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CERTAIN 4-(THIAZOLYL) AND 4-(OXAZOLYL) PYRIDINIUM SALTS

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No Drawing. Continuation-in-part of application Ser. No. 669,705, Sept. 22, 1967. This application Nov. 10, 1969, Ser. No. 875,525

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U.S. Cl. 260—294.8 5 Claims

ABSTRACT OF THE DISCLOSURE

The preparation of quaternary lower alkoxy(lower) alkylthiazolylpyridinium salts and quaternary lower alkoxy(lower)alkyl-oxazolylpyridinium salts is described. These compounds are useful as hypoglycemic agents evidenced by their ability to lower blood sugar levels.

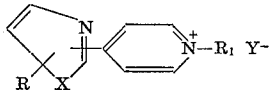
This application is a continuation-in-part of our application Ser. No. 669,705, filed Sept. 22, 1967, now abandoned.

PRIOR ART

Applicants are aware of British Pat. 875,887, directed to pyridinium salts. However, the present invention is directed to subject matter not disclosed in the patent and to an entirely different use.

SUMMARY OF THE INVENTION

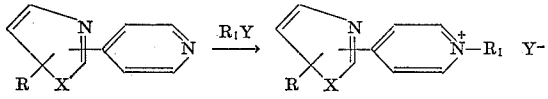
The new quaternary compounds of the present invention may be illustrated by the following formula:



R is selected from the group consisting of hydrogen and lower alkyl; R_1 is lower alkoxy(lower)alkyl; X is a sulfur or an oxygen atom, and Y is a pharmaceutically acceptable anion such as, for example, chloride, bromide, iodide, and the like. The term lower alkoxy as well as the term lower alkyl is intended to include those having 1 to 4 carbon atoms present.

In general, the compounds are crystalline solids, soluble in water.

The quaternary compounds of the present invention may be prepared by reaction of a thiazolylpyridine or an oxazolylpyridine with a lower alkoxy(lower)alkyl halide at a temperature of 0 to 150° C. with or without a solvent, such as an alcohol, for a period of time of several minutes to twenty-four hours in an open vessel or a sealed bomb. The time necessary to complete the reaction is dependent upon the temperature and other conditions of the reaction. This reaction can be illustrated schematically by the following equation:



wherein R, R_1, X and Y are as described hereinbefore.

Among the quaternary compounds of the present invention are, for example:

1-(2-ethoxyethyl)-4-(4-methyl-2-thiazolyl)-pyridinium iodide;

1-(2-methoxyethyl)-4-(4-methyl-2-thiazolyl)-pyridinium chloride;

1-methoxymethyl-4-(4-ethyl-2-thiazolyl)-pyridinium bromide;

1-(3-ethoxypropyl)-4-(2-thiazolyl)pyridinium chloride;

1-(2-ethoxyethyl)-4-(2-methyl-4-thiazolyl)pyridinium iodide;

1-(2-ethoxyethyl)-4-(2-oxazolyl)pyridinium iodide;

1-(2-ethoxyethyl)-4-(4-methyl-2-oxazolyl)pyridinium bromide;

1-(2-ethoxyethyl)-4-(5-oxazolyl)pyridinium chloride;

1-(2-methoxyethyl)-4-(2-oxazolyl)pyridinium chloride; and the like.

The quaternary compounds of the present invention show hypoglycemic activity which indicates them to be useful as medicaments in the lowering of blood sugar levels. When the compounds are administered orally to normal mice, a reduction of blood sugar levels is observed. The compounds of this invention are administered by gavage as saline solutions to CF–1 mice (Carworth Farms, 18–25 grams, 4–6 animals). Control animals receive an equivalent volume of saline. Food is withheld from animals after dosing. Blood glucose is determined on 0.05 milliliter samples of blood by the method of Hoffman [J. Biol. Chem., 120, 51 (1937)] as adapted to the Technicon AutoAnalyzer® and is expressed in the table hereinafter.

TABLE.—DECREASE IN BLOOD GLUCOSE IN NORMAL MICE AFTER ORAL ADMINISTRATION OF THIAZOLYLPYRIDINIUM SALTS AND OXAZOLYLPYRIDINIUM SALTS

Compound	Dose mmoles/kg.	Hours after dosing	Percent decrease in blood glucose
1-(2-ethoxyethyl)-4-(4-methyl-2-thiazolyl)pyridinium chloride	1.5	3	84±5
1-(2-ethoxyethyl)-4-(2-methyl-4-thiazolyl)pyridinium chloride	1.5	3	53±11

The above results show that the quaternary compounds of the present invention are useful in lowering the blood glucose concentration in normal mice.

The quaternary compounds of the present invention may be used to lower blood sugar levels in warm-blooded animals at a dose of from 0.5 to 100 milligrams per kilogram of body weight.

The quaternary compounds of this invention can be used in composition such as tablets; the principal active ingredient is mixed with conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, gums, and fractionally similar materials as pharmaceutical diluents or carriers. The tablets or pills of the novel compositions can be laminated or otherwise compounded to provide a dosage form affording the advantage of prolonged or delayed action or predetermined successive action of the enclosed medication. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids or mixtures of polymeric acids with such materials as shellac, shellac and cetyl alcohol, cellulose acetate and the like. A particularly advantageous enteric coating comprises a styrene maleic acid copolymer together with known materials contributing to the enteric properties of the coating. The term dosage form as described herein refers to physically discrete units suitable as unitary dosage for warm-blooded animal subjects, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical diluent, carrier or ve-

hicle. Examples of suitable oral dosage forms in accord with this invention are tablets, capsules, pills, powder packets, granules, wafers, cachets, teaspoonfuls, dropperfulls, ampules, vials, segregated multiples of any of the foregoing and other forms as herein described.

DETAILED DESCRIPTION

The preparation of the intermediates and final products of this invention will be described in greater detail in conjunction with the followng examples.

EXAMPLE 1

Preparaton of 4-(4-methyl-2-thiazolyl)pyridine

A mixture of 10 g. of thioisonicotinamide and 10.8 g. of chloroacetone in 50 ml. of ethanol is refluxed for 6 hours. The reaction mixture is concentrated under reduced pressure and the residue is dissolved in water. The aqueous solution is made alkaline with sodium hydroxide solution and extracted with ether. The ether extracts are dried and concentrated to an oily residue, which on distillation at 120–125° C./2.5 mm. gives an oil. The oil solidifies on standing and is recrystallized from hexane to give colorless crystals, melting point 72–73° C.

EXAMPLE 2

Preparton of 4-(5-methyl-2-thiazolyl)pyridine

A mixture of 2 g. of α-isonicotinamidoacetone and 3 g. of phosphorus pentasulfied is heated in an oil bath at 110–140° C. until gas evolution ceases. The solid mass is heated with excess 1 N potassium hydroxide solution and the resulting mixture is extracted with chloroform. The chloroform solution is dried and concentrated to give a tan solid. Sublimation at 65° C./0.05 mm. provides yellow crystals, melting point 88°–90° C.

EXAMPLE 3

Preparation of 4-(2-methyl-4-thiazolyl)pyridine

A mixture of 2.3 g. of thioacetamide and 4.2 g. of 4-bromoacetylpyridine hydrobromide in 350 ml. of methanol is refluxed for 0.5 hour. The reaction mixture is concentrated to give a solid residue, to which are added water and sodium hydroxide solution. The aqueous alkaline solution is extracted with chloroform. The chloroform extracts are dried and concentrated. The residue is recrystallized from cyclohexane to give pale yellow crystals, melting point 69–72.5° C.

EXAMPLE 4

Preparation of 4-(2-methyl-5-thiazolyl)pyridine

A mixture of 1.5 g. of 4-acetylaminoacetylpyridine and 2.3 g. of phosphorus pentasulfide is heated in an oil bath at 110–140° C. until gas evolution ceases. The solid mass is heated with excess 1 N potassium hydroxide solution, and the resulting mixture is extracted with chloroform. The chloroform solution is dried and concentrated to an amber oil. The material is sublimed at 70° C./0.05 mm. to provide colorless crystals, melting point 30° C.

EXAMPLE 5

Preparation of 3-methyl-4-(4-methyl-2-thiazolyl)pyridine

The compound is prepared by the reaction of 3-methylthioisonicotinamide and chloroacetone by the method descirbed in Example 1.

EXAMPLE 6

Preparation of 4-(2-oxazolyl)pyridine

A solution of 4.3 g. of N-(2,2-diethoxyethyl)isonicotinamide, 22 ml. of concentrated sulfuric acid, and 0.5 g. of phosphorus pentoxide is heated at 150° C. for 20 minutes and then poured onto 300 ml. of ice. The solution is made basic with sodium hydroxide and extracted with chloroform. The chloroform solution is dried over anhydrous magnesium sulfate and concentrated to a tan solid. Recrystallization from hexane provides colorless needles, melting point 102–103° C.

EXAMPLE 7

Preparation of 4-(5-methyl-2-oxazolyl)pyridine

A solution of 3.6 g. of α-isonicotinamidoacetone and 4.4 ml. of 85% phosphoric acid in 50 ml. of acetic anhydride is refluxed for 1.5 hours. The reaction mixture is cooled and the excess solvent is decanted leaving an oily residue. The oily residue is treated with dilute sodium hydroxide solution to give a white solid. Recrystallization from water gives colorless crystals, melting point 98.5–99.5° C.

EXAMPLE 8

Preparation of 4-(2-methyl-5-oxazolyl)pyridine

A solution of 1.8 g. of 4-(acetylaminoacetyl)pyridine in 27 ml. of acetic anhydride is treated with 2.2 ml. of 85% phosphoric acid. The solution is heated at reflux for 1 hour and is then cooled. The supernatant liquid is decanted and the tarry residue is treated with 1 N sodium hydroxide solution. The aqueous alkaline solution is extracted with chloroform. The chloroform extracts are dried over magnesium sulfate and concentrated to give an off-white solid. Sublimation of the crude solid at 85–95° C./12 mm. gives colorless needles, melting point 79–80.5° C.

EXAMPLE 9

Preparation of 1-(2-ethoxyethyl)-4-(4-methyl-2-thiazolyl) pyridinium chloride

A mixture of 5.2 g. of 4-(4-methyl-2-thiazolyl)pyridine and 5 ml. of 2-chloroethyl ethyl ether is heated at 90° C. in a bomb for 18 hours. The excess 2-chloroethyl ethyl ether is evaporated and the solid residue is recrystallized from acetonitrile-ether to afford yellow crystals. Recrystallization from acetone affords pale yellow needles, melting point 89–92° C.

EXAMPLE 10

Preparation of 1-(2-ethoxyethyl)-4-(2-methyl-4-thiazolyl) pyridinium chloride

A mixture of 2.6 g. of 4 - (2-methyl-4-thiazolyl)pyridine and 5 ml. of 2-chloroethyl ethyl ether is heated at 110° C. in a bomb for 18 hours. The dark solid residue is washed with cold acetone and then recrystallized from acetone to afford pale yellow crystals, melting point 79.5–80° C.

EXAMPLE 11

Preparation of 1-(2-ethoxyethyl)-4-(2-oxazolyl)pyridinium chloride

A mixture of 2.1 g. of 4-(2-oxazolyl)pyridine and 10 ml. of ethoxyethyl chloride is heated at 100° C. in a bomb for 4 hours. The excess 2-ethoxyethyl chloride is allowed to escape, and the residual solid is recrystallized from isopropyl alcohol to provide crystals.

EXAMPLE 12

Preparation of 1-(2-ethoxyethyl)-4-(5-methyl-2-oxazolyl) pyridinium iodide

A solution of 1 g. of 4-(5-methyl-2-oxazolyl)pyridine and 5 ml. of 2-ethoxyethyl iodide in 20 ml. of ethanol is refluxed 1 hour, cooled and filtered to remove the product as a crystalline solid.

EXAMPLE 13

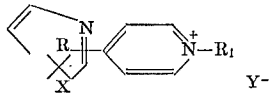
Preparation of 1-(2-methoxyethyl)-4-(2-oxazolyl)pyridinium bromide

A mixture of 2 g. of 4-(2-oxazolyl)pyridine and 5 ml. of 2-methoxyethyl bromide is heated at 110° C. in a bomb for 4 hours. The excess 2-methoxyethyl bromide is al-

lowed to evaporate and the residue is recrystallized from ethanol-ether to give crystals of the above product.

We claim:

1. A quaternary pyridinium salt of the formula:



wherein R is selected from the group consisting of hydrogen and lower alkyl; R_1 is lower alkoxy(lower)alkyl; X is selected from the group consisting of sulfur and oxygen and Y is a pharmaceutically acceptable anion.

2. The quaternary pyridinium salt according to claim 1: 1 - (2-ethoxyethyl)-4-(4-methyl-2-thiazolyl)pyridinium chloride.

3. The quaternary pyridinium salt according to claim

1: 1 - (2-ethoxyethyl)-4-(2-methyl-4-thiazolyl)pyridinium chloride.

4. The quaternary pyridinium salt according to claim 1: 1 - (2 - methoxyethyl)-4-(2-oxazolyl)pyridinium bromide.

5. The quaternary pyridinium salt according to claim 1: 1 - (2-ethoxyethyl)-4-(5-methyl-2-oxazolyl)pyridinium iodide.

References Cited

FOREIGN PATENTS

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ALAN L. ROTMAN, Primary Examiner

U.S. Cl. X.R.

260—295, 296, 999