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THERAPEUTIC COMPOSITIONS

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This invention relates to improvements in the production of halogenated esters of vegetable fatty acids. It includes new halogenated esters as well as processes by which they are advantageously produced.

Halogenated vegetable oils, such as iodized or brominated oils, are used as contrast media for roentgenographic (X-ray) work. For such purposes, the oils are injected into the body cavities, such as the lungs, sinuses, etc. As the halogenated oils are opaque to Roentgen or X-rays, they permit the taking of shadow pictures. Brominated vegetable oils, besides being useful for X-ray diagnostic work, are useful for the treatment of chronic bronchitis, certain types of asthma, and in place of bromides as sedatives acting gradually and over a long period of time.

The new halogenated esters of vegetable oil fatty acids of the present invention are useful for much the same purposes as the previously known brominated vegetable oils but have important advantages, including greatly increased stability as compared with the previously known brominated oils. As it is important that halogenated oils and the like, when used, be free from any appreciable amount of free halogen or free acid, the increased stability of the new products of this invention makes them particularly advantageous for therapeutic and diagnostic use.

In accordance with the present invention, non-drying vegetable oils, containing, in combined form, a substantial proportion of unsaturated fatty acids, such as sunflower seed oil, corn oil, walnut oil, soya bean oil, sesame oil, etc., or the lower alkyl esters, including the methyl, ethyl, propyl, etc. esters, of the fatty acids derived from such vegetable oils, are caused to react with or absorb both bromine and chlorine, with production of bromo-chloro compounds, containing both bromine and chlorine in organic combination. By causing the esters of the fatty acids of such oils to combine with chlorine as well as bromine, a brominated oil or ester having greater stability than previously known, brominated oils is produced.

The proportions of bromine and chlorine which may be combined with the oils or esters in preparing the new products of the present invention may be varied over a relatively wide range, with the production of products having somewhat different characteristics, depending upon the amount of combined halogen, but all having increased stability as compared with simple brominated oils or esters of comparable bromine content. Where the products are intended for

use as sedatives in place of bromides or the like, the amount of combined bromine may be around 10% or somewhat less, and the amount of combined chlorine a small fraction, for example 1%, of the amount of combined bromine. For other purposes, particularly for use as a contrast medium in bronchography, bronchiectasis, or for myelography, oils or esters of higher specific gravity, containing, for example, around 35% or somewhat more bromine and 3% or somewhat more chlorine in organic combination are used with advantage.

In general, the halogenated glycerides are more viscous and of greater specific gravity than the halogenated esters, such as the bromo-chloro ethyl esters, and hence have advantages where high viscosity is desired, for example, in making X-ray pictures of the lungs. The bromo-chloro ethyl esters of the sunflower seed, walnut seed, corn or soya bean oil fatty acids have an unusually low viscosity, less than that of water, approaching the viscosity of body fluids, and hence have important advantages for use where a halogenated oil of low viscosity is desired.

The invention will be further illustrated by the following specific examples, but it is not limited thereto.

Example 1.—2000 parts of sunflower seed oil, neutralized and purified by treatment with cold alcoholic caustic potash, are placed in a suitable vessel equipped with a mechanical stirrer and two dropping funnels. 1000 parts of dry ether are added and the stirring is started. 1000 parts of a freshly prepared chloro-bromine mixture (10% of chlorine in bromine) are gradually added through the dropping devices with constant stirring while maintaining the temperature of the mixture at about 0 to 5° C. The chloro-bromine mixture is added over a period of eight hours or more. When this addition is completed, stirring is continued for another hour. The reaction product is then poured into 2000 parts of ethylene dichloride and is washed repeatedly with water until the washings no longer give any reaction with brom phenol blue. The solution is then separated from the water and dried over anhydrous sodium sulfate. After drying, the solvent is removed by distillation under reduced pressure while maintaining the temperature below about 45° C. 1% of neutralized and purified sunflower seed oil is then added to the product to absorb any hydrohalide which may be liberated during storage. For storage and distribution, the final product is bottled under nitrogen in amber bottles.

This product is fairly viscous, is pale yellow in color and has an oleaginous taste and odor. It is soluble in ether, benzene and chloroform but is insoluble in alcohol and water. It contains an extremely small amount of free acid and free halogen. Treatment of the oil with concentrated sulfuric acid liberates the chlorine and bromine.

The product is quite stable. It is an excellent contrast medium for roentgenographic work and is useful for other therapeutic purposes.

Example 2.—1000 parts of sunflower seed oil are placed in a suitable vessel equipped with a reflux condenser and a mixture of 2000 parts of ethyl alcohol and 50 parts of concentrated sulfuric acid are added. The mixture is refluxed for 15 hours on a steam bath. On standing, the reaction mixture separates into two layers. The oily layer is decanted and is repeatedly washed with saturated salt solution until the washings no longer give an acid reaction with Congo red paper. The ester so produced is dried for two days over anhydrous sodium sulfate and is finally purified by distillation under reduced pressure. The pressure used in the distillation should be less than 10 mm. to prevent decomposition. These ethyl esters boil at 180–230° C./2–3 mm. The product is a very light colored, oily liquid.

2000 parts of the ethyl esters of sunflower seed oil fatty acids, produced as described, are placed in a vessel provided with a mechanical stirrer and two dropping funnels. 1000 parts of dry ether are added and the mixture is cooled to about 5° C. by the use of an ice bath. The stirrer is started, and 1000 parts of a chloro-bromine mixture (10% chlorine in bromine) are added through the dropping devices slowly, with as good dispersion of the halogen through the oil as possible. The temperature of the reaction mixture should not be allowed to exceed 10° C., and the addition of the 1000 parts of the chloro-bromine mixture should require six hours or more. After all of the halogen has been added, stirring is continued about one hour longer. The reaction mixture then poured into 2000 parts of ethylene dichloride and is repeatedly washed with water until the washings no longer give a reaction with brom phenol blue. The product is then dried over anhydrous sodium sulfate, filtered, and the solvent is distilled off under a reduced pressure, with the temperature advantageously maintained below 40° C. After the removal of all of the solvent, the oil is placed in amber bottles under nitrogen.

The product has an unusually low viscosity, less than that of water, approaching the viscosity of the body fluids. It has a specific gravity of about 1.15. It contains extremely little free acid or free halogen and is non-irritating to mucous membranes. It contains about 30% of bromine and 3% of chlorine in organic combination. It is a pale yellow color, has an oleaginous taste, is soluble in benzene, ether and chloroform, slightly soluble in alcohol and insoluble in water.

The product is an excellent contrast medium for roentgenographic work, and because of its low viscosity, is of value for introduction into body cavities difficultly injectable by oils of relatively high viscosity.

The proportions of combined bromine and chlorine in the new products may be varied over a relatively wide range, depending upon the properties desired. In the examples given, products

containing 30% or more of combined halogen (10% chlorine on the bromine) are described. Other useful products may be produced in substantially the same way, with the use of different proportions of ester and halogen, or different proportions of bromine and chlorine, such products having the same improved stability. For example, the products may contain from 10% or less combined bromine to 35% or more combined bromine, and from ½% or less combined chlorine to 3 to 5% or even more combined chlorine. The viscosity, opacity to X-rays, therapeutic properties, etc., will naturally vary with the content of combined halogen; but all will have increased stability because of the inclusion of combined chlorine. Also, the bromine and chlorine need not be added simultaneously or in admixture, but may be reacted separately with the esters, with the production of products containing both combined chlorine and bromine, although the simultaneous addition of the chlorine and bromine is advantageous.

It will, of course, be understood that other oils than sunflower seed oils, such as other non-drying oils containing a substantial proportion of esters derived from unsaturated fatty acids, including corn oil, walnut oil, soya bean oil, sesame oil, etc., or the alkyl esters of the fatty acids of such vegetable oils, may be used with the production of corresponding halogenated products. However, products derived from sunflower seed oil and the ethyl esters of sunflower seed oil fatty acids have important advantages over products derived from such other oils or esters.

I claim:

1. As new products, alkyl esters of fatty acids of non-drying vegetable oils organically combined with bromine and chlorine, the amount of combined chlorine not exceeding 10% of the amount of combined bromine.

2. As new products, non-drying vegetable oils organically combined with bromine and chlorine, the amount of combined chlorine not exceeding 10% of the amount of combined bromine.

3. As new products, ethyl esters of fatty acids of non-drying vegetable oils combined with bromine and chlorine, the amount of combined chlorine not exceeding 10% of the amount of combined bromine.

4. As new products, non-drying vegetable oils organically combined with about 30% bromine and about 3% chlorine.

5. Sunflower seed oil organically combined with bromine and chlorine, the amount of combined chlorine not exceeding 10% of the amount of combined bromine.

6. Ethyl esters of the fatty acids of sunflower seed oil organically combined with chlorine and bromine, the amount of combined chlorine not exceeding 10% of the amount of combined bromine.

7. Walnut seed oil organically combined with bromine and chlorine, the amount of combined chlorine not exceeding 10% of the amount of combined bromine.

8. As new products, compounds of the class consisting of non-drying vegetable oils and alkyl esters of fatty acids of non-drying vegetable oils organically combined with bromine and chlorine, the amount of combined chlorine not exceeding 10% of the amount of combined bromine.

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