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2,783,241

## 5-ACYLIMINO-4-SUBSTITUTED- $\Delta^2$ -1,3,4-THIAZOLINE-2-SULFONAMIDES AND METHODS FOR THEIR PREPARATION

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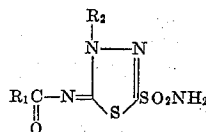
12 Claims. (Cl. 260—306.8)

This invention relates to a new series of organic compounds. More particularly, this invention is concerned with certain 5 - acylimino - 4 - substituted -  $\Delta^2$ -1,3,4-thiazoline-2-sulfonamides and methods for their preparation.

The sulfanamide drugs have come into prominence in recent years with the discovery by Clapp and Roblin (U. S. Patent No. 2,554,816) that certain heterocyclic sulfonamides are desirable diuretic agents because of their ability to inhibit the enzyme "carbonic anhydrase." Because of this property, these agents have found utility in the treatment of certain diseases associated with fluid retention in the body such as congestive heart failure.

We have now discovered a new series of compounds which are also capable of inhibiting carbonic anhydrase. In vivo tests of these compounds indicate that they are longer-acting inhibitors and that therapeutic levels of these drugs may be maintained over a longer period of time resulting in greater diuresis. The tests also show that our compounds are able to penetrate into the cerebrospinal fluid through the blood:brain barrier and into the ocular fluid through the blood:ocular fluid barrier. For this reason they are superior to other known compounds of this class in the treatment of glaucoma and epilepsy.

The compounds of the present invention may be represented by the following general formula:



wherein  $R_1$  is a hydrogen atom, a lower alkyl or a monocyclic aralkyl substituent and  $R_2$  is a lower alkyl or a monocyclic aralkyl substituent. As examples of lower alkyl radicals may be given methyl, ethyl, propyl, isopropyl, butyl and isobutyl. Suitable aralkyl substituents are benzyl,  $\alpha$ -phenethyl, phenylpropyl and phenylbutyl.

Compounds of the present invention can be prepared by chlorinating the 5-acylimino-4-substituted-2-benzylmercapto- $\Delta^2$ -1,3,4-thiazoline starting material to the corresponding 2-sulfonyl chloride derivative. The chlorination may be accomplished by passing chlorine gas through either a suspension or a solution of the starting material in an aqueous acid. The latter is preferred since it enables the operator to determine quickly the point at which the reaction is complete by a color change from colorless to yellow whereas this point is difficult to determine when a suspension is employed. It is to be noted, however, that either form is suitable and may be employed with equal advantage. The resulting sulfonyl chloride is then converted to the corresponding sulfonamide upon treatment with ammonia in the form of liquid ammonia or ammonium hydroxide, diluted with water, filtered and the solution acidified with a mineral acid such as hydrochloric acid or sulfuric acid.

The preferred medium for chlorinating the starting material is a 10% aqueous solution of acetic acid in which the starting materials are completely soluble. If a higher

2

concentration is used, as for example a 33% solution, the starting materials will not dissolve and a suspension results. As mentioned above, because of the ease of manipulation it is preferred to employ solutions of the starting material. Other, and equally useful, carriers are hydrobromic acid and hydrochloric acid as well as the lower fatty acids such as formic, propionic or butyric. The mineral acids such as sulfuric acid, hydrochloric acid and phosphoric acid are also useful for this purpose.

The starting materials employed in this invention—namely the 5 - acylimino-4-substituted-2-benzylmercapto- $\Delta^2$ -1,3,4-thiazolines, may be prepared by alkylating the corresponding 2 - acylamino-5-benzylmercapto-1,3,4-thiazazole with an alkyl halide under suitable reaction conditions. Methyl iodide and benzyl bromide are examples of alkylating agents which may be used. The reaction is preferably conducted in the presence of a sodium alkoxide such as sodium methoxide. The details relating to the preparation of the starting material are completely set forth in the copending U. S. application S. N. 492,298 of Richard W. Young and Kathryn H. Wood, filed concurrently herewith.

The utility of the present invention is illustrated by the following examples, which are intended to be merely illustrative and not limitative upon the scope thereof. All parts are by weight unless otherwise specified.

### Example I

A suspension of 6 parts by weight of 5-acetylimino-4-methyl-2-benzylmercapto- $\Delta^2$ -1,3,4-thiazoline in 180 parts by volume of 33% aqueous acetic acid was chlorinated at 5° C. for 30 minutes. The solid was filtered off, dried, and added portion-wise to 100 parts by volume of liquid ammonia. The ammonia was removed under a stream of dry nitrogen. The residual solid was partially dissolved in 10 parts by volume of water, filtered, and acidified to give 5-acetylimino-4-methyl -  $\Delta^2$  - 1,3,4-thiazoline-2-sulfonamide. The product was purified by two recrystallizations from hot water.

### Example II

A 1.18 parts by weight sample of 5-acetylimino-4-benzyl-2-benzylmercapto- $\Delta^2$ -1,3,4-thiazoline was suspended in 30 parts by volume of 33% acetic acid and the mixture chlorinated at 5° C. for 30 minutes. The solid sulfonyl chloride derivative was filtered off, washed with water and dissolved in 50 parts by volume of ether. This solution was dried and added to about 10 parts by volume of liquid ammonia. The excess ammonia and solvent were removed by distillation and the residue was redissolved in cold water. On acidifying this solution, the crude 5-acetylimino-4-benzyl- $\Delta^2$ -1,3,4-thiazoline-2-sulfonamide was precipitated as a colorless solid. The product was purified by crystallization twice from 50% ethanol and then from a mixture of ethyl acetate and petroleum ether.

### Example III

A suspension of 6 parts by weight of 5-acetylimino-4-ethyl-2-benzylmercapto- $\Delta^2$ -1,3,4-thiazoline in 180 parts by volume of 33% aqueous acetic acid was chlorinated at 5° C. for 30 minutes. The solid was filtered off, dried, and added portion-wise to 100 parts by volume of liquid ammonia. The ammonia was removed under a stream of dry nitrogen. The residual solid was partially dissolved in 10 parts by volume of water, filtered, and acidified to give 5-acetylimino-4-ethyl- $\Delta^2$ -1,3,4-thiazoline-2-sulfonamide. The product was purified by two recrystallizations from hot water.

### Example IV

A 1.18 parts by weight sample of 5-propionylimino-4-methyl-2-benzylmercapto- $\Delta^2$ -1,3,4-thiazoline was sus-

## 3

pended in 30 parts by volume of 33% acetic acid and the mixture chlorinated at 5° C. for 30 minutes. The solid sulfonyl chloride derivative was filtered off, washed with water and dissolved in 50 parts by volume of ether. This solution was dried and added to about 10 parts by volume of liquid ammonia. The excess ammonia and solvent were removed by distillation and the residue was redissolved in cold water. On acidifying this solution, the crude 5-propionylimino-4-methyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide was precipitated as a colorless solid. The product was purified by crystallization twice from 50% ethanol and then from a mixture of ethyl acetate and petroleum ether.

## Example V

A suspension of 6 parts by weight of 5-propionylimino-4-ethyl-2-benzylmercapto- $\Delta^2$ -1,3,4-thiadiazoline in 180 parts by volume of 33% aqueous acetic acid was chlorinated at 5° C. for 30 minutes. The solid was filtered off, dried, and added portion-wise to 100 parts by volume of liquid ammonia. The ammonia was removed under a stream of dry nitrogen. The residual solid was partially dissolved in 10 parts by volume of water, filtered, and acidified to give 5-propionylimino-4-ethyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide. The product was purified by two recrystallizations from hot water.

## Example VI

14 parts by weight of 5-acetylimino-4-methyl-2-benzylmercapto- $\Delta^2$ -1,3,4-thiadiazoline was dissolved in a solution containing 150 parts by volume of glacial acetic acid and 50 parts by volume of water. The mixture was chlorinated for 10 minutes at 10° C. to 15° C. with chlorine gas until the colorless solution turned a permanent yellow color. The reaction mixture was poured into a mixture of 100 parts by volume of water and 100 parts by weight of ice. A white solid was immediately deposited and was filtered off. The dry solid was added to 75 parts by volume of liquid ammonia and the excess evaporated under nitrogen. The reaction mixture was diluted with 100 parts by volume of water, leaving a cloudy solution. Upon acidification with hydrochloric acid, a solid of 5-acetylimino-4-methyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide was deposited, which was filtered off and dried.

## Example VII

Following the procedure set forth in Example VI, 5-acetylimino-4-benzyl-2-benzylmercapto- $\Delta^2$ -1,3,4-thiadiazoline may be dissolved in a 10% solution of acetic acid and the mixture chlorinated for 10 minutes at 5° C., with chlorine gas until the solution turns a permanent yellow color. The sulfonyl chloride derivative is obtained by pouring the reaction mixture into a mixture of 100 parts by volume of water and 100 parts by weight of ice. The white solid which deposits, is filtered off. The dry solid is added to 75 parts by volume of liquid ammonia and the excess is evaporated under nitrogen. Dilution with 100 parts by volume of water leaves a cloudy solution which, upon acidification with hydrochloric acid, yields 5-acetylimino-4-benzyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide, which is filtered off and dried.

The following listed compounds may be prepared by following the procedure described in Example I, employing as a starting material the appropriate 5-acylimino-4-substituted-2-benzylmercapto- $\Delta^2$ -1,3,4-thiadiazoline:

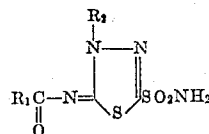
- 5-formylimino-4-methyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide
- 5-butylimino-4-methyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide
- 5-butylimino-4-benzyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide
- 5-acetylimino-4-p-nitrobenzyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide
- 5-acetylimino-4-butyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide

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5-propionylimino-4-butyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide

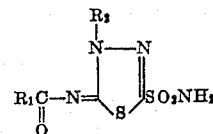
We claim:

1. A compound selected from the group consisting of those having the general formula:



wherein  $R_1$  is a member selected from the group consisting of hydrogen atoms, lower alkyl and lower-alkyl and phenyl-lower-alkyl radicals and  $R_2$  is a member selected from the group consisting of lower alkyl and phenyl-lower-alkyl radicals.

2. The compound 5-acetylimino-4-methyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide.
3. The compound 5-acetylimino-4-benzyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide.
4. The compound 5-acetylimino-4-ethyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide.
5. The compound 5-propionylimino-4-methyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide.
6. The compound 5-propionylimino-4-ethyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide.
7. A method for preparing compounds selected from the group consisting of those having the general formula:



wherein  $R_1$  is a member selected from the group consisting of hydrogen, lower alkyl and phenyl-lower-alkyl radicals and  $R_2$  is a member selected from the group consisting of the lower alkyl and phenyl-lower-alkyl radicals which comprises chlorinating a member selected from the group consisting of 5-acylimino-4-lower alkyl-2-benzylmercapto- $\Delta^2$ -1,3,4-thiadiazolines and 5-acylimino-4-phenyl-lower-alkyl-2-benzylmercapto- $\Delta^2$ -1,3,4-thiadiazolines in aqueous acid to obtain the corresponding sulfonyl chloride derivative, and then reacting said derivative with ammonia.

8. A method for preparing 5-acetylimino-4-methyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide which comprises chlorinating 5-acetylimino-4-methyl-2-benzylmercapto- $\Delta^2$ -1,3,4-thiadiazoline in aqueous acid, and then reacting the resulting sulfonyl chloride derivative with ammonia.

9. A method for preparing 5-acetylimino-4-benzyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide which comprises chlorinating 5-acetylimino-4-benzyl-2-benzylmercapto- $\Delta^2$ -1,3,4-thiadiazoline in an aqueous acid and then reacting the resulting sulfonyl chloride derivative with ammonia.

10. A method for preparing 5-acetylimino-4-ethyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide which comprises chlorinating 5-acetylimino-4-ethyl-2-benzylmercapto- $\Delta^2$ -1,3,4-thiadiazoline in an aqueous acid and then reacting the resulting sulfonyl chloride derivative with ammonia.

11. A method for preparing 5-propionyl-4-methyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide which comprises chlorinating 5-propionylimino-4-methyl-2-benzylmercapto- $\Delta^2$ -1,3,4-thiadiazoline in an aqueous acid and then reacting the resulting sulfonyl chloride derivative with ammonia.

12. A method for preparing 5-propionyl-4-ethyl- $\Delta^2$ -1,3,4-thiadiazoline-2-sulfonamide which comprises chlorinating 5-propionylimino-4-ethyl-2-benzylmercapto- $\Delta^2$ -1,3,4-thiadiazoline in an aqueous acid and then reacting the resulting sulfonyl chloride derivative with ammonia.

## References Cited in the file of this patent

## UNITED STATES PATENTS