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UCRL-2394
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Contract No. W-7405-eng-48

PREPARATION OF DIETHYL MALONATE-2-C^{14}

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November, 1953

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ABSTRACT

Diethyl malonate-2-C^{14} was prepared in 60-70% yield from sodium acetate-2-C^{14} via chloroacetic, cyanoacetic and malonic acids and silver salt esterification of the malonic acid.

*The work described in this paper was sponsored by the U. S. Atomic Energy Commission.

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Diethyl malonate is a well known synthetic intermediate, but relatively little work has been reported on the preparation of diethyl malonate-2-C^{14} for use in isotopic tracer studies. Ropp[1] prepared diethyl malonate-2-C^{14} in 19% yield by the condensation of ethyl acetate-2-C^{14} with ethyl oxalate and pyrolysis of the resulting ethyl oxalacetate. Gidez and Karnovsky[2] reported about 59% yield of diethyl malonate-2-C^{14} from barium carbonate by formation of malonic acid via bromoacetic acid and cyanoacetic acid and then esterification of the calcium malonate salt with dry ethanol in the presence of anhydrous hydrogen chloride.

Malonic-2-C^{14} acid has been prepared in good yield (76%, 84%)[1,3] but esterification is often difficult on the small scale required for isotopic tracer work. In the present work malonic acid synthesis by a method similar to that of Gidez and Karnovsky went smoothly, but several attempts to esterify the calcium salt resulted in low yields of about 30%. However, the reaction between silver malonate and ethyl iodide proved to be a satisfactory means of esterification, and a procedure was developed which yielded 60-70% redistilled ester from 20-25 millimoles sodium acetate-2-C^{14}.

EXPERIMENTAL

Diethyl malonate-2-C^{14} was prepared by the following series of reactions, using modifications of the methods of Hughes and Tolbert[4] and Weiner.[5]

$$C^{14}H_3COONa \text{ anhydrous} \xrightarrow{HCl(g)} C^{14}H_3COOH \text{ anhydrous} \xrightarrow[P,\ I_2]{Cl_2} ClC^{14}H_2COOH \xrightarrow[2)\ NaCN]{1)\ Na_2CO_3}$$

$$NCC^{14}H_2COON \xrightarrow{NaOH} C^{14}H_2(COONa)_2 \xrightarrow{AgNO_3} \underline{C^{14}H_2(COOAg)_2} \xrightarrow{C_2H_5I}$$

$$C^{14}H_2(COOC_2H_5)_2$$

Anhydrous acetic acid was prepared by treating anhydrous sodium acetate-2-C^{14} (2.0 g., 24.5 mmoles, 0.016 μc/mg.) with about 36 mmoles of anhydrous hydrogen chloride. Sodium acetate was placed in the removable bottom of a gas-solid reactor (Figure 1) and the apparatus reassembled with silicone lubricant and attached to the high vacuum manifold. The last traces of water were removed by evacuation to a pressure of 50 microns. A 5 l. storage bulb was evacuated and then filled with tank hydrogen chloride which had first been dried by passing through a concentrated sulfuric acid bubbler and a phosphorus pentoxide tower. About 36 mmoles of this hydrogen chloride was admitted to the gas solid reactor by carefully opening the stopcock of the reactor and measuring a pressure drop of 130 mm. Hg in the 5 l. bulb.

The gas-solid reactor was then removed from the vacuum manifold and the

finger containing the solid was heated carefully over a Bunsen burner. The apparatus was held at such an angle that the acetic acid distilled into the bulb and did not drain back on the hot solid. The cake of solid was loosened by gently shaking, and heating continued until the solid became powdery grey. After cooling, the apparatus was connected to the vacuum manifold and acetic acid distilled *in vacuo* into a liquid nitrogen-cooled trap. The trap was warmed with a dry ice-isopropanol bath and most of the excess hydrogen chloride removed by evacuation. Acetic acid was distilled *in vacuo* into the chlorination apparatus (Figure 2) which contained 30 mg. red phosphorus, 15 mg. iodine and 0.2 ml. acetyl chloride. The reaction mixture was heated to about 40° to allow any water present to react with the acetyl chloride. Suitable precautions were taken to accommodate any excess pressure. The bottom of the reaction tube was cooled in liquid nitrogen until all gaseous materials were collected. The liquid nitrogen was then replaced by a dry ice-isopropanol bath and excess hydrogen chloride removed by evacuation. The apparatus and its frozen contents were then transferred to a steam bath, and the condenser was filled with dry ice-isopropanol and opened to the atmosphere through a drying tube. Chlorine gas was passed through a concentrated sulfuric acid bubbler and a phosphorus pentoxide tower and then bubbled through the reaction mixture at 100° for two hours. The condenser required constant refilling with small chunks of dry ice to prevent loss of product. Toward the end of this period a yellow solid usually formed in the arm of the tube. The mixture was allowed to cool and solidify, the dry ice-isopropanol mixture was drained from the condenser and most of the chlorine allowed to escape by evaporation. The condenser stopcock was closed and the

reaction tube immediately immersed in liquid nitrogen to prevent pressure build-up. The chloroacetic acid product was distilled into the bottom of the tube by filling the finger of the condenser with boiling water and gently flaming other exposed parts of the apparatus. One milliliter of water was added, the mixture warmed to room temperature and residual chlorine allowed to escape through the stopcock. Immediately after chlorination, the product was transferred with 50 cc. of water to a 200 cc. round-bottomed flask, warmed to 50°C., neutralized with sodium carbonate (monohydrate, 1.7 g., 13.7 mmoles) and then cooled. Sodium cyanide (1.2 g., 24.4 mmoles) dissolved in about 10 cc. water was slowly added to the rapidly stirred solution, which was cooled if the reaction became too exothermic. The flask was heated on a steam bath for 1 hour to insure complete reaction. The solution was cooled and sodium hydroxide (1.0 g., 25.0 mmoles) slowly added. The flask was heated on a steam bath in a hood and steam bubbled through the solution to aid the removal of ammonia. A stream of air was blown across the liquid surface to increase the rate of evaporation and thereby control the total volume of solution. Hydrolysis was considered complete when the vapor was neutral to moist litmus (about 3-4 hours). The clear yellow solution was filtered through sintered glass to remove a small amount of dark brown precipitate and collected in a 200 cc. round-bottomed flask containing a side arm fitted with a sintered glass filter (Figure 3). Silver nitrate (8.5 g., 50 mmoles) dissolved in about 25 cc. water was slowly added to the rapidly stirred solution, and a copious grey precipitate formed. The supernatant liquid was filtered through the side arm and the filtrate tested with silver nitrate solution to insure the absence of soluble malonate. The

precipitate was washed once with a small quantity of water and then dried by evacuation (overnight on an aspirator and then 4-8 hours on a high-vacuum line). Ethyl iodide (30 cc., 372 mmoles) was poured over the dry silver precipitate, the flask fitted with a reflux condenser and the side arm capped. The mixture was refluxed and agitated with a glass-sealed magnetic stirrer for three hours and then stirred overnight at room temperature. Diethyl malonate and excess ethyl iodide were filtered through the side arm into a 60 cc. dropping funnel. The precipitate was washed 4-5 times with a total of 20 cc. ethyl ether and the washings combined with the filtrate. The ether and ethyl iodide were flash-distilled from a 30 cc. 2-neck pear-shaped flask at atmospheric pressure. The apparatus was then assembled for vacuum distillation at about 30 mm. Hg. Evacuation at room temperature for 1/2 hour removed the residual ether and ethyl iodide, and then the bulk of the product was distilled at 97-103°C. This distillate was collected in a 30 cc. pear-shaped flask which was then assembled for another vacuum distillation at 30 mm. Hg and the fraction distilling at 105-106°C. was collected.

ANALYSIS OF DIETHYL MALONATE PRODUCTS

	Literature and Theoretical Values	Inactive Preparation	Active Preparation
Yield from sodium acetate			
Crude		81.0%	85.2%
Redistilled		59.0%	68.3%
Boiling point at 30-31 mm. Hg	101°C.[6]	98-100°C.	105-106°C.
Refractive index	1.4143 (20°C.)[7]	1.4133 (21°C.)	1.4130 (23°C.)
Saponification equivalent	80.09	81.23	84.36
Chemical analysis			
C	52.50	52.44	52.47
H	7.50	7.76	7.81
Specific activity of ester	8.14×10^{-3} μc/mg.	--	7.63×10^{-3} μc/mg

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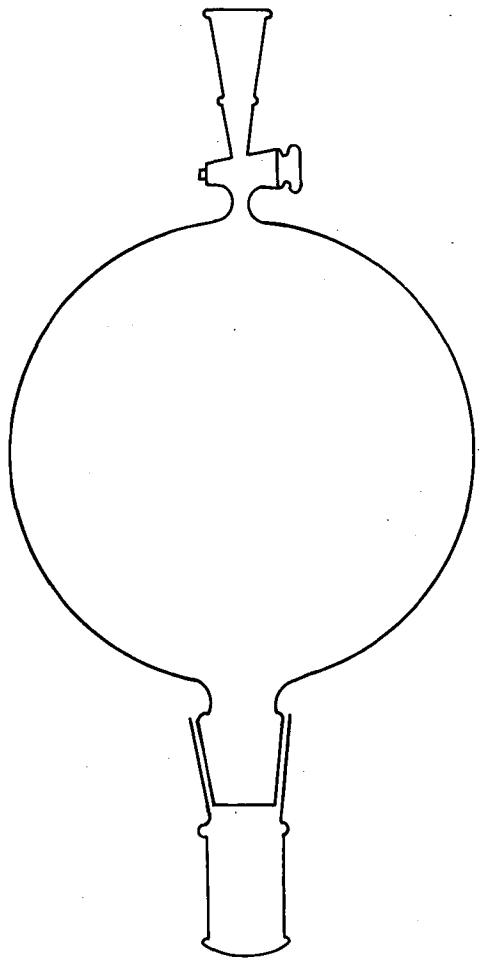
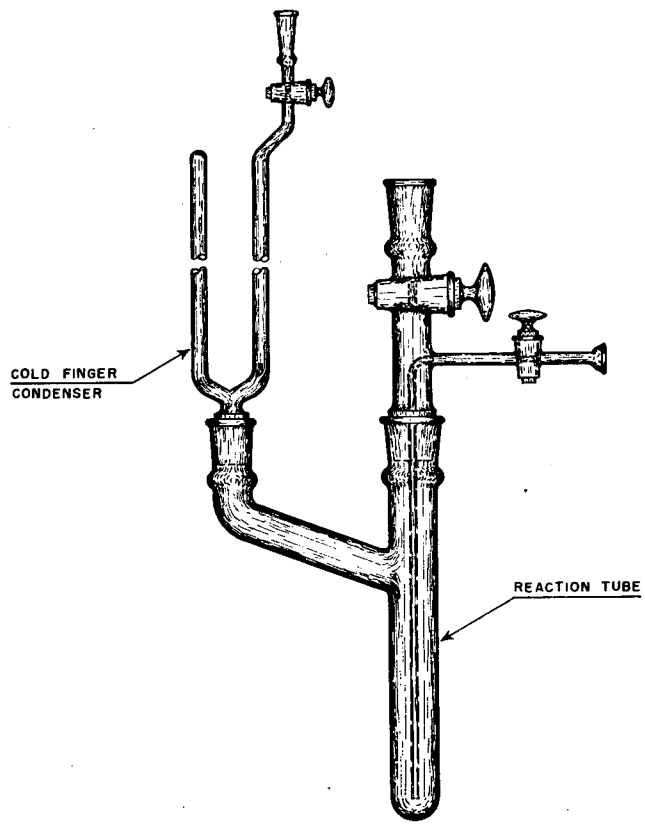


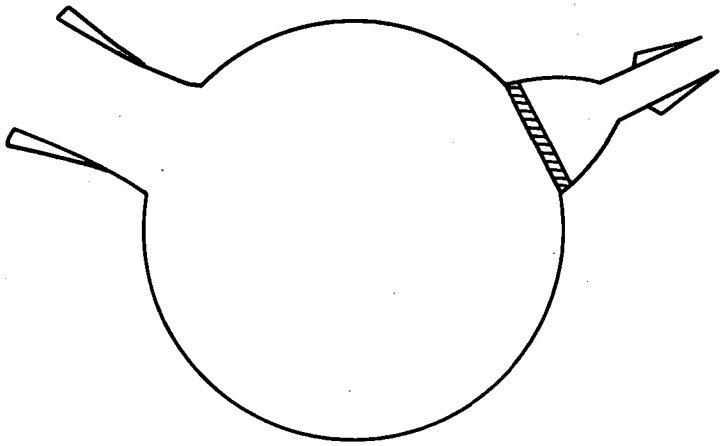
GAS SOLID REACTOR
(CAPACITY = 2 L)

Fig. 1



CHLORINATION APPARATUS.

Fig. 2



ESTERIFICATION FLASK
(200 ml. capacity)

Fig. 3