

ETHYL β,β,β -TRICHLOROPROPIONATE

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[Manuscript received March 22, 1971]

When tested for the choline-sparing action shown in rats by ethyl trichloroacetate,¹ the title compound (1) exhibited an unexpected and severe toxicity which is attributed to a marked inhibition in mitochondrial respiration and a greatly stimulated ATP-ase activity.² In view of the extreme physiological activity of (1), the existence of an incorrect description of the substance (1) in the literature,³ and the difficulties experienced in its preparation, a synthesis which has been found satisfactory is described in the Experimental section.

The ester (1) was obtained by diazoethane esterification of β,β,β -trichloropropionic acid (2), prepared by the patented method of Houtman,⁴ with slight but important modifications to both the dimerization of the vinylidene chloride to 2,4,4,4-tetrachlorobut-1-ene, and the subsequent oxidation of this olefin to the acid (2).

A preparation of (1) by Arndt-Eistert homologation of trichloroacetic acid was described by Brown and Musgrave³ in 1953, but in our hands their procedure was unsatisfactory and did not produce more than a trace of the ester, as detected by gas chromatography, the main products being higher-boiling fractions and non-volatile material. It is doubtful whether Brown and Musgrave obtained the ester (1) in even moderate purity, since their reported refractive index (n_D^{20} 1.5140) is not compatible with structure (1) and differs considerably from that (n_D^{20} 1.4597) of our preparation of (1). Their very low yields of malonic acid derivative (4%) from alkaline hydrolysis of the preparation, and of trichloropropionamide (5%) from their diazoketone intermediate, suggest that their preparations were, at best, grossly impure. Two of our preparations of the diazoketone showed infrared absorption at 2120 (strong) and 2170 cm^{-1} , but differed greatly between 1800 and 900 cm^{-1} . P.m.r. spectral evidence was consistent with excessive methylene insertion.

Experimental

Vinylidene Chloride

Prior to use, the commercial product is shaken several times with freshly prepared 5% sodium bisulphite solution, dried (Na_2SO_4), and distilled (b.p. 31°) in semi-darkness. Any white powder observed in the vinylidene chloride should not be separated by filtration prior to the

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¹ Kratzing, C. C., and Windrum, G. M., *Aust. J. exp. Biol. med. Sci.*, 1959, **37**, 321.

² Kratzing, C. C., and Mainbridge, J. N., unpublished data.

³ Brown, F., and Musgrave, W. K. R., *J. chem. Soc.*, 1953, 2087.

⁴ Houtman, T., U.S. Pat. 2,724,005, 1955.

bisulphite treatment since the very explosive peroxide adsorbs on the precipitated polymer and may detonate with shock or heating.⁵

2,4,4,4-Tetrachlorobut-1-ene

To a three-necked 1-l. flask fitted with a sealed stirrer and a thermometer reading to -30° is added vinylidene chloride (200 g) in ethylene dichloride (100 g). Anhydrous aluminium chloride (13.5 g) is weighed into a small conical flask over the neck of which is fitted a 6-in. length of wide bore rubber tubing. The latter is closed with a rubber stopper pierced by a stout glass rod, which is used for crushing the aluminium chloride without exposure to moisture, and is then withdrawn. The rubber tubing is then closed by a clamp and, after removing the rubber stopper, the open end is slipped over the third neck of the reaction vessel. The contents of the flask are then cooled to about -70° after which all the aluminium chloride is added and stirring commenced. The temperature is allowed to rise to -20° and is then maintained between -15° and -18° by regulation with a cooling bath (-20° to -22°) of acetone and dry ice, constant care being necessary to prevent a rapid temperature rise. After 8 hr, the reaction mixture is treated with excess ice water, the lower layer being separated, dried, and stored under refrigeration.

The temperature-time regime (24 hr at -21 to -28°) recommended by Houtman³ is inconvenient and probably is effective only in the upper part of the temperature range. A reaction mixture stirred at -21 to -28° for 4 hr and then stored in a refrigerator at -30° was lost by violent ebullition, and another stirred in the lower range of -21 to -28° for 12 hr yielded no dimer.

The solution is concentrated, using a fractionating column and reduced pressure (40 mm), to remove vinylidene chloride and ethylene dichloride until the pot temperature rises to 55° . The residue is then fractionally distilled under 5 mm pressure (higher pressures cause some loss) to yield pure 2,4,4,4-tetrachlorobut-1-ene (b.p. $45^{\circ}/5$ mm) in 25–27% yield, or is steam-distilled in several portions to yield somewhat impure dimer which is suitable for oxidation.

β,β,β -Trichloropropionic Acid

Into a 1-l. flask which is fitted with a very vigorous stirrer and a thermometer, are added tetrachlorobutene (6 g), sodium carbonate (1 g), water (250 ml), and potassium permanganate (13.7 g). Stirring brings about heat evolution, the temperature being controlled to 45° by ice-water cooling. At 15 min intervals further portions of the butene and permanganate are added to a total of 30 g of tetrachlorobutene. After the reaction mixture has cooled to room temperature (3–4 hr), stirring is stopped and sulphur dioxide is passed into the flask until the manganese dioxide has dissolved. Extraction with ether (4×250 ml) and evaporation of the dried solution yields a crystalline residue which may be recrystallized from light petroleum to give the pure acid, m.p. 77° (lit.³ 75 – 77°) (Found: neutr. equiv. 175. Calc. for $C_3H_3Cl_3O_2$: 177.4) in c. 70% yield.

The larger proportion of permanganate recommended by Houtman⁴ is excessive and leads to much reduced yields. The reaction cannot be safely carried out by shaking in a closed glass vessel since considerable gas is evolved. Stirring must be very vigorous for rapid and complete oxidation.

Ethyl β,β,β -Trichloropropionate

The acid is esterified by treatment with an excess of diazoethane in ether solution for a few minutes, the yield being essentially quantitative. The ester (b.p. $68^{\circ}/5$ mm) is distilled under reduced pressure to remove polyethylene and some colour, but if prepared from crude acid rather than recrystallized material, an impure fraction, b.p. 52 – $67^{\circ}/5$ mm, requires removal by fractional distillation. The pure ester (Found: C, 29.6; H, 3.5. $C_5H_7Cl_3O_2$ requires C, 29.3; H, 3.4%), n_D^{20} 1.4597, δ (CCl₄) 4.23 (2H, q, 7 Hz), 3.68 (2H, s), 1.31 (3H, t, 7 Hz), shows one peak on gas chromatography on Apiezon M at 100° , but a second peak due to decomposition appears if the injector or oven temperature is much higher.

Despite the acute toxicity of the ester by injection, breathing its vapour appeared to cause no ill effects.

⁵ Reinhardt, R. C., *Chem. Engng News*, 1947, **25**, 2136.