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ALIPHATIC SULPHONATE SALTS OF LOCAL-ANESTHETIC ORGANIC BASES

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The present application is a continuation in part of my co-pending application Serial No. 156,938, filed August 2, 1937.

It is the object of my present invention to produce certain new aliphatic sulphonates of local-anesthetic organic bases, to obtain products which are sufficiently stable, are water-soluble, and have greater lipid solubility than have the known water-soluble salts of such organic bases.

The local-anesthetic organic bases—organic bases which have local anesthetic action—of which I produce aliphatic sulphonates are in the class containing the following:

Cocaine—methylbenzoyllecgonine,
Procaine—p-aminobenzoyldiethylaminoethanol,
γ-12-methyl-piperidinol-propyl benzoate,
p-Amino-benzoyl-dimethylamino-methylbutanol,
p-Aminobenzoyl-γ-di-n-butylaminopropanol,
p-Aminobenzoyl-2-2-dimethyl-3-diethylamino-propanol,
Monoisobutylaminoethyl-p-aminobenzoate,
Piperidinopropanediol-di-phenylurethane,
2-butyloxyquinolinecarboxylic acid-4-diethyl-ethylene-diamide, and
γ-Diethylaminopropylcinnamate.

The first seven of these local-anesthetic organic bases are local-anesthetic esters of a nitrogenous alcohol and a benzoic acid of the class consisting of benzoic acid and p-aminobenzoic acid.

I have discovered that local-anesthetic organic bases will react with certain aliphatic sulphonic acids to produce therapeutically effective aliphatic sulphonates which also have local-anesthetic action, and which in many cases have certain advantages over the known salts of these bases, as for instance by reason of decreased toxicity, and/or lengthened action, and/or effectiveness in smaller dosages, and combined stability, water-solubility, and greater lipid-solubility than known water-soluble salts.

The aliphatic sulfonic acids which I have found effective for this are those in which there is an aliphatic substituent having at least four but not to exceed eighteen carbon atoms. This aliphatic substituent may be either primary straight-chain or primary branched-chain or secondary, and either saturated or unsaturated. In general, by the term aliphatic sulfonic acid I mean one which is represented by the following formula:



in which R represents such an aliphatic hydro-

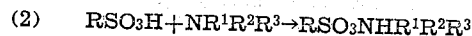
carbon group as has just been defined and contains a carbon atom that is directly joined to the sulphur atom of the sulphonic acid group. Among such aliphatic groups may be mentioned the following: butyl, amyl, hexyl, heptyl, octyl, nonyl, lauryl, myristyl, cetyl, stearyl, and oleyl.

The aliphatic sulphonic acids of my invention thus differ from the compounds which are sometimes called "mineral oil sulphonic acids"; for those so-called "mineral oil sulphonic acids" are complex mixtures of compounds having formulas which have never been satisfactorily demonstrated, and are probably mixtures of esters of sulphuric acid, rather than derivatives of true sulphonic acid, in that in their structure an oxygen atom almost certainly intervenes between the sulphur atom and the aliphatic group, and in any case they are at best a group of unknown things mixed together.

In making these new aliphatic sulphonates, I first prepare the desired aliphatic sulphonic acid. The various aliphatic sulphonic acids may be prepared by general methods described in the literature. For instance, see:

Annalen, vol. 148, p. 90, Strecker,
Annalen, vol. 148, p. 96, Bender,
Jour. Am. Chem. Soc., vol. 55, p. 1091, Noller and Gordon, and
Jour. Am. Chem. Soc., vol. 57, p. 570, Read and Tartar.

After the desired aliphatic sulphonic acid is obtained, it may be caused to react, in solution in a suitable solvent, with the desired local-anesthetic organic base, to produce the desired aliphatic sulphonate. These local-anesthetic organic bases all contain a trivalent nitrogen atom. The reaction may be represented in general as follows:



in which R has the same significance as before, and R¹, R², and R³ represent hydrogen atoms or organic radicals which are united to the nitrogen atom in the initial local-anesthetic organic base and at least one of which is an organic radical. The following are some examples of my process, and of the product obtained thereby.

Example 1.—n-Hexyl sulphonic acid, and procaine, are dissolved in separate portions of ethyl ether, and the two ethereal solutions are put together, in the cold. As an example, dissolve 9.44 grams (0.04 mole) of procaine in about 200 cc. of the ether, and 9.05 grams (slightly more than a molecular equivalent) of n-hexyl sulphonic

acid in about 100 cc. of the ether, and gradually add the latter to the former, preferably with stirring and cooling. Reaction occurs, and the desired procaine n-hexyl sulphonate precipitates. This precipitate may be suitably separated, as by filtration and decantation, and purified by recrystallization—as by dissolving it in a minimum amount of hot isopropyl or other suitable alcohol, and then chilling to produce crystals. These crystals of procaine n-hexyl sulphonate are hygroscopic, and melt at about 84–87° C., uncorrected.

Example 2.—Instead of using n-hexyl sulphonic acid as in Example 1, I may use any of the following sulphonic acids, in amounts substantially molecularly equivalent to the amount of n-hexyl sulphonic acid given in Example 1:

n-Butyl sulphonic acid,
1-methyl-butyl sulphonic acid,
n-Hexyl sulphonic acid,
1-methyl-pentyl sulphonic acid,
1,3-dimethyl-butyl sulphonic acid,
2-ethyl-butyl sulphonic acid,
n-Heptyl sulphonic acid,
2,4-dimethyl-pentyl sulphonic acid,
1-methyl-heptyl sulphonic acid,
2-ethyl-hexyl sulphonic acid,
n-Nonyl sulphonic acid,
Lauryl sulphonic acid,
Myristyl sulphonic acid,
Cetyl sulphonic acid,
Stearyl sulphonic acid, and
Oleyl sulphonic acid.

These sulphonic acids may all be made, by known process, with sodium sulphite and the respectively corresponding bromides or chlorides.

The procaine salts of these substituted sulphonic acids are sometimes obtained as solids, and sometimes obtained as viscous syrups. They are soluble in methyl, ethyl, and isopropyl alcohol, more soluble in water, somewhat soluble in oils, and relatively insoluble in ether.

The following are examples of these procaine aliphatic sulphonates;

Procaine n-butyl sulphonate,
Melts at about 121 to 122° C., uncorrected.
Procaine n-amyl sulphonate,
Melts at about 106.5 to 107.5° C.
Procaine 1-methyl-butyl sulphonate,
Obtained as a syrup.
Procaine 2-ethyl-butyl sulphonate,
Melts at about 118 to 119.5° C.
Procaine n-heptyl sulphonate,
Obtained as a syrup.
Procaine 2,4-dimethyl-pentyl sulphonate,
Melts at about 70–72° C.
Procaine 1-methyl-heptyl sulphonate,
Melts at about 76–78° C.
Procaine myristyl sulphonate,
Melts at about 86–90° C.
Procaine lauryl sulphonate,
Obtained as whitish crystals.

Example 3.—Instead of using procaine as the organic base, as in Examples 1 and 2, I may use γ -[2-methyl-piperidinol]-propyl benzoate. This will react, in the same general manner as does procaine, with the various aliphatic substituted sulphonic acids, to produce γ -[2-methyl-piperidinol]-propyl-benzoate aliphatic sulphonates. As an example of this reaction, I dissolve one molecular proportion of γ -[2-methyl-piperidinol]-propyl benzoate in ethyl ether, and dissolve in a separate portion of ether slightly more than one

molecular proportion of n-hexyl sulphonic acid. I then pour the ethereal solution of the sulphonic acid slowly with stirring into the ethereal solution of the γ -[2-methyl-piperidinol]-propyl benzoate. Reaction occurs between the γ -[2-methyl-piperidinol]-propyl benzoate and the n-hexyl sulphonic acid, and the desired γ -[2-methyl-piperidinol]-propyl-benzoate-n-hexyl sulphonate which is formed separates out to form a sticky precipitate. This is separated from the supernatant liquid and washed many times with ether. It is then dried under vacuo, forming a viscous syrup.

Example 4.—Instead of using n-hexyl sulphonic acid as in Example 3, I may use n-nonyl sulphonic acid to react with the γ -[2-methyl-piperidinol]-propyl benzoate. This also produces a sticky precipitate, of γ -[2-methyl-piperidinol]-propyl benzoate-n-nonyl sulphonate.

Example 5.—Instead of using procaine or γ -[2-methyl-piperidinol]-propyl benzoate as the organic base, I may use cocaine. For example, 2 grams of cocaine may be dissolved in 100 cc. of anhydrous ether. This may be chilled in an ice bath, and to it is added slowly, with stirring, 1 gram of n-amyl sulphonic acid dissolved in 20 cc. of anhydrous ether. A precipitate forms, which is cocaine-n-amyl sulphonate. This solid is separated, and recrystallized in a solution of alcohol and ether, to obtain whitish crystals which are hygroscopic and water-soluble.

Example 6.—Instead of using procaine, γ -[2-methyl-piperidinol]-propyl benzoate, or cocaine, I may use p-aminobenzoyl-dimethylamino-methylbutanol. I dissolve one molecular proportion of p-aminobenzoyl-dimethylamino-methylbutanol in ether, cool this solution, and add to it slowly, with stirring, more than a molecular proportion of n-hexyl sulphonic acid dissolved in ether. A reaction occurs, and the p-aminobenzoyl-dimethylamino-methylbutanol-n-hexyl sulphonate separates out, either in syrupy form or by careful manipulation as a non-crystalline solid.

Example 7.—Instead of using the local-anesthetic organic bases specifically named in Examples 1 to 6 inclusive, other local-anesthetic organic bases may be used as the organic base, as has been indicated in the list already given. These are caused to react with the desired aliphatic sulphonic acid in the general manner of Examples 1–6, with the aliphatic sulphonic acid in solution in anhydrous ether, and with the local-anesthetic organic base also in solution in ether. The reaction between the aliphatic sulphonic acid and the local-anesthetic organic base produces precipitates, sometimes as solids and sometimes as viscous syrups, which are readily separable from the supernatant liquid, as by filtration or decantation.

Among the aliphatic sulphonates thus obtainable are those of the following local-anesthetic organic bases:

Monoisobutylaminoethyl-p-aminobenzoate,
p-Aminobenzoyl- γ -di-n-butylaminopropanol,
p-Aminobenzoyl-2,2-dimethyl-3-diethylaminopropanol,
Piperidinopropanediol-di-phenylurethane,
2-butyloxyquinolinecarboxylic acid-4-diethylethylene-diamide, and
 γ -Diethylaminopropylcinnamate.

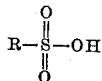
These aliphatic sulphonates of local anesthetic bases are in general either white or whitish solids, or viscous syrups; and are soluble in water, and relatively insoluble in ether. Those which are

obtained in solid form may be purified by recrystallization, in a manner already indicated for other aliphatic sulphonates.

These aliphatic sulphonates of local-anesthetic organic bases all have local-anesthetic actions, corresponding in general to the actions of the local-anesthetic organic bases from which they are derived.

I claim as my invention:

1. A local-anesthetic salt of an aliphatic sul-
phonic acid which has the formula:



in which R represents an aliphatic hydrocarbon

substituent which has between four and eighteen carbon atoms and is of the class consisting of primary straight-chain and primary branched-chain and secondary groups and has one of its carbon atoms directly linked to the sulphur atom of the sulphonic-acid group, and of a local-anesthetic which is an ester of a nitrogeous alcohol and a benzoic acid.

2. A local-anesthetic salt as set forth in claim 1, in which the ester is cocaine.

3. A local-anesthetic salt as set forth in claim 1, in which the ester is procaine.

4. A local-anesthetic salt as set forth in claim 1, in which the ester is γ -12-methyl-piperidinol-propyl benzoate.

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