

SYNTHESIS OF [4,4,4-²H₃]BUTANOIC ACID

Frans R. Visser

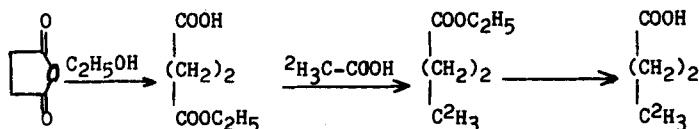
Department of Scientific and Industrial Research
Applied Biochemistry Division
Palmerston North
NEW ZEALAND.

SUMMARY

The synthesis of [4,4,4-²H₃]butanoic acid with 10% yield from deuterated acetic acid is described. The structure is confirmed by n.m.r. and mass spectroscopy and the percentage of labelling is established as >98.5% [²H₃]butanoic acid.

Key words: [4,4,4-²H₃]butanoic acid; anodic synthesis.

Two syntheses leading to [4,4,4-²H₃]butanoic acid have been reported, both starting from a deuterated bromoalkane (1,2). Another option is the electrolytic coupling of acetic acid and monoethyl succinate (3) using deuterated acetic acid as starting material. We choose this latter procedure as it is quick and deuterated acetic acid is readily and cheaply available. Monoethyl succinate is readily made from the anhydride and ethanol (4).



The best results were obtained by using the electrolytic coupling procedure of von Miller and Hofer (3), with the exception that equimolar amounts of potassium acetate and potassium ethyl succinate were used, followed by saponification of the deuterated ethyl butanoate formed.

Although the yield from starting materials is low (10%), this method has the advantage over earlier published procedures that deuterated acetic acid is more readily available and much cheaper than terminally deuterated ethyl- and n-propylbromide. Also the purity of the final product and the high percentage of isotopic labelling make this a very attractive method. Establishing the percentage of deuterium labelling from the parent ion of the acid is not possible due to the very low intensity of the isotope cluster in the parent ion region. Therefore small amounts of labelled and unlabelled butanoic acid were separately converted to the anilides, which do show a parent ion from which the isotopic purity was calculated as >98.5%.

EXPERIMENTAL

Ethyl [4,4,4- $^2\text{H}_3$]butanoate.

Two electrodes were made of tightly spiralled 22 cm long platinum wire of 0.5 mm diameter (about 3.5 cm² surface area), each guided through a Pasteur pipette. The power source was a DC-Power Supply (Redfern, Auckland, New Zealand). Monoethyl succinate was made by a described procedure (4,5). It was purified by distillation and the product was collected between 101 - 115°C at maximum waterjet vacuum (lit. 109 - 112°/2 mm) (4). Yield 53.6 g (73%), $n_{\text{D}}^{20} = 1.4326$ (lit. $n_{\text{D}}^{21} = 1.4323$) (5).

A solution of 3.2 g (0.05 mol) [$^2\text{H}_4$]acetic acid (ex Merck, art. 2902 >99%), 7.3 g (0.05 mol) monoethyl succinate, and 5.6 g (0.1 mol) potassium hydroxide in 15 ml water, and the anode were placed in a short length of dialysis tubing (about 2.5 cm diameter, ex Union Carbide). This was suspended in a 100 ml beaker containing a solution of 6 g potassium carbonate in 50 ml water. The cathode, thermometer, and gas inlet tube for carbon dioxide were also suspended in the beaker. The cathode solution was stirred magnetically and externally cooled with ice water. This equipment is much simpler than the complicated apparatus of Hofer (6). The electrolysis was carried out for one hour at 13 Volt and 1.5 Ampère, after which gas evolution from the anode solution had greatly decreased. During electrolysis the temperature was kept between 17 and 19°C, and carbon

dioxide was passed through the cathode solution to neutralise the potassium hydroxide which resulted from the migrated potassium ions. After the electrolysis the contents of the dialysis tubing, consisting of two separate phases, were acidified and extracted with ether. The crude ester was rapidly distilled by short application of vacuum when the heating bath had reached 145°C. Yield 1.13 g (19%). Capillary GC showed only a very small contamination by ethyl 2-methylbutanoate (OV 101 BP1, 25 m x .33 mm, 1 ml He/min. 5 min at 40°C, 6°C/min to 240°C, hold 10 min. Injector 220°C, FID. 270°C N₂ make up).

[4,4,4-²H₃]Butanoic acid.

A mixture of 1.13 g (9.50 mmol) ethyl [4,4,4-²H₃]butanoate and 10 ml aqueous sodium hydroxide (20% w/v) was heated under reflux for 1 hr and then extracted with ether. The solvent was removed and the crude butyric acid was purified by bulb-to-bulb distillation. Yield 440 mg (51%). The ¹H n.m.r. spectrum (80 MHz) of neat deuterated butanoic acid was recorded at 50°C on a Bruker WP80-SY spectrometer with a digital resolution of 0.11 Hz. Chemical shifts are given in ppm downfield from TMS, followed by multiplicities and coupling constants in Hz. δ = 2.30, t 7.3; δ = 2.31, t 7.3; (AB)_X-CH₂, 2H. δ = 1.62, t, broad 7.3; β -CH₂, 2H.

Mass spectra were recorded on a low resolution electron impact (70 eV), double beam AEI MS 30 mass spectrometer. The mass spectrum of labelled butanoic acid was comparable with that of unlabelled butanoic acid (7). Fragment masses and relative peak heights for unlabelled butyric acid are given in brackets for comparison. Parent ion: m/z 91, 3% (88, <1%); 74, 7% (71 <1%); 73, 38% (73, 30%); 61, 100% (60, 100%); 46, 17% and 44, 14% (both 43, 25%); 45, 16% (45, 20%); 31, 15% (29, 20%).

Approximately 10 mg each of labelled and unlabelled butanoic acid were separately heated with approximately 20 mg of freshly distilled aniline for 2 hrs at 140°C. The crude products were purified by preparative t.l.c. (Merck Aluplates, 60 F254, eluent: benzene). The following peak heights for the molecular ion clusters were obtained. Unlabelled anilide: m/z=165, 0.94%; 164, 11.90%; 163, 100%; 162, 1.36%; 161, 0.09%; 160,

0%. Labelled anilide: $m/z=168$, 1.17%; 167, 11.93%; 166, 100%; 165, 2.42%; 164, 0.22%; 163, 0.17%.

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