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2(2'-PROPENYLIDENE-AMINO)-1,3,4-THIADIAZOLE-5-SULFONAMIDE

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4 Claims. (Cl. 260—306.8)

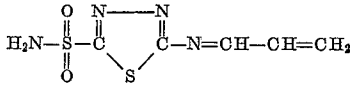
This invention is directed to an improved diuretic and to its method of preparation and use.

Diuretics are employed to promote the excretion of water and sodium chloride that have accumulated in excess in the interstitial tissues or serous cavities. Such accumulations are associated chiefly with afflictions of the heart, kidneys or liver. The diuretic agents currently available have their greatest usefulness in the adjunctive treatment of congestive heart failure and portal cirrhosis of the liver. Their effectiveness is variable in nephrotic edema or the edema associated with chronic nephritis of the glomerular or vascular type. They are virtually ineffective and even may be harmful in the treatment of acute nephritis. In all cases in which the edema is attributable to renal disease, diuretic agents must be used cautiously, particularly when there is nitrogen retention.

The organic mercurials are the most powerful diuretics now available. To increase their effectiveness and reduce the disagreeable side effects they are combined with theophylline or sodium thioglycollate. For this reason, the mercurials that are not thus combined have largely dropped out of use. The once popular xanthine derivatives when used alone are relatively weak and unpredictable diuretics and are rarely employed for this purpose except when use of mercurials is contraindicated or when it is desirable to give a diuretic orally.

For these reasons attention has turned to a recent addition to that group of drugs which produces diuresis by depressing tubular reabsorptive transport of electrolyte. Typical of this group is Diamox, the term used for acetazoleamide, 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide. The present invention provides a drug of this family having excellent diuretic activity. Accordingly the object of this invention is to provide a useful diuretic of the Diamox type.

The novel diuretic of this invention is 2-(2'-propenylideneamino)-1,3,4-thiadiazole-5-sulfonamide, having the formula



This compound exerts its diuretic action by depressing tubular reabsorption capacity. It effects the reabsorption of a specific anion, bicarbonate, and tends to produce a metabolic acidosis. This diuretic action is associated with an increase in the excretion of potassium. In contrast to the mercurials it is well tolerated when given orally. It may be given alone for the mobilization of edema fluid. Its action is not as rapid or dramatic as that of an organic mercurial, but, nevertheless, a steady decline in weight to an edema-free level can be achieved. It can be successfully combined with mercurials, each drug being given on alternate days. This would seem to be particularly desirable in the rapid mobilization of edema fluid since one compound corrects for the disturbance in acid-base balance produced by the other.

Thereby the development of refractoriness to either drug can be avoided.

It is effective in preventing the accumulation of edema fluid. A single dose given daily or every other day can maintain a high percentage of cardiac patients in an edema-free state. If necessary, a mercurial diuretic can be added to the regimen. In such cases the interval between mercurial injections is much more prolonged than if the mercurial alone was used.

2-(2'-propenylideneamino) - 1,3,4-thiadiazole-5-sulfonamide is administered orally in tablet form. An effective single dose is 250–500 mgm. As a diuretic it should be given once daily or every other day.

This diuretic may be tabletted or encapsulated by conventional means, then subjected to enteric coating of such type that the therapeutic components are not liberated until the tablet or capsule has reached the intestines. The tablets may, of course, be compounded to contain the usual excipients, fillers, dyestuffs, etc. For example, one may use as excipients and fillers materials such as starch, powdered cane sugar, lactose, etc.; and as binding agents, one may use solutions of lac, zein or polyvinyl pyrrolidone in ethanol or isopropanol, or a solution of Carbowax in carbon tetrachloride. Lubricants and disintegrating agents may also be added. Typical lubricants are calcium or magnesium stearate, mineral oil, Carbowax 1540 or hydrogenated vegetable oil. As disintegrating agents, one may use potato starch, etc. In practice, dry granulations are normally made to contain the active ingredients, fillers, binders and, if desired, dyestuffs, etc. This mixture is then compressed (e.g. in the standard single punch or rotary multiple punch machine or hand machines) to obtain the tablets in form for enteric coating.

When capsules are used, the granulations may be prepared as described above for the preparation of tablets, then filled in accordance with standard procedures. Hard capsules (made of gelatin and water and molded in two sections) are preferred and are filled with a suspension of resin in vegetable or mineral oil, i.e., corn oil, sesame oil, etc.

The enteric coating (on either the tablet or capsule) is desirably a cellulosic derivative which contains free carboxyl groups. Preferably, the enteric coating material is a cellulose lower fatty acid ester phthalate, particularly cellulose acetate phthalate. However, other cellulose derivatives may be used. For example, cellulose ethers or mixed ether-esters may be substituted for the cellulose esters. Thus, among the enteric coating materials which may be used (in addition to cellulose acetate phthalate) are the materials formed by reacting cellulose acetate, cellulose propionate, cellulose acetate-butyrate, ethyl cellulose, butyl cellulose, etc. with phthalic or maleic anhydrides or the like, in the presence of a tertiary organic base (or in the presence of a solvent). The materials used for this purpose are known substances and their preparation is described in U.S. Patent Nos. 2,093,462; 2,093,464; and 2,126,460.

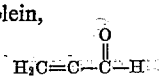
To effect coating, the tablets or capsules may be dipped, sprayed, etc., with the solution of cellulosic derivative until a coating of the desired thickness is obtained. Of course, the thickness of the coating may obviously also be controlled by control of the concentration of cellulose derivative in the solution being utilized. Plasticizers such as triacetin and other desirable materials insoluble in acid may also be added, if desired.

Although the cellulose derivatives referred to above are preferred for use in the invention, other enteric coating materials, such as salol, keratin, stearic acid, casein, shellac, mixtures of these materials, etc. may be used.

The preparation of the diuretic of this invention is illustrated by the following example.

Example I

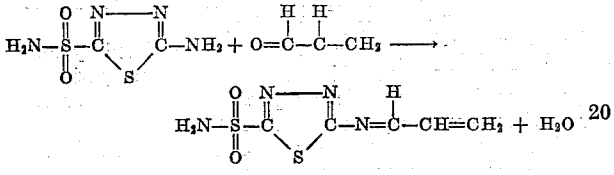
Thirty grams acrolein,



was added to 90 grams of 2-amino-1,3,4-thiadiazole-5-sulfonamide in one liter of 3% acetic acid and the mixture allowed to stand at room temperature. After 48 hours the solution was evaporated to dryness under reduced pressure and the residue heated with 500 cc. of alcohol. Filtration yielded 70 grams of compound decomposing at 230–231° C.

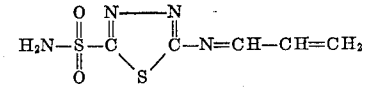
Calculated for $C_5H_6O_2N_4S_2H_2O$; S, 25.22; N, 22.03. Found: S, 25.36, 25.44; N, 21.15, 20.94.

This reaction is illustrated as follows:



We claim:

1.



2-(2'-propenylideneamino)-1,3,4-thiadiazole - 5 - sulfonamide.

2. A process for the preparation of 2-(2'-propenylideneamino)-1,3,4-thiadiazole-5-sulfonamide comprising reacting acrolein with 2-amino-1,3,4-thiadiazole-5-sulfonamide.

3. Process of claim 2 wherein the reaction is conducted at room temperature in an acid solution.

4. Process of claim 3 wherein the reaction solution is evaporated at the completion of the reaction, the residue heated with alcohol, and the product recovered by filtration.

No references cited.