Preparation of Tritium Labelled Dioctyl Adipate

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The vapour pressure of a plasticizer, di(2-ethyl-hexyl) adipate (DOA), was to be studied at relatively low temperatures. The vapour pressures of plasticizers are very low and very difficult to determine. Several methods for the determination of low pressures have been used in the past but they are not very accurate. However, radioactive tracer methods possess certain advantages and are, moreover, relatively accurate. There are two suitable isotopes for the labelling of the molecules, *viz.* ^{14}C and T. Since a high sensitivity and thus high specific activities are needed and since also large amounts were required, ^{14}C would be too expensive. Besides it is more difficult to incorporate ^{14}C into the molecule.

Tritium can be introduced into a molecule in several ways but, in this case, only two were tried, *viz.* labelling by direct exposure to tritium gas according to Wilzbach [1] and catalytic hydrogenation.

The Wilzbach method is very simple. It consists merely in placing the substance to be labelled in contact with T-gas (usually of purity > 90 %). The substance then becomes labelled with tritium due to the catalytic influence of the radiation. The product has to be carefully purified since, of course, other substances are also formed.

In order to get high specific activities, the pressure of the tritium gas should be high (this means that the volume of the reaction vessel should be relatively small) and the surface area of the sample should be large. Thus, solid samples are usually powdered and liquid samples shaken vigorously so that the liquid forms a foam during the tritiation. The DOA is quite viscous and it was found to be impossible, when working with small volumes, to produce a foam from small amounts of DOA. It was found necessary to use a volume of 30–40 ml and more than 5 g DOA to obtain the conditions desired. This meant that the pressure of the gas was reduced considerably but it was thought that the low pressure should be more than compensated for by the large surface area obtained by the vigorous shaking. This was obviously not the case since the specific activity of the product (6.3 g) was only 2.2 μC/g. This is fairly low compared with those activities obtained by other authors [2] who had employed tritium pressures of about 1 atm. It therefore seems probable that a high pressure for the tritium gas is more important than a large surface area.

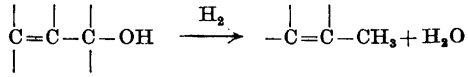
There is also another possible explanation for the poor result. Tables of G_T values seem to show that hydrogen atoms activated by polar groups in their neighbourhood are more readily exchanged by T-atoms than ordinary hydrogen atoms in saturated hydrocarbons. DOA contains some activated hydrogen atoms but most of them are not particularly activated and should thus exchange less readily.

The G_T value of this reaction is 0.0003.

Because the Wilzbach labelling failed, the conclusion was that the best way for getting high specific activities and sufficiently large amounts was to introduce the tritium gas by catalytic hydrogenation. A synthesis was required in which the tritium gas was introduced as late as possible in the synthesis run in order to avoid losses during the earlier stages. The following was considered a suitable way for doing this.

The starting material was 2-ethyl-3-propyl acrolein which is an intermediate product in the preparation of DOA. This was reduced to the corresponding alcohol which was then esterified with adipic acid. The unsaturated ester was then tritiated. However, when the product was subjected to a trial hydrogenation, it was found that 30–40 % more hydrogen was needed than the amount calculated. This was first thought to be due to the fact that the compound was not pure but, even after a very careful purification, more hydrogen was needed than expected. The following is a possible explanation.

It is known [3] that, in the catalytic hydrogenation of olefinic linkages, the following reaction occurs readily:



If the double bond is not so easily reduced, as in this case where one of the unsaturated carbon atoms is a tertiary one, then this serves to labilize the C–O linkage with the resultant reduction indicated above. Now, it is assumed that the catalyst contained some small amounts of acid impurities

which caused the hydrolysis of the ester to a certain extent. The unsaturated alcohol would then be reduced both at the double bond and the hydroxyl group. The free adipic acid, thus formed, would catalyze the further hydrolysis of other ester molecules and we would therefore get an accelerating hydrolysis of the ester, *i.e.* a chain reaction. In addition, it is possible that the double bond also activated the ester bonding, thus making the hydrolysis proceed faster.

Since neither of the two previous methods were successful, a third method for preparing this substance was chosen. Muconic acid was prepared from pyrocatecol. The muconic acid was then tritiated and esterified with 2-ethyl-hexanol. This method was successful.

Procedure. I. The tritium gas, obtained from AERE, England, was 96 % pure. It was introduced into a dispenser apparatus [4] and, from this, about 1 C was transferred to a tritium container. The transference of T-gas to the reaction vessel was somewhat more complicated since the reaction vessel must be cooled with liquid air in order to prevent evaporation during the evacuating. A simple, modified Toepler pump was designed for the transference of the T-gas to the reaction vessel (Fig. 1). The tritiating was carried out in a 50 ml bottle with 10 g of DOA of commercial grade. The flask was shaken vigorously for six days. The vessel was then connected with a U-tube (filled with activated carbon) and this was connected in turn to the Toepler pump. The vessel and the tube were cooled in liquid air. The tritium gas was then pumped back to the container. By this arrangement, the gases formed during the tritiating were either condensed in the bottle or adsorbed in the U-tube and thus the T-gas pumped back was quite clean. The DOA was then dissolved in 50 ml ether and washed three times with 10 ml saturated $NaHCO_3$-solution. After boiling off the ether, the DOA was distilled in a spinning band column at 206°C.

II. 2-Ethyl-3-propyl acrolein was distilled at 83°C, 10 mm Hg. The product was reduced with $LiAlH_4$ to the alcohol using a procedure given by Nystrom and Brown [5]. The product was distilled at 98—99°C, 23 mm Hg. The yield was 75 %. The ester was prepared by esterification with adipyl chloride. The crude ester was then distilled in a spinning band column at 206°—210°C, 6—7 mm Hg. The yield was 61 %. When the identity of the ester was investigated, it was found that 30—40 % more hydrogen was needed for the hydrogenation than the amount calculated. It was first thought that this was due to some decomposition during the distillation. The ester was molecularly distilled but there was still an over-consumption of hydrogen. This method was therefore abandoned.

III. The muconic acid [6] prepared, the identity of which was confirmed by catalytic hydrogenation (0.0596 mg muconic acid, 20.7 ml

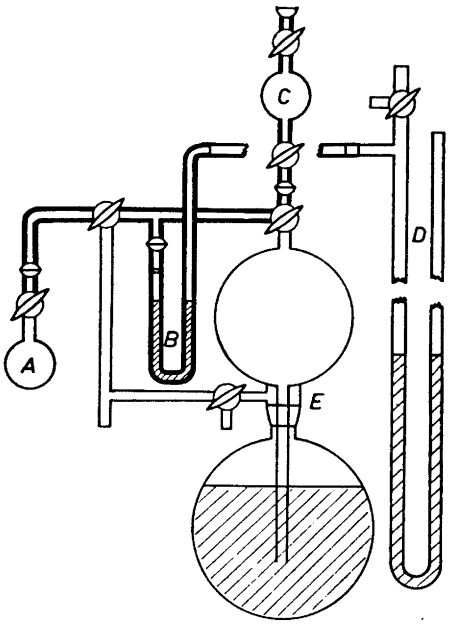


Fig. 1. Modified Toepler pump for the transference of tritium gas from the ampoule to the tritiating vessel and back again for Wilzbach labelling. Such an apparatus is particularly suitable for the labelling of liquids since the vessel can be cooled.

A) Reaction vessel, B) Zero-manometer,
C) T-container, D) Main Hg-manometer,
E) Toepler pump.

The "zero"manometer is used in order to keep the volumes between the reaction vessel and Toepler pump as small as possible. When reading the pressure, the "zero"manometer is set at zero by letting in air or pumping air out through the upper stopcock of the manometer. The pressure is read on the main manometer. The "zero" manometer is equipped with a glass filter under the ball joint in order to prevent mercury getting into the apparatus.

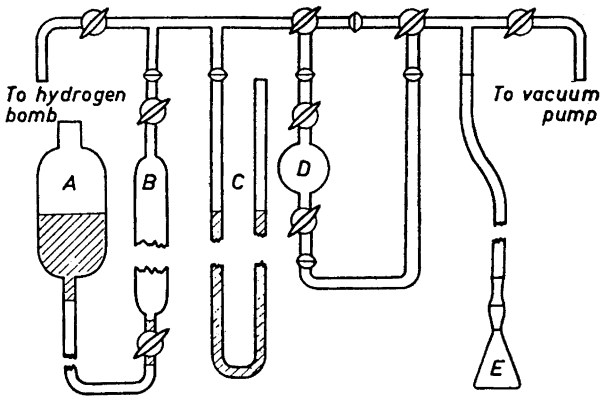


Fig. 2. Tritiating apparatus: A) mercury bottle, B) 50 ml gas burette, C) Hg manometer, D) tritium container, E) hydrogenation flask. Capillary glass tubes were used (D = 2 mm).

H_2, theor. 20.2 ml H_2) was tritiated in a modified tritiating apparatus (Fig. 2). Muconic acid (0.356 g) was dissolved in 10 ml *p*-dioxane (p.a.) in the hydrogenation flask and 25.5 mg Adams catalyst was added. The mixture was cooled with dry ice and the apparatus evacuated. The flask was the allowed to warm to room temperature and the reduction of the catalyst with hydrogen started. When ~ 8 ml H_2 had been consumed, the reduction was stopped by cooling once more with dry ice and the flask was then evacuated again. Hydrogen was introduced again into the apparatus but this time through the tritium gas container which, so to speak, forced the gas into the hydrogenation flask. The amount of tritium gas was ~ 200 mC. The total amount of hydrogen consumed was 58.7 ml, theor, calc. 57.3. Adipic acid (3 g) was then added as carrier and the combined acids were crystallized from the solution and recrystallized from dioxane. 1.00 g of the T-adipic acid and 4.85 g adipic acid were then esterified at 160°C with 13 g (theor. 10.43 g) of 2-ethylhexanol. The reaction was completed after 4 h. The crude product was dissolved in ether and washed three times with saturated $NaHCO_3$-solution. The ether-solution was dried, the ether boiled off and the residue distilled in a spinning band column at 206—208°C and 6 mm Hg. The yield was 11.85 g (78 %). The activity of the product was 0.65 mC/g. Taking into account the losses and dilution during the synthesis, this meant that the yield of tritium from the tritiating was ~ 65 %.

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