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2-SUBSTITUTED-4-ALKYLCARBOXYL-1,3-DITHIACYCLOHEXANE TETRAOXIDES

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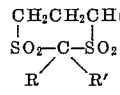
5 Claims. (Cl. 260—327)

This invention relates to new organic compounds. More particularly, it relates to saturated heterocyclic disulfones and a method of preparing the same.

The preparation of diaromatic sulfones such as substituted diphenyl sulfones is well known. These compounds have been used as tuberculostatic agents and for other purposes. The prior art, however, has not described fatty acid substituted saturated heterocyclic disulfones.

The compounds of the present invention can be represented by the following structural formula:



in which R and R′ are hydrogen, alkyl or carboxyl radicals and *n* is a small whole number not less than 2 nor more than 6. Since the present compounds contain carboxylic acid groups, they will form salts such as alkali metal, alkaline earth metal salts, etc. which are intended to be included within the scope of the present invention.

The compounds of the present invention as the free acid are partially soluble in water. In general, they are solids having a definite melting point. In the form of their salts they are soluble in water.

The present compounds are prepared by oxidizing the corresponding 1,3-dithiacyclohexyl fatty acids. These intermediates can be compounds such as 4,6-methylenedithiohexanoic acid; 4,6-ethylidenedithiohexanoic acid; 5,7-methylenedithioheptanoic acid; 5,7-ethylidenedithioheptanoic acid; 5,7-isopropylidenedithioheptanoic acid; 6,8-methylenedithiooctanoic acid; 6,8-ethylidenedithiooctanoic acid; 6,8-isopropylidenedithiooctanoic acid; 7,9-methylenedithiononanoic acid; 7,9-ethylidenedithiononanoic acid; 7,9-isopropylidenedithiononanoic acid; 8,10-methylenedithiodecanoic acid; 8,10-ethylidenedithiodecanoic acid, and the like.

The above intermediates in turn can be prepared by reacting the corresponding fatty acid dimercaptan with an aldehyde or ketone such as pyruvic acid, formaldehyde, acetaldehyde, acetone, and the like to form the 1,3-dithiacyclohexyl fatty acid as shown hereinafter in the examples.

In carrying out the present process the dithiacyclohexyl fatty acids are dissolved in a solvent such as glacial acetic acid, formic acid, tertiary butyl alcohol, water under neutral or alkaline conditions, and the like. The 1,3-dithiacyclohexyl fatty acid is then oxidized to the corresponding cyclicdisulphonyl compound. We have found that the oxidation will take place readily when hydrogen peroxide (Superoxol) is used as the oxidizing agent. Other oxidizing agents can be used such as other peroxides, peracids, permanganates such as sodium, potassium or barium, dichromates such as sodium, or potassium (in the presence of mineral acid), and the like. The reaction is generally exothermic, and the reaction mixture is preferably kept between 0° C. to 75° C. for the initial reaction. The reaction is completed when using peroxides and peracids by heating the mixture at refluxing temperatures for a short period of time. The solvent is removed and the product purified by recrystallization.

The compounds of the present invention are biologically active in stimulating the growth of microorganisms requiring protogen. For example, they stimulate the growth of species of corynebacterium in a synthetic medium containing no protogen. They are therefore useful in the study of the growth requirements of bacteria. Since these compounds are structurally related to thioctic acid they are useful in the study of the metabolism of vital keto acids such as alpha-keto-glutaric acid and pyruvic acid.

The following examples describe in greater detail the preparation of representative saturated heterocyclic disulfones of the present invention.

EXAMPLE 1

6,8-methylenedisulfonyloctanoic acid

6,8-dithioloctanoic acid was prepared by reducing 8.24 g. (0.040 mole) of 6-thioctic acid with 2.92 g. (.127 g. at.) of sodium in 250–300 ml. of liquid ammonia. After the blue color persisted 30 minutes 6.7 g. (.127 mole) of ammonium chloride was added, the ammonia was allowed to evaporate, the residue was taken up in dilute hydrochloric acid and the dithiol acid was extracted into chloroform. The chloroform extracts were dried and the chloroform removed under vacuum. The residual oil was taken up in 25 ml. of glacial acetic acid and treated in 4.2 ml. of 37% formaldehyde in the presence of .2 ml. of 12 N hydrochloric acid. After several hours the test for SH-groups was very weak. Removal of the solvent and excess reagents under vacuum left a crystalline residue. Recrystallization from nitromethane gave 6.12 g. (69%) of 6,8-methylenedithiooctanoic acid, melting at 98°–99° C.

A 4.40 g. (0.020 mole) sample of the product prepared above was suspended in 30 ml. of glacial acetic acid and 10 ml. (.229 eq. of H_2O_2) of hydrogen peroxide (Superoxol) was added over a few minutes. The mixture warmed spontaneously and the solid went into solution. After three hours of refluxing the solvent was removed at the water pump and the crystalline residue was recrystallized from 30 ml. of hot water to give 4.21 g. (74%) of product melting at 160°–167° C. A sample crystallized several times from ethanol, then from water, melted at 166.2°–167.2° C.

EXAMPLE 2

6,8-ethylidenedisulfonyloctanoic acid

A 4.13 g. (0.020 mole) sample of 6-thioctic acid was reduced in liquid ammonia (250 ml.) with 1.45 g. (0.063 g. atm.) of sodium for 20 minutes. The blue color was discharged with ammonium chloride, the ammonia was allowed to evaporate, the residue was taken up in hydrochloric acid and extracted with chloroform. The chloroform extract was dried with sodium sulfate and the solvent was removed at the water pump. The dihydrothioctic acid was taken up in 20 ml. of glacial acetic acid and cooled until the mixture set to a fine mush. Then 1.13 ml. (0.020 mole) of acetaldehyde and 0.1 ml. of 12 N hydrochloric acid were added. After two hours at room temperature the mixture gave a negative nitroprusside test. The mixture was diluted with 80 ml. of water and extracted three times with 20 ml. portions of chloroform. The chloroform extracts were washed with water and dried with sodium sulfate. Removal of the solvent left an oil which crystallized on cooling. Recrystallization from cyclohexane yielded 2.15 g. (42.5%) of fine needles, melting at 86.5°–88.0° C. Several recrystalli-

zations gave an analytical sample, melting at 89°–90° C., of 6,8-ethylidenedithiooctanoic acid.

In 4 ml. of glacial acetic acid .50 g. (2.13 m. mole) of the compound prepared above was treated with .98 ml. (22.6 m. eq.) of hydrogen peroxide (Superoxol). The mixture became warm spontaneously and was refluxed one hour. The solution was allowed to evaporate overnight in a watch glass and the crystalline residue was recrystallized from ethanol to give 51 g. (80.4%) of needle clusters, melting at 179°–181.5° C. Two more crystallizations from ethanol followed by one crystallization from water gave an analytical sample, melting point 176.5°–177.5° C. This compound appeared to be polymorphic showing at different times large irregular rods as well as clusters of needles and showing various melting points (180°–181° C. from alcohol).

EXAMPLE 3

6,8 - isopropylidenedisulfonyloctanoic acid

A 4.86 g. (0.0236 mole) sample of 6-thioctic acid, was reduced in liquid ammonia (300 ml.) with 1.65 g. (0.072 g. at.) of sodium for 30 minutes. The blue color was discharged with 3.9 g. of ammonium chloride, the ammonia was allowed to evaporate, the residue was taken up in hydrochloric acid and extracted with chloroform. The chloroform was dried, and removed at the water pump to leave a residue of dihydrothioctic acid as 4.58 g. (97.5%) of colorless oil. This oil was taken up in 20 ml. of glacial acetic acid, 1.73 ml. (0.0236 mole) of acetone was added and then 0.10 ml. of 12 N hydrochloric acid was added. The solution warmed spontaneously. It was allowed to stand overnight and then was refluxed one hour. The reaction mixture was poured into 80 ml. of water and the product extracted into chloroform. The chloroform was washed with water, dried with sodium sulfate and removed at the water pump. The residue was distilled at 0.05 mm. to give a material distilling 160°–161° C. On crystallizing from ligroin (60°–70°) 3.68 g. (63%) were obtained. An analytical sample melted at 58.5°–59.5° C.

In 17 ml. of glacial acetic acid 2.96 g. (.0119 mole) of the compound prepared above was treated with 6 ml. (.137 eq. of H_2O_2 by titration of aliquot) of hydrogen peroxide (Superoxol) dropwise, then refluxed two hours. The solvent was removed at the water pump and the residue crystallized from hot water to yield 3.30 g. (89%) of disulfone, melting 138°–140.5° C. An analytical sample melted at 138.5°–140.5° C.

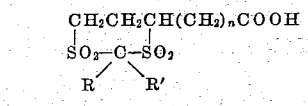
EXAMPLE 4

A 3.57 g. (0.0172 mole) sample of 6,8-dithioloctanoic acid (prepared with sodium and liquid ammonia as above)

was treated with 1.55 g. (0.0176 mole) of pyruvic acid and 0.1 ml. of 12 N hydrochloric acid in 17 ml. of glacial acetic acid. The test for SH became weaker as the mixture stood. After three days the solvent was removed in vacuum to leave 5-(2'-carboxy-2'-methyl-1', 3'-dithiacyclohexyl-4')pentanoic acid, a clear, viscous oil, soluble in cold acetonitrile, ethanol and chloroform; insoluble in cold water, cyclohexane, benzene, carbon tetrachloride and nitromethane. It was somewhat soluble in hot nitromethane. This product can then be oxidized as described above to produce the disulfone.

We claim:

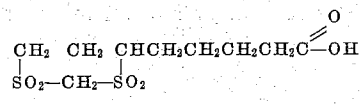
1. Compounds of the group consisting of those having the formula



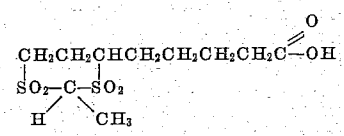
in which R is a member of the group consisting of hydrogen, lower alkyl and carboxyl radicals, R' is a member of the group consisting of hydrogen and lower alkyl radicals and n is a whole number not less than 2 nor greater than 6, and salts thereof.

2. Compounds in accordance with claim 1 in which R and R' are lower alkyl radicals.

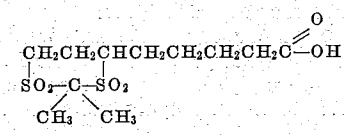
3. The compound 6,8-methylenedisulfonyloctanoic acid having the formula:



4. The compound 6,8-ethylidenedisulfonyloctanoic acid having the formula:



5. The compound 6,8-isopropylidenedisulfonyloctanoic acid having the formula:



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