

1

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HEPARIN-AMINO BENZOATE COMPOSITIONS

Marvin Jay Fahrenbach, Pearl River, and Kenneth Austen Burke, Nanuet, N. Y., assignors to American Cyanamid Company, New York, N. Y., a corporation of Maine

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This invention relates to new compositions of matter which have useful therapeutic effects. The invention includes the new substances, preparations containing the same, their use and methods by which they are prepared.

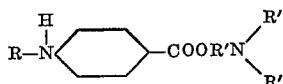
In recent years certain sulfated polysaccharides, notably heparin, have had an increased use in medicine in the treatment of diseases of the vascular system. These substances have been known for some time to be anti-coagulants and when injected into an animal increase the blood clotting time. It has also been found that heparin and related anti-coagulants have an effect on the lipoproteins in the bloodstream; in pathological conditions low density lipo-proteins are thus converted to higher density molecules, which reduces the tendency to form deposits of these materials in the vascular system. For this latter purpose, it is desirable that relatively low levels of the anti-coagulants be present in the bloodstream over a considerable period of time.

The anti-coagulant action of heparin and related anti-coagulants is found to be of comparatively short duration and in injection of 50 to 100 mg. of heparin, for example, in an adult patient may lose its effect on blood-clotting in 5 or 6 hours due to the fact that it is rapidly excreted or broken down in the body. Although some progress in prolonging the action of heparin following injection has been made by incorporating it in a menstruum which delays the absorption, yet it is found that these are only partially successful and unduly painful to the patient. As a result, many patients are reluctant to continue medication with the drug and the full advantages of such therapy cannot be generally realized.

We have discovered that heparin and other sulfated polysaccharides having anti-coagulant activity can be reacted with certain local anesthetics of the amino-benzoate type to form insoluble compounds which can be injected in the patient with less pain. Of perhaps greater importance is the surprising discovery that these compounds maintain a therapeutic level of the anti-coagulant in the bloodstream of sufficient effect to allow the lipoproteins to reach their normal density, and this effect is maintained for a matter of days. Accordingly, it is possible by the use of the compositions of the present invention to maintain in the patient satisfactory levels of the drugs with a single relatively painless injection the effects of which last for several days. This enables the clotting time of the blood to be prolonged for a protracted period and also enables the effect of the heparin on the lipoproteins to be maintained.

The anti-coagulant sulfated polysaccharides which may be reacted in accordance with the present invention to provide new compositions of matter are generally of high molecular weight. Several of these are commercially available and their use in the process of the present invention is shown in specific examples which follow.

The amino benzoates which may be reacted with the sulfated anti-coagulants have the following general formula:



2

in which R is hydrogen or an alkyl radical and R' are alkyl radicals. Representative local anesthetics of this class are shown in the following specific examples.

In order that the invention may be illustrated with greater exactness, the following examples are given. In these examples, the parts are by weight unless otherwise indicated. It will be understood that other high molecular weight sulfated polysaccharides having anti-coagulant activity and other amino benzoates having local anesthetic action may be used in place of those that are particularly illustrated.

Example 1

To a solution of 1 part sodium heparinate in 25 volumes of water at 25° C. was slowly added a solution of 3 parts 3-dibutylaminopropyl p-aminobenzoate sulfate, sold under the name Butacaine sulfate, in 75 volumes of water. A white, finely divided precipitate formed immediately. The pH of this slurry was about 5.0. After stirring for 10 minutes at 25° C., the white solid was filtered on a sintered glass funnel, washed with 50 volumes of water, then redissolved in 200 volumes of 50% alcohol. This solution had a colloidal appearance. After filtration of the solution, the filtrate and wash (250 volumes) still remained slightly colloidal in appearance. By drying an aliquot, it was shown that there were 3 parts of the Butacaine-heparin salt present.

Dilution of one part of the above solution to 18 and 180 parts by volume with water resulted in a solution which contained 0.00067 and 0.000067 part respectively of heparin-butacaine per volume. Injection of 0.5 volume of these two solutions into white rats once a day for 3 days resulted in no gross toxicity. By the virtue of the high molecular weight and variable composition of heparin, the products that are obtained in accordance with the above procedure and in other examples are not sharply characteristic in physical properties such as melting point or crystalline structure.

Example 2

To a solution of 5 parts sodium heparinate in 200 volumes of water at 45° C. was slowly added a solution of 15 parts Butacaine sulfate in 400 volumes of water; a cream colored finely divided solid precipitated immediately. This solid was separated from the supernatant by centrifugation for 15 minutes at 1850 R. P. M. The deep cream colored residue was washed three times with 150 volumes of water, each time removing the supernatant by centrifugation for 15 minutes at 1850 R. P. M. Weight of the wet residue of Butacaine-heparin was 30.6 parts. A 5.2 part aliquot of this residue was dried in a vacuum desiccator over concentrated sulfuric acid to give 1.6 parts of a light tan colored solid which pulverized easily to a fine particle size. The product melted to a viscous oil between 80–125° C.

Example 3

To a solution of 1 part of the sulfuric acid ester of polyanhydromannuronic acid, sold under the name Paritol-A, in 25 volumes of water at 25° C. was slowly added with stirring a solution of 3 parts Butacaine sulfate in 25 volumes of water. A heavy white finely divided precipitate formed immediately and settled quickly. This white Butacaine-Paritol-A salt was filtered on a sintered glass funnel, washed with 50 volumes of water, and dried in a vacuum desiccator over anhydrous magnesium sulfate to give 2.61 parts of a hard vitreous solid, which was readily pulverized in a mortar and pestle to a fine white powder. The product melted to a viscous oil between 124–140° C. with decomposition.

Example 4

To 0.05 part of the sodium salt of sulfated polygalact-

3

uronic acid methyl ester methyl glycoside, sold under the name Treburon, in 2 volumes of 0.9% sodium chloride solution was slowly added 3.08 volumes of 0.1 N silver nitrate solution in order to remove chloride ions. The precipitate of silver chloride was removed by centrifugation. To the supernatant solution of Treburon at 25° C. was slowly added 0.15 part of Butacaine sulfate in 5 volumes of water. A white, finely divided solid precipitated. This Butacaine-Treburon salt was filtered on a sintered glass funnel, washed with 20 volumes of water and dried in a vacuum desiccator over anhydrous magnesium sulfate to give 0.110 part of a hard vitreous solid, which was readily pulverized in a mortar and pestle to a fine white powder. The product melted to a viscous oil between 155–165° C. with slight decomposition.

Example 5

To a 2 volume portion of a 30% aqueous solution of sodium heparinate was slowly added 2 volumes of a 30% aqueous solution of 2-dimethylaminoethyl p-butylaminobenzoate hydrochloride. An oily colloidal solution was formed which changed slowly to a gummy very finely divided solid after standing at room temperature. The solids were separated by centrifugation, washed twice with 10 volumes of water and dried in a vacuum desiccator over anhydrous magnesium sulfate to a gummy vitreous solid.

Example 6

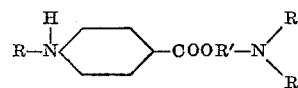
To a 2 volume portion of a 30% aqueous solution of sodium heparinate is slowly added 2 volumes of a 30% aqueous solution of 3-dimethylamino-1,2-dipropyl p-aminobenzoate hydrochloride. An oily colloidal solution was formed which changed to a gummy very finely divided solid after standing at room temperature. The solid was separated by centrifugation, washed twice with 10 volumes of water and dried in a vacuum desiccator over anhydrous magnesium sulfate to a gummy vitreous solid.

What we claim is:

1. A new composition of matter comprising the solid product obtained by reacting substantially equivalent

4

amounts of heparin and an aminobenzoate local anesthetic having the following formula



in which R is a member of the group consisting of hydrogen and alkyl radicals and R' represents alkyl radicals.

2. A new composition of matter comprising the solid reaction product of 3-dibutylaminopropyl p-aminobenzoate sulfate and heparin.

3. A new composition of matter comprising the solid reaction product of 2-dimethylaminoethyl p-butylaminobenzoate hydrochloride and heparin.

4. A new composition of matter comprising the solid reaction product of 3-dimethylamino-1,2-dipropyl p-aminobenzoate hydrochloride and heparin.

References Cited in the file of this patent

UNITED STATES PATENTS

2,100,054	Hopkinson	Nov. 23, 1937
2,487,975	Koree	Nov. 15, 1949
2,508,433	Snyder	May 23, 1950
2,561,384	Lee	July 24, 1951

FOREIGN PATENTS

653,368	Great Britain	May 16, 1951
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OTHER REFERENCES

- Loomis: J. Pharmacol. and Exptl. Therap., vol. 104, No. 1, pp. 87–92, January 1952. (Rec'd for publication Oct. 8, 1951.) (Copy in POSL 167–65.5A).
- Vorzimer: J. A. M. A., vol. 138, No. 10, pp. 747–8. Clinical Medicine, August 1948, p. 197.
- Pundel: Presse Med., vol. 57 (Dec. 3, 1949), pp. 1120–1.
- J. A. M. A., vol. 139, No. 13, p. 883, March 26, 1949.
- Scott: Royal Soc. Canada, 3rd series, sect. V, 1942, pp. 49–51.
- Proc. Staff Meetings Mayo Clinic, Dec. 10, 1947, pp. 567–570.