

UNITED STATES PATENT OFFICE

2,129,376

OIL-SOLUBLE MERCURIALS AND PROCESS
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Lilly and Company, Indianapolis, Ind., a corpo-
ration of IndianaNo Drawing. Application September 23, 1936,
Serial No. 102,161

12 Claims. (Cl. 260—505)

My invention relates to oil-soluble substituted-ammonium salts of acidic organo-mercuric compounds, and their production from oil-insoluble or relatively oil-insoluble acidic organo-mercuric compounds.

There are many acidic organo-mercuric compounds which are of therapeutic value, but which are oil-insoluble or very nearly so not only in themselves but particularly so in the form of ordinary salts; and that oil-insolubility limits their therapeutic use.

Among those acidic organo-mercuric compounds are organo-mercuric derivatives of organic acids which contain one or more carboxyl or sulfonic-acid groups, as well as organo-mercuric compounds which though they do not contain a carboxyl or sulfonic-acid group nevertheless do contain an ionizable hydrogen replaceable in a water solution by an alkali metal.

I have discovered that such oil-insoluble or relatively oil-insoluble organo-mercuric compounds which contain a carboxyl or a sulfonic-acid group or an ionizable hydrogen may be made oil-soluble, or more oil-soluble if they already have some oil solubility, by forming salts of them with certain long-chain aliphatic amines, preferably saturated alkyl amines, containing between 6 and 18 carbon atoms in the alkyl radical. Such alkyl radicals may be either straight or branched, saturated or unsaturated. The amine may be either primary, secondary, or tertiary; and while the number of carbon atoms in any single substituent may be smaller with secondary and tertiary amines than with primary amines for comparably good results, in all cases there should be at least six carbon atoms in at least one substituent.

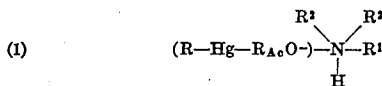
By this procedure, I am able to produce oil-soluble organo-mercuric compounds which have substantially the same therapeutic effectiveness as do the oil-insoluble organo-mercuric compounds from which they are derived but which in addition are soluble not only in such vegetable oils as cottonseed oil and olive oil, but also, and of even more importance, in mineral oils, both light and heavy.

In forming my oil-soluble substituted-ammonium salts of these acidic organo-mercuric compounds, I suspend the initial organo-mercuric compound in mineral oil, and add to it the desired long-chain alkyl amine. A reaction between them occurs, usually in the cold, to form the desired oil-soluble compound and thus change the suspension into a solution; although in some in-

stances, where the reaction is slow, it is desirable to facilitate it by warming.

The substituted-ammonium salts which are thus formed are different in character from the alkali or alkaline-earth metal salts of the same initial organo-mercuric substances, in their oil-solubility; for the metal salts are in general fairly oil-insoluble, even though they may be water-soluble.

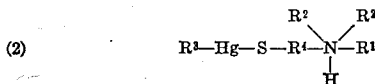
My new compounds may be represented by the following general formula:



in which R represents a univalent negative substituent, whether atom or radical, that may combine with mercury, preferably an alkyl radical; $R_{Ac}O^-$ represents an organic-acidic radical that has an oxygen atom by which it is capable of combining with hydrogen to form an acid or with a basic atom or radical to form a salt; R^1 represents an alkyl radical, whether straight-chain or branched-chain, having between 6 and 18 carbon atoms; and each R^2 represents a univalent substituent of the class consisting of hydrogen and the alkyl radicals.

The following are examples:

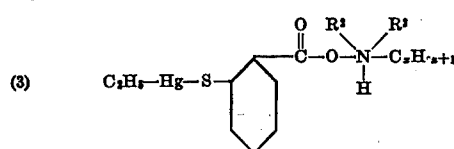
Example 1.—Any of the alkyl-mercuric-sulfur compounds of the type set forth in my prior Patent No. 1,672,615, granted June 5, 1928, may be made oil-soluble by being combined with any of the long-chain alkyl amines of the type above defined, in which there is an alkyl radical having between 6 and 18 carbon atoms. The resultant compounds are represented by the following general formula:



in which R^1 and R^2 have the same significance as before, R^3 represents an alkyl radical, and R^4 represents an organic radical having an oxygen-containing acid group (carboxyl or otherwise) which has a free valence bond capable of being attached either to hydrogen to form an acid or to a metal or an amine to form a salt of such acid, and in which R^3 and R^4 have carbon atoms bonded directly to the mercury atom and to the sulfur atom respectively. Thus by my invention I combine a long-chain alkyl amine of the type defined with an oxygen atom of R^4 to form the substituted-ammonium salts.

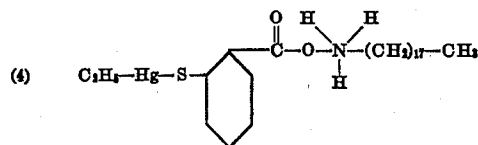
An instance of this is a substituted-ammonium

salt of ethylmercurithiosalicylic acid; the sodium salt of which acid is on the market under the trade-mark "Merthiolate." Both ethylmercurithiosalicylic acid and its sodium salt are substantially oil-insoluble. I form a suspension of such ethylmercurithiosalicylic acid in mineral oil, and add to it the desired long-chain alkyl amine. For example, I may use heptadecyl, stearyl, N-dimethyl stearyl, N-diethyl-stearyl, lauryl, hexyl, iso-hexyl, heptyl, or a secondary-octyl amine. The amines of which these are examples combine with the ethylmercurithiosalicylic acid to form compounds which may be represented by the following formula:

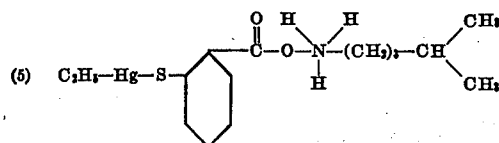


where R^2 has the same significance as before, and x represents an integer between 6 and 18 inclusive.

Thus if the amine is stearyl amine, for instance, the formula of the resultant substituted-ammonium salt of ethylmercurithiosalicylic acid has the following formula:

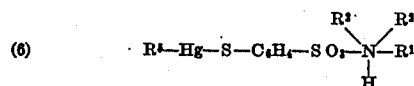


If the amine is isohexyl amine, as another instance, the resultant substituted-ammonium salt of ethylmercurithiosalicylic acid has the following general formula:

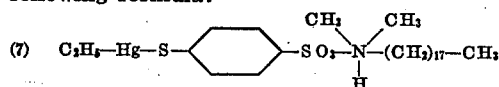


These compounds, of Formulas 4 and 5 for example, are quite readily soluble in cottonseed oil, olive oil, and mineral oil; and are very effective bactericidal and fungicidal agents.

Another instance of alkyl-mercuric-sulfur compounds of my Patent No. 1,672,615 are the alkyl-mercurisulfobenzene sulfonic acids. When a suspension of such an acid is formed in mineral oil, and a long-chain alkyl amine added, a substituted-ammonium salt is formed that is oil-soluble and that has the following general formula:



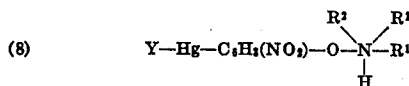
in which R^1 represents an alkyl radical, and R^2 and R^3 have the same significance as before. If the amine is N-dimethyl-stearyl amine, and the acid is p-ethylmercurisulfobenzene sulfonic acid, the resultant substituted-ammonium salt has the following formula:



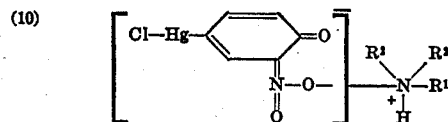
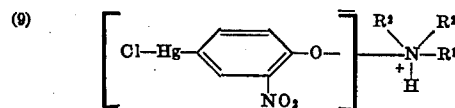
Example 2.—Instead of using a carboxylic or sulfonic acid as the organo-mercury compound to be solubilized, I may use organo-mercury substances which though they are acidic in solution

and have a replaceable hydrogen attached to oxygen are ordinarily not classed as true acids.

Among them are the mercury compounds of the nitrophenols and of substituted nitrophenols, especially of ortho- and para-nitrophenols. With the long-chain alkyl amines they form salts one of the tautomers of which can be represented by the following general formula:



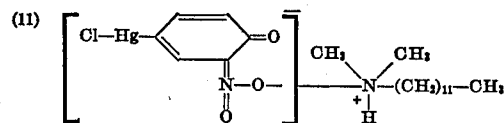
in which Y represents a member of the class consisting of hydroxyl and the halogens, and R^1 and R^2 have the same significance as before. For instance, o-nitrophenol-p-mercuric chloride is a bactericidal agent of some merit, and is substantially oil-insoluble. If a suspension of it is formed in a suitable oil, such as mineral oil or olive oil, and a long-chain alkyl amine added, preferably a tertiary amine, there is a reaction which changes the suspension into a solution by the formation of the corresponding substituted-ammonium salt of the initial compound. Formulas 9 and 10 below represent the possible tautomeric forms of the salt.



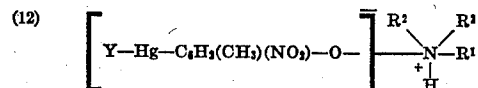
in which R^1 and R^2 have the same significance as before.

Formula 10 is the preferred structure for ortho- and para-nitrophenols, while Formula 9 is usually preferred in the case of the meta-nitrophenols or substituted meta-nitrophenols.

Thus, if the amine is N-dimethyl-lauryl amine, a formula of the resultant tautomeric salt is as follows:

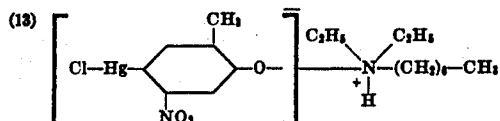


Also among these acidic organo-mercuric compounds which may be made soluble by my invention are the mercury compounds of the nitrocresols. With long-chain alkyl amines they form compounds of the following general formula:



in which Y, R^1 , and R^2 have the same significance as before. An instance of these is 5-nitro-4-chloromercuriorthocresol. When a suspension of this is formed in oil, such as mineral oil or olive oil or cottonseed oil, and the desired long-chain alkyl amine added to it, there results an oil-soluble substituted-ammonium salt of the initial 5-nitro-4-chloromercuriorthocresol. It should be borne in mind that the weaker the acidic properties of the initial organo-mercuric compound, the greater the desirability of a stronger base of the long-chain amine type. So it is desirable in this instance to employ a tertiary long-chain amine of the type of N-dimethyl stearyl amine or N-diethyl heptyl amine. If N-diethyl heptyl amine

is the amine used, the resultant compound is represented by the following formula:



In all the foregoing examples, the substituted-ammonium salt has been formed in oil solution. Such a solution may be used as such, in whatever oil is desired as the solvent.

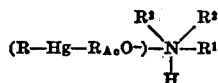
If, however, it is desired to obtain the substituted-ammonium salt in solid form, that can readily be done by carrying out the reaction in a low-boiling hydrocarbon solvent, such as ligroin for example, instead of in the oil desired for the solution; and the salt may be obtained upon evaporation of the hydrocarbon solvent.

In such event, the initial organo-mercury compound is suspended in the ligroin, or other low-boiling hydrocarbon solvent, and the desired long-chain alkyl amine is added thereto. A reaction ensues, and the substituted-ammonium salt of the organo-mercury compound is formed. This salt is soluble in the ligroin. Upon evaporation of the solvent, the salt is obtained in solid form.

Similarly, instead of using a low-boiling hydrocarbon as the solvent, other organic solvents may be used; such for example as ether or acetone.

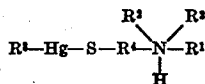
I claim as my invention:

1. An oil-soluble salt of an organo-mercury compound, having the following general formula:



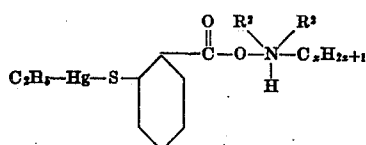
in which R represents a member of the class consisting of the lower alkyls, hydroxyl, and the halogens; R_AO^- represents a non-metal benzenoid radical that has an oxygen atom by which it is capable of combining with hydrogen or with a basic atom or radical; R^1 represents an alkyl radical having between 6 and 18 carbon atoms; and each R^2 represents a member of the class consisting of hydrogen and the lower alkyl radicals.

2. An oil-soluble salt of an alkyl-mercuric-sulfur compound, having the following general formula:



in which R^1 represents an alkyl radical having between 6 and 18 carbon atoms; each R^2 represents a univalent substituent of the class consisting of hydrogen and the alkyl radicals; R^3 represents an alkyl radical; and R^4 represents a non-metallic benzenoid radical having an acid oxygen-containing group which has a free valence bond capable of being attached either to hydrogen or to a metal or an amine, and in which R^3 and R^4 have carbon atoms bonded directly to the mercury atom and to the sulfur atom respectively.

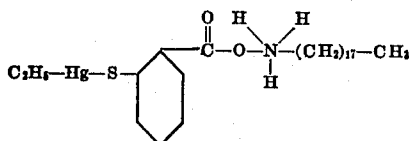
3. An oil-soluble salt of ethylmercurithiosalicylic acid, having the following general formula:



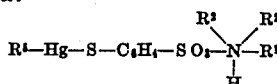
in which each R^2 represents a member of the class consisting of hydrogen and the lower alkyl

radicals, and x represents an integer between 6 and 18 inclusive.

4. The stearyl-amine salt of ethylmercurithiosalicylic acid, having the following general formula:

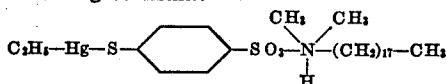


5. An oil-soluble salt of an alkyl-mercurisulfobenzene sulfonic acid, having the following general formula:

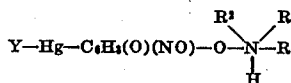


in which R^1 represents an alkyl radical, R^2 represents an alkyl radical having between 6 and 18 carbon atoms, and each R^3 represents a member of the class consisting of hydrogen and the lower alkyl radicals.

6. The N-dimethylstearyl amine salt of p-ethylmercurisulfobenzene sulfonic acid, having the following formula:

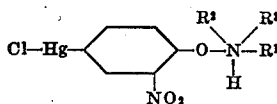


7. An oil-soluble salt of a mercuri-nitrophenol, having the following general formula:



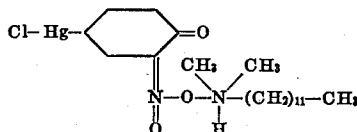
in which R^1 represents an alkyl radical having between 6 and 18 carbon atoms, each R^2 represents a member of the class consisting of hydrogen and the lower alkyl radicals, and Y represents a member of the class consisting of hydroxyl and the halogens.

8. An oil-soluble salt of o-nitrophenol-p-mercuric chloride, having the following formula:

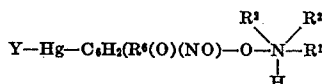


in which R^1 represents an alkyl radical having between 6 and 18 carbon atoms, and each R^2 represents a member of the class consisting of hydrogen and the lower alkyl radicals.

9. An oil soluble salt of o-nitrophenol-p-mercuric chloride having the following formula:



10. An oil-soluble salt of a nitro-organo-mercury compound, having the following general formula:



in which R^1 represents an alkyl radical having between 6 and 18 carbon atoms, each R^2 represents a member of the class consisting of hydrogen and the lower alkyl radicals, R^4 represents a member of the class consisting of hydrogen and the methyl group, and Y represents a member of

the class consisting of hydroxyl and the halogens.

11. The process of forming an oil-soluble salt of an organo-mercury compound, which consists in bringing together in a non-aqueous liquid a relatively oil-insoluble benzenoid organo-mercury compound that has an oxygen atom which is capable of combining with hydrogen or with a basic atom or radical, and a long-chain alkyl amine having a substituent alkyl radical containing between 6 and 18 carbon atoms.

12. The process of forming an oil-soluble salt of an organo-mercury compound, which consists in bringing together in a non-aqueous liquid a relatively oil-insoluble benzenoid organo-mercury compound having acidic properties and that has an oxygen atom which is capable of combining with hydrogen or with a basic atom or radical, and a long-chain alkyl amine having a substituent radical containing between 6 and 18 carbon atoms.

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