the 2-ethylamino-4-morpholino-6-(2-succinyloxyethyl)-amino-s-triazine



precipitated out. Yield: 29 g. (79% of theory). Melting point: 196–199° C.

EXAMPLE 7

25.5 g. (0.1 mol) of 2-methoxy-4-morpholino-6-ethanolamine-s-triazine were stirred together with 10 g. (0.1 mol) of triethylamine in 150 ml. of methylene chloride, whereupon the temperature rose to 42° C. and solution occurred. After extraction with water and adjustment of the pH of the extract to 6, crystallization of 2-methoxy-4-morpholino-6-(2-succinyloxyethyl)-amino-s-triazine

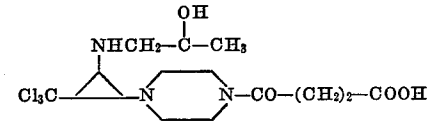


occurred. Yield: 39 g. (90% of theory). Melting point: 212–217° C.

EXAMPLE 8

35.6 g. (0.1 mol) of 2-trichloromethyl-4-piperazino-6-(2-hydroxypropyl)-amino-s-triazine were stirred in 150 ml. of methylene chloride together with 10.1 g. (0.1 mol) triethylamine. The 10 g. of succinic acid anhydride were added thereto at room temperature over a period of ½ hour, whereupon the reaction mixture heated to 35° C. and solution occurred.

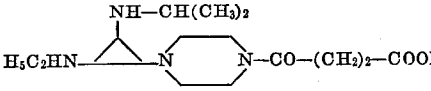
The triethylammonium salt which formed was extracted from the methylene chloride solution with water and HCl added to the extract to adjust the pH to 6, whereupon 2-trichloromethyl-4-N-succinylpiperazino - 6 - (2-hydroxypropyl)amino-s-triazine



precipitated out. Yield: 42 g. or 92% of theory. Melting point: 200–202° C.

EXAMPLE 9

26.5 g. of 2-ethylamino-4-i-propylamino-6-piperazino-s-triazine were stirred with 8 g. (0.1 mol) of pyridine in 150 ml. of methylene chloride. Then 10 g. of succinic acid anhydride were added thereto at room temperature over a period of ½ hour, whereupon the reaction mixture heated to 35° C. and solution occurred. The pyridium salt which was formed was extracted from the methylene chloride solution with water and HCl added to the extract to adjust its pH to 6, whereupon 2-ethylamino-4-i-propylamino-6-N'-succinylpiperazino-s-triazine

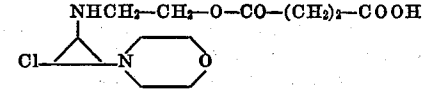


precipitated out. Yield: 32 g. or 88% of theory. Melting point: 183–185° C.

EXAMPLE 10

26 g. of 2-chloro-4-morpholino-6-ethanolamino-s-triazine were stirred with 8 g. (0.1 mol) of pyridine in 200 ml. of ethylene chloride and 10 g. of succinic acid anhydride added. The mixture was allowed to stand overnight at room temperature. The pyridine salt produced was extracted with water and converted to the free acid with

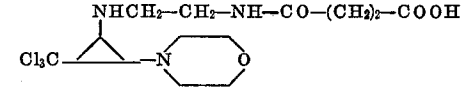
HCl. Yield: 24 g. or 67% of theory of 2-chloro-4-morpholine-6-succinyloxyethylamino-s-triazine



Melting point: 173–178° C.

EXAMPLE 11

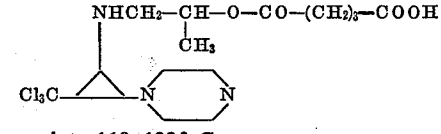
34.2 g. of 2-trichloromethyl-4-morpholino-6-ethylenediamine-s-triazine were stirred with 10.1 g. of triethylamine in 200 ml. of methylene chloride at room temperature. 10 g. of succinic acid anhydride were added thereto over a period of ½ hour while cooling to 25° C. After 2 hours the methylene chloride solution was extracted with water and the extract adjusted to a pH of 4 with HCl. 2-trichloromethyl - 4 - morpholino-6-N'-succinylethylene diamine-s-triazine



precipitated out. Yield: 38 g. or 86% of theory. Melting point: 187–190° C.

EXAMPLE 12

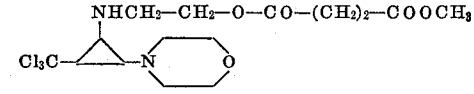
35.7 g. of 2-trichloromethyl-4-morpholino-6-(2-hydroxypropyl)-amino-s-triazine were suspended in 200 ml. of ethyl acetate and refluxed for 1 hour with 12 g. of 95% glutaric acid anhydride and 10.1 g. of triethylamine, whereupon solution occurred. The resulting salt was extracted with water and the aqueous extract adjusted to a pH of 6 with HCl, whereupon a syrupy product separated out which was then taken up in 150 ml. of methylene chloride. The resulting solution was boiled down and the residue stirred with 1:1 ether-hexane, whereupon crystallization occurred. Yield: 33 g. or 70% of theory of 2-trichloromethyl-4-morpholino-6-(2 - oxyglutarylpropyl)-amino-s-triazine



Melting point: 119–122° C.

EXAMPLE 13

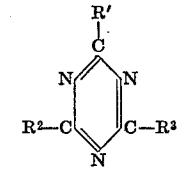
34.3 g. (0.1 mol) of 2-trichloromethyl-4-morpholino-6-ethanolamino-s-triazine were suspended in 300 ml. of ethyl acetate and 11.1 g. of triethylamine. Then 16.5 g. (0.1 mol) of succinic acid methyl ester chloride were added while cooling to 30° C. and stirred. After 2 hours standing the resulting solution was washed with water and boiled down. The residue was stirred with petroleum ether, whereupon crystallization occurred. Yield: 35 g. or 76.6% of theory of 2-trichloromethyl-4-morpholino-6-(methoxysuccinyloxyethyl)-amino-s-triazine



Melting point: 78–82° C.

I claim:

1. An s-triazine of the formula



wherein R^1 is CCl_3 and R^2 is morpholino and R^3 is

—NH—Alk—O—CO—$(CH_2)_2$—COOH

wherein Alk is straight or branched alkylene of 1 to 4 carbon atoms, a pharmacologically acceptable salt or a 1 to 4 alkyl ester thereof.

2. 2 - trichloromethyl - 4 - morpholino - 6 - (2-succinyloxyethyl)amino-s-triazine.

3. 2 - trichloromethyl - 4 - morpholino-6-(2-succinyloxypropyl)-amino-s-triazine.

4. 2 - trichloromethyl - 4 - morpholino - 6-(methoxysuccinyloxyethyl)-amino-s-triazine.

No references cited.

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U.S. Cl. X.R.

260—249.9; 424—248, 249