This invention relates to an improved method for the production of diethyl isonitrosomalonate and diethyl acetylacetonate. It relates in particular to a method in which diethyl isonitrosomalonate may be obtained in crystalline form, if desired, but in which diethyl acetylacetonate may be obtained from malonic ester without necessity for isolation or purification of any intermediate, should this be desired.

The chemical literature is replete with disclosures of various ways in which diethyl acetylacetonate may be made from malonic ester. These methods involve, in sequence, the nitrosation of malonic ester, reduction of the isonitrosocompound, and acetylation of the resulting amine. A yield of diethyl isonitrosomalonate as high as 90 percent is reported. Reduction of the isonitrosocompound to the amine should proceed quantitatively, yet there are reports of 47 and 65 percent yields of the amine, based on the original malonic ester. While other reports indicate that high overall yields of the diethyl acetylacetonate have been attained at times in the laboratory, it has been applicants’ experience that the prior processes give overall yields of diethyl acetylacetonate from diethyl malonate of the order of 50 percent when carried out on a commercial scale, and this confirms some of the results reported in the literature. The difficulty is traceable principally to the quality of the isonitrosocompound produced by the prior methods. The diethyl isonitrosomalonate has been reported to be an oily liquid. It has been found, in carefully controlled operations, that the oily form of the isonitrosocompound does not absorb the theoretical amount of hydrogen, when it is attempted to convert it to the amine. This is an indication that the oil has constituents other than the isonitrosocompound. It has now been found that this compound, when pure, is a crystalline solid. Hence, yield calculations based on the weight of an allegedly pure but actually impure oil are unreliable.

In any event, it is desired, and it is the object of this invention, to provide a method which may be used in large scale operations to convert malonic ester to diethyl acetylacetonate in high yields. A related object is to provide a method in which diethyl isonitrosomalonate may be obtained in crystalline form. Another object is to provide a method whereby malonic ester may be converted to diethyl acetylacetonate in good yield without necessity for isolating either of the intermediate products.

In accordance with the present invention, the foregoing and related objects are attained by carrying out at least the nitrosation step of the process and preferably all of the series of reactions, in an inert solvent for diethyl malonate, diethyl isonitrosomalonate, diethyl acetylacetonate, and diethyl acetylacetonate which is separable from the desired product by distillation and which is not appreciably miscible with water. Examples of suitable solvents are methylene chloride, methylene bromide, chloroform, carbon tetrachloride, ethylene chloride, ethylene bromide, ethylene chlorobromide, the trichloroethanes, the tetrachloroethanes, pentachloroethene, trichloroethylene, perchloroethylene, the monochloro propanes, propylene chloride, benzene, toluene, the xylenes, ethyl benzene, monochlorobenzene, monobromobenzene, orthodichlorobenzene, and the monochlorotoluenes. Of these, the bromo- and chloroaliphatic hydrocarbons, aromatic hydrocarbons (including alkyl aromatic hydrocarbons) and the chloroaromatic hydrocarbons having boiling points at atmospheric pressure between 40° and 150° C. are preferred. Toluene is a most convenient solvent for use in the method of the present invention.

In carrying out the reaction, diethyl malonate is diluted with from one-third to its volume to about 3 times its volume of toluene, or other of the type of solvent suggested above (preferably not over about 1.6 times as much solvent as ester being used), and there is suspended in this solution enough sodium nitrite for the nitration reaction. It is preferred to use at least 1.25 mols of sodium nitrite per mol of ester. The sodium nitrite should contain (or the reaction should be carried out in the presence of) from 1 to 10, and preferably from 3 to 5 per cent by weight of water based on the weight of sodium nitrite. If less water is present, the reaction does not proceed satisfactorily, while, if more water is present, the disadvantages of the prior art processes are encountered, and yields are low in both cases. Glacial acetic acid is added gradually to the suspension of sodium nitrite in the toluene solution of diethyl malonate. The nitrous acid, liberated by the reaction between acetic acid and sodium nitrite in the presence of the stated limited amount of water, reacts smoothly with the diethylnitrosomalonate, and there is precipitated the by-product sodium acetate. When the nitrosation reaction is complete, the solution of diethyl isonitrosomalonate in toluene, or other water-immiscible solvent, is treated to remove sodium acetate.
The diethyl isonitrosomalonate can be crystallized from the toluene solution, if desired, by distilling part of the toluene to concentrate the solution, followed by chilling of the concentrated solution. Diethyl isonitrosomalonate is a white crystalline solid, melting at about 86.5° to 88° C. in the purity in which it has been obtained up to the present time.

The diethyl isonitrosomalonate need not be separated from the solution in which it is prepared, and this solution can be reduced to diethyl aminomalonate by the action of hydrogen over palladium-on-charcoal as the catalyst. After reduction, the solution of the ester of aminomalonic acid is filtered away from the catalyst. Acetic anhydride is added to the solution to acetylate the amine, and the reaction is effected in the presence of ice to prevent runaway temperatures. The diethyl acetamidomalonate is obtained in crystaline form, after the acetylation reaction, by concentration of its solution in toluene or other inert solvent and mixing the concentrate with water. The solvent may be recovered and reused in the process.

In attempts to carry out the process here concerned, under various conditions, the following observations were made. When all of the reagents are dry, the nitrosation reaction does not proceed satisfactorily, there is residual nitrous acid and sometimes residual sodium nitrite when the reaction should be complete, and the resulting solution of presumed diethyl isonitrosomalonate absorbs little hydrogen, often from 15 to 50 per cent of the amount theoretically required to form the amine. When there is over 10 per cent as much water as sodium nitrite, brown fumes of the oxides of nitrogen are evolved, showing low efficiency in the nitrosation and suggesting side reactions may be occurring, and a low yield of the desired isonitroso compound is obtained. When the required water is introduced along with the acetic acid by dilution of that reagent, the initial reaction rate is lower than when all the water is introduced at the start of the reaction. When the temperature of nitrosation is 30° C. or lower, there is little reaction, while at temperatures of 70° C. or higher the reaction does not produce the desired compound in yields of over 50 per cent in most cases, yet temperatures of 40° to 60° C. favor smooth, rapid reactions and good yields. The yields fall off somewhat from the preferred high level if the original malonic ester is dissolved in much more than 1:6 times its own volume of the water-immiscible inert solvent, and the advantage of using such a solvent is lost if its volume is much less than one-third that of the malonic ester.

The following examples illustrate both laboratory scale and commercial scale operation of the process.

**Example 1**

The following materials were mixed in a one-liter flask fitted with stirrer, thermometer, dropping funnel and reflux condenser:

<table>
<thead>
<tr>
<th></th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mol diethyl malonate</td>
<td>160</td>
</tr>
<tr>
<td>1.5 mols sodium nitrite</td>
<td>102.5</td>
</tr>
<tr>
<td>Water</td>
<td>930</td>
</tr>
<tr>
<td>Toluene</td>
<td>200</td>
</tr>
</tbody>
</table>

To this mixture, warmed to 40° C., there was added dropwise over the course of two hours 1.66 mols (100 g.) of glacial acetic acid. Periodic cooling was necessary to keep the temperature of the slightly exothermic reaction from exceeding 50° C. When all the acetic acid had been added, stirring was continued for another four hours. There was then added 200 ml. of water to dissolve the sodium acetate and unreacted nitrous acid. The toluene solution was separated from the aqueous layer and washed with dilute (3 per cent) sodium chloride solution. After separating the saline wash liquor, the toluene solution was hydrogenated at 30 to 50 pounds per square inch (gage) pressure at 40° to 50° C. over 5 per cent palladium-on-charcoal catalyst. The mixture took up 1.454 mols of hydrogen, or 94.1 per cent of the theoretical amount. The toluene solution was filtered away from the catalyst and was mixed thoroughly with 160 ml. of acetic anhydride. Sufficient ice was added to keep the temperature below 20° C. Most of the toluene was distilled away from the mixture, and 800 ml. of water was added to hydrolyze the excess acetic anhydride. The mixture was concentrated to 400 ml. volume under vacuum. Crystals separated during the concentration step and when the mixture was chilled a mass of crystals was obtained which weighed 146 grams after being washed with ice water and dried. Further concentration of the filtrates yielded an additional 16 grams of diethyl acetamidomalonate having a melting point of 57°–58° C. The total yield was thus 74.8 per cent of theoretical, based on the initial charge of malonic ester.

When the same charge was employed and the same nitrosation conditions were used, the toluene solution of diethyl isonitrosomalonate, after filtration to remove most of the sodium acetate, could be heated to distill part of the toluene and the remaining solution, on cooling, yielded successive crops of crystalline diethyl isonitrosomalonate. On recrystallization, it melted at 86.5–88° C.

**Example 2**

Into a 100-gallon glass-lined kettle there was charged:

<table>
<thead>
<tr>
<th></th>
<th>Pounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethyl malonate</td>
<td>160</td>
</tr>
<tr>
<td>Sodium nitrite</td>
<td>28</td>
</tr>
<tr>
<td>Water</td>
<td>4</td>
</tr>
<tr>
<td>Toluene</td>
<td>200</td>
</tr>
</tbody>
</table>

The mixture was stirred vigorously and was treated in the course of four hours with 100 pounds of glacial acetic acid, with the reaction temperature being held at 50°–57° C. Any liberated oxides of nitrogen were absorbed in a water-washed scrubbing tower. Stirring was continued an additional four hours at the same temperature. The mixture contained considerable undissolved sodium acetate, and this was removed by washing with 25 U. S. gallons of water and then with two successive batches of the same volume of 5 per cent salt solution. The organic layer was pumped to a stainless steel autoclave where it was mixed with 5 pounds of 5 per cent palladium-on-charcoal. The vessel was sealed, air was swept out with nitrogen, and the solution was hydrogenated at 50–100 pounds gauge pressure at 50° C. Hydrogenation proceeded so slowly that over 4 pounds of hydrogen had been absorbed in four hours. The toluene solution was filtered away from the catalyst and was mixed with 100 pounds of crushed ice and 100 pounds of acetic anhydride. The temperature did not rise above 30° C. After thorough mixing, toluene was removed at 35 millimeters absolute pressure. About 15 gallons of water was added and an additional 15 gallons of distillate removed, containing much
of the by-product acetic acid. The residue was cooled in a large steel tub, and diethyl acetamidomalonate crystallized out. The mixture stood overnight and the crystals were recovered in a centrifugal filter. After being washed with ice water, and dried, they weighed 167.5 pounds, representing a yield of 77.2 per cent of theory.

The recovered toluene was washed with water to remove acetic acid, and was used with like results in the next batch.

When Example 1 was repeated using 400 grams of toluene, instead of 200 grams, the yield of the final acetamidomalonate was down to 73 per cent, and when only 50 grams of toluene was used a yield of 71 per cent was obtained. When the toluene was omitted entirely, yields of only 45 to 50 per cent were experienced.

The invention has been illustrated with toluene as the inert, water-immiscible solvent. The invention is not so limited, however, as any solvent may be used which is inert to the reagents employed and is immiscible with water and readily separable by distillation from the desired product.

We claim:

1. A method which comprises dissolving diethyl malonate in from one-third to 3 times its volume of a water-immiscible inert solvent which is separable by distillation from the final product; suspending in said solution at least as many mols of sodium nitrite as the number of mols of diethyl malonate present, and from 1 to 10 per cent by weight of water, based on the weight of sodium nitrite; and adding glacial acetic acid gradually to the suspension while the latter is maintained at a temperature between 30° and 70° C. until the nitrosation of the ester is complete.

2. The method as claimed in claim 1 in which the inert solvent is toluene.

3. A method which comprises dissolving diethyl malonate in from one-third to 3 times its volume of a water-immiscible inert solvent which is separable by distillation from the final product; suspending in said solution at least as many mols of sodium nitrite as the number of mols of diethyl malonate present, and from 1 to 10 per cent by weight of water, based on the weight of sodium nitrite; adding glacial acetic acid gradually to the suspension while the latter is maintained at a temperature between 30° and 70° C. until the nitrosation of the ester is complete; separating the solution from undissolved sodium acetate; and recovering crystalline diethyl isonitrosomalonate from the solution.

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