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METHOD OF BONDING BODY TISSUE TOGETHER USING METHYLENEMALONIC ACID ESTERS

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This application is a continuation-in-part of our co-pending application Serial No. 63,463, filed October 19, 1960, now abandoned.

This invention relates to a method for the surgical bonding of tissues by the use of a rapid-setting adhesive composition and to novel adhesive compositions adapted for surgical use. More particularly, it relates to the surgical use of novel compositions comprising monomeric dialkyl esters of methylenemalonic acid.

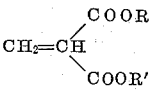
The usual methods for closing incisions in flesh and for setting bone fractures, by the use of sutures, clamps, pins or the like, have many drawbacks. The use of an adhesive substance for these surgical purposes has the advantage of permitting rapid joining of the damaged members and of permitting natural healing. However, the common adhesives are unsuitable for surgical purposes. Most adhesives need too much time to form a bond. Many require the use of heat or pressure or the evaporation of a solvent, all of which make them unsuitable as surgical adhesives. Furthermore, many adhesives, including some that might otherwise be suitable for surgical use, are irritating to the body tissues.

The present invention is based on our discovery that monomeric dialkyl esters of methylenemalonic acid are unexpectedly useful for bonding living tissues. We have, accordingly, developed a novel method for the surgical bonding of tissue with such esters and novel surgical adhesive compositions containing such esters. Without the use of heat or pressure, our novel compositions form rapid-setting bonds of sufficient strength for closing flesh incisions, setting bones, etc. The novel adhesive compositions form bonds that do not interfere with natural healing and that are assimilated by the body without toxic effects. Other advantages will appear in the discussion hereinafter.

The method of our invention for bonding separated surfaces of body tissues, in general, comprises applying to at least one of such surfaces a thin film of an adhesive composition comprising a monomeric dialkyl ester of methylenemalonic acid, bringing together the surfaces to be bonded and polymerizing the thin film of monomer while in contact with both of the surfaces.

The adhesive compositions of the invention comprise, as the major active constituent, a monomeric dialkyl ester of methylenemalonic acid prepared in high purity, preferably in admixture with one or more substances, such as, an acidic polymerization inhibitor, an antiseptic, a thickening agent, a plasticizer or the like, adapted to improve the surgical utility of the monomer.

The esters of methylenemalonic acid that are effective in accordance with the invention are represented by the formula:



wherein R and R′ are the same or different alkyl radicals of 1 to about 8 carbon atoms. Typical examples of such monomeric esters that can be employed in accordance with the invention include dimethyl methylenemalonate, diethyl methylenemalonate, di-n-propyl methylenemalonate, diisobutyl methylenemalonate, methyl ethyl methylenemalonate, di-n-butyl methylenemalonate, di-n-amyl methylenemalonate, di-2-ethylhexyl methylenemalonate, di-n-octyl methylenemalonate, methyl n-octyl methylenemalonate and related esters of methylenemalonic acid.

Descriptions of the preparation of dialkyl methylenemalonates are in the literature. However, the standard procedures yield products that are not useful as adhesives. We have found that for use as a surgical adhesive the methylenemalonate monomer must be synthesized in high purity. Even though the monomer is later blended with other substances to form an adhesive composition it should be synthesized initially in high purity. If the monomer is synthesized even with small amounts of impurities that influence polymerization the adhesive utility will be impaired. Acidic impurities prevent the anionic polymerization of the monomers and lead to sluggish or ineffective adhesive activity. Basic impurities accelerate the anionic polymerization and lead to products that are unstable and useless as adhesives because they polymerize prematurely. The preferred surgical compositions of the invention comprise the methylenemalonate monomer synthesized in such a manner as to contain no more than about 100 parts by weight of impurities per million parts of monomer (abbreviated hereinafter as "p.p.m."). The especially preferred compositions of the highest adhesive activity for surgical purposes comprise the methylenemalonate monomer synthesized so as to contain no more than 10 p.p.m. of impurities that accelerate or retard polymerization. The monomer can be blended with minor amounts of additives, as discussed hereinafter, to form compositions comprising methylenemalonate monomers as the major component. In such compositions the monomer is preferably at least about 75 weight percent of the composition. Even in such mixtures, the monomer must have been prepared in high purity, preferably with less than 100 p.p.m. impurities.

Our preferred method for preparing the high purity monomeric esters having utility as surgical adhesives is a modification of the method described in Organic Syntheses, vol. 38, pages 22–25 (John Wiley and Sons, Inc., New York, 1958). Our modification of the procedure produces monomeric methylenemalonates of a quality that has not previously been reported.

In our preferred method the monomeric esters are prepared by hydrogenating the olefinic bond of a dialkyl alkoxy-methylenemalonate and pyrolyzing the reaction product. The reactions can be represented by the following equations:

(1)
$$CH_2CH_2OCH{=}C\left(\begin{matrix}O\\ \|\\ C{-}OR\end{matrix}\right)_2 \xrightarrow{H_2} CH_3CH_2OCH_2CH\left(\begin{matrix}O\\ \|\\ C{-}OR\end{matrix}\right)$$

(2)
$$CH_3CH_2OCH_2CH\left(\begin{matrix}O\\ \|\\ C{-}OR\end{matrix}\right)_2 \xrightarrow{\Delta}$$
$$CH_2{=}C\left(\begin{matrix}O\\ \|\\ C{-}OR\end{matrix}\right)_2 + CH_3CH_2OH$$

Suitable hydrogenation catalysts for reaction (1) include Raney nickel, palladium on an alumina support, and other hydrogenation catalysts adapted to hydrogenate selectively the olefinic double bonds of unsaturated carbonyl compounds rather than the carbonyl double bonds. In our improved method the pyrolysis reaction (2) is effected in the presence of a polymerization inhibitor, such as phosphorous pentoxide, to inhibit polymerization of the unsaturated monomer and the pyrolysis product is vacuum distilled at a low temperature to prevent contamination of the monomer with pyrolytic products that commonly result from high temperature distillation.

The important differences between our improved method of preparation and the method of the Organic Syntheses citation include the use of a polymerization in-