United States Patent Office 2,967,130
Patented Jan. 3, 1961

2,967,130

p-SULFAMYL β-HYDROXYETHYL CARBANILATE DIURETIC COMPOSITIONS

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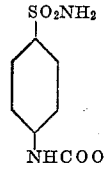
No Drawing. Filed Sept. 5, 1957, Ser. No. 682,076

3 Claims. (Cl. 167—65)

This invention relates to therapeutic compositions and more particularly to therapeutic compositions which are effective to inhibit carbonic anhydrase activity.

This application is a continuation-in-part of our application Serial Number 456,639, filed September 16, 1954, now abandoned, and of copending application Serial Number 532,113, filed September 1, 1955, now U.S. Patent No. 2,920,012.

Briefly, the present invention is directed to therapeutic compositions comprising a compound having the formula:



wherein R is ethyl, β-hydroxy ethyl and allyl, and a pharmaceutical carrier. Of the above-noted compounds, we preferably employ p-sulfamyl β-hydroxy ethyl carbanilate.

Among the several objects of the invention may be noted the provision of therapeutic compositions and methods which are effective to inhibit the activity of the enzyme carbonic anhydrase; the provision of such therapeutic compositions which are effective diuretic compositions; and the provision of therapeutic compositions of the class described which are stable and nontoxic. Other objects and features will be in part apparent and in part pointed out hereinafter.

The invention accordingly comprises the products and methods hereinafter described, the scope of the invention being indicated in the following claims.

The enzyme carbonic anhydrase plays an important role in the acidification of the urine through its catalysis of the reversible reaction:

$$H_2O+CO_2 \rightleftarrows H_2CO_3$$

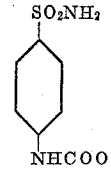
The carbonic acid so form yields hydrogen and bicarbonate ions through the reversible reaction:

$$H_2CO_3 \rightleftarrows H^+ + HCO_3^-$$

Thus, carbonic anhydrase activity indirectly determines the number of hydrogen ions which are available to replace sodium ions in buffer compounds from the blood, such as, for example, disodium phosphate and sodium bicarbonate. The sodium ions thus replaced are conserved and return to the blood, and carbonic acid formed in the above reaction catalyzed by carbonic anhydrase also returns to the blood.

In accordance with the present invention, it has been found that carbonic anhydrase activity can be effectively inhibited and the excretion of water, sodium and potassium in the urine increased by the use of therapeutic

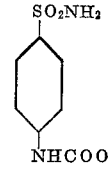
compositions including a p-sulfamyl carbanilate compound having the following formula:



wherein R is ethyl, β-hydroxy ethyl or allyl. The inhibition of carbonic anhydrase activity by the compositions of the present invention results in a reduction of hydrogen ions available for the acidification of the urine. As a consequence, the pH of the urine increases, fewer sodium ions of the buffer compounds are replaced by hydrogen ions, and larger amounts of sodium, chloride and bicarbonate are excreted in the urine. Further, because the formation of carbonic acid from carbon dioxide and water is inhibited, water excretion is increased. Thus, the diuretic action provided by the compositions of the invention is useful to relieve edema, for example, caused by congestive heart failure or other causes.

The p-sulfamyl carbanilate compounds specified herein are not only compatible with other components employed in therapeutic compositions, but they are also stable and nontoxic. For example, intraperitoneal doses of p-sulfamyl β-hydroxy ethyl carbanilate up to 1600 mg./kg. were tolerated by male white rats, and only three animals out of a group of nine receiving 1800 mg./kg. intraperitoneally died. Moreover, oral doses up to 1500 mg./kg. of this carbanilate compound did not produce any ill effect in male white rats. Three groups of white rats, with six animals in each group, received 600, 900 and 1200 mg./kg. respectively of p-sulfamyl β-hydroxy ethyl carbanilate per day for twelve days and showed a normal gross pathology after being sacrificed and autopsied on the thirteenth day.

The carbanilate compounds of the novel therapeutic compositions of the invention have the formula:



wherein R represents ethyl, β-hydroxy ethyl or allyl. The therapeutic compositions of the present invention comprise a compound of the above-mentioned class and a pharmaceutical carrier which may be either a liquid or solid material. It is preferred that the pharmaceutical carrier be a solid material such as, for example, starch, gelatin, lactose, talc, calcium stearate or the like. Any of the pharmaceutical carriers conventionally used in therapeutic compositions may be utilized where such materials are compatible with the aforementioned carbanilate compounds. These compositions include tablets, capsules and the like, and may include a liquid pharmaceutical carrier and be in the form of solutions, dispersions, suspensions, elixirs and the like.

The percentage of the carbanilate compound incorporated in the therapeutic compositions of the invention may be varied considerably. Exemplary compositions may contain approximately 80% by weight of one of the above-mentioned carbanilate compounds, although greater or smaller amounts than 80% may also be used in the practice of the invention. The daily dosage administered to a patient may also vary considerably, depending upon the patient's condition and the amount prescribed by the physician in charge. In the case of

edema, the daily dosage of these novel compositions may be such that the patient ingests on the order of 250 mg. to 500 mg. and up to as high as 2000 mg. of one of the carbanilate compounds per day.

These diuretics are effective in cases of hypertensive cardiovascular disease, arteriosclerotic heart disease and rheumatoid heart disease. Surprisingly enough, they are also useful diuretics in Laennec's cirrhosis, especially p-sulfamyl β-hydroxy ethyl carbanilate.

The following example illustrates the invention.

Example

Therapeutic diuretic tablets were prepared having the following composition:

Component	G.
p-Sulfamyl β-hydroxy ethyl carbanilate	0.5
Corn starch, U.S.P	0.1
Calcium stearate	0.005

The tablets were prepared by grinding the p-sulfamyl β-hydroxy ethyl carbanilate through a No. 24 screen, adding the corn starch and calcium stearate and, after thoroughly mixing the components, compressing into tablets.

It will be understood, of course, that the therapeutic compositions of the invention may be employed in the treatment of any condition where the inhibition of carbonic anhydrase activity will produce a beneficial result.

In view of the above, it will be seen that the several objects of the invention are achieved and other advantageous results attained.

As various changes could be made in the above products and methods without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

We claim:

1. A therapeutic composition useful as a diuretic comprising a dosage form of p-sulfamyl β-hydroxy ethyl carbanilate in combination with a pharmaceutical carrier.

2. A therapeutic composition useful as a diuretic comprising a dosage unit form of p-sulfamyl β-hydroxy ethyl carbanilate in combination with a solid pharmaceutical carrier.

3. A therapeutic composition useful as a diuretic comprising a dosage unit form of p-sulfamyl β-hydroxy ethyl carbanilate in combination with a liquid pharmaceutical carrier.

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