# A Convenient Synthesis of 4-Oxobutanoic Acid (Succinic Semialdehyde) from 1,5-Cyclooctadiene

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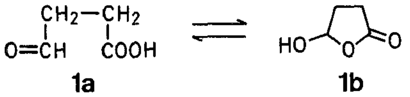
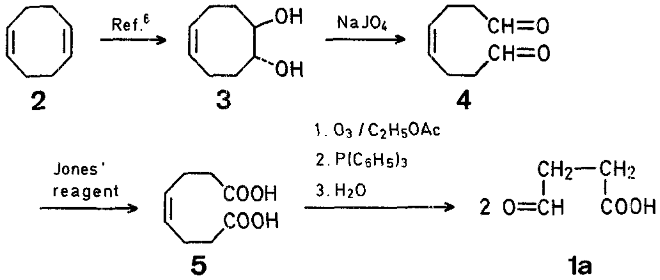
Succinic semialdehyde (4-oxobutanoic acid; **1a**) is formed from 4-aminobutanoic acid (GABA) by transamination in the brain and in microorganisms and is therefore of relevance in neurochemistry[1] and in pharmacology[2]. The oxoacid **1a** is rather unstable, since it easily polymerizes to the corresponding trioxane and is in equilibrium with the cyclic form of 5-hydroxy-4,5-dihydro-2(3*H*)-furanone (**1b**)[3]. The equilibrium can be completely shifted to the lactone **1b** form in water at room temperature, although a hydrate structure cannot be excluded[4].




Recently, Wermuth has effected a synthesis in which aqueous hydrolysis of $\gamma$-ethoxybutyrolactone, in turn prepared from diethyl succinate, furnishes good yields of succinic semialdehyde (**1a**)[3]. We also have described an easy synthesis of **1a**, suitable for biochemical preparations[5]. Generally, the major byproduct of reductive ozonolysis, formaldehyde, was removed under a stream of nitrogen. However, in some cases formaldehyde was not completely eliminated from the aqueous solution of **1a** and, although these aqueous solutions could be stored for several months at $-20\,°C$ without appreciable changes of concentration, and the presence of formaldehyde did not interfere with enzymatic determinations of **1a**, a synthesis with no contamination of by-products seemed desirable.

We reasoned that ozonolysis of 4-octene-1,8-dioic acid (**5**) and reduction of the formed ozonide should afford **1a** as the sole product. Therefore **5** was prepared in 35% yield from commercially available and inexpensive *cis,cis*-1,5-cyclooctadiene (**2**) as shown below[6,7]. The diacid **5** was ozonized in ethyl acetate at $-78\,°C$. Treatment of the ozonide with a solution of triphenylphosphine in ethyl acetate at $-78\,°C$, followed by extraction with water, afforded an aqueous solution of **1a** in 70% yield from **5**. The 2,4-dinitrophenylhydrazone of **1a** was obtained quantitatively and the concentration of **1a** was determined enzymatically as described[5]. Distillation of **1a** from water was effected under reduced pressure and afforded pure succinic semialdehyde with physical properties in agreement with those reported in the literature[3]. The aqueous solution of **1a** could also be liophylized and almost pure **1a** could be easily recovered.




Treatment of **1a** with an ethereal solution of diazomethane quantitatively afforded methyl 4-oxobutanoate, which could in turn be characterized as its 2,4-dinitrophenylhydrazone. When **1a** was treated with gaseous hydrogen chloride in excess ethanol, a mixture of $\gamma$-ethoxybutyrolactone and ethyl 4,4-diethoxybutanoate was formed, as established by $^1$H-N.M.R. analysis of the reaction mixture.

In conclusion, the easy synthesis of **1a** outlined above should furnish an additional example of the versatility of the ozonolysis reaction. A suitable functionalized alkene, in fact, could be the best starting material for the preparation of sensitive molecules such as **1a**[8].

**4-Octene-1,8-dial (4):**

*trans*-1,8-Dihydroxy-cyclooct-4-ene [**3**; 5.86 g, 0.041 mol; obtained from *cis,cis*-1,5-cyclooctadiene (**2**) according to Ref.[6]] is oxidized with sodium metaperiodate (10.62 g, 0.046 mol) following the procedure of Ref.[7] to give the dial **4**; yield: 5.6 g, which is used without further purification.

$^1$H-N.M.R. (CDCl$_3$): $\delta$=2.5 (m, 8H); 5.5 (m, 2H); 10.0 ppm (s, 2H).

**(*Z*)-4-Octene-1,8-dioic Acid (5):**

Crude dial **4** (5.6 g) is dissolved in acetone (distilled over potassium permanganate, 165 ml) and, after cooling at $-10\,°C$, Jones' reagent is added dropwise until a reddish colour persisted (~21 ml). Addition of 2-propanol (1 ml) destroys excess of oxidant and the green mixture is filtered through Celite. After evaporation of the solvents, the residue is dissolved in ether (60 ml), washed with water (10 ml), and then extracted with saturated sodium hydrogen carbonate solution (3 × 10 ml). This solution is washed with ether (10 ml), acidified with 4 normal hydrochloric acid (10 ml), and extracted with ether (3 × 15 ml). After drying with sodium sulfate and evaporation of the solvent, the diacid **5** is crystallized from pentane/diethyl ether; yield: 2.8 g (40% based on **3**); m.p. 96–98 °C (Ref.[7], m.p. 97–98 °C).

| | | | |
|---|---|---|---|
| $C_8H_{12}O_4$ | calc. | C 55.80 | H 7.03 |
| (172.2) | found | 55.95 | 7.10 |

I.R. (Nujol): $\nu$=1740, 1650 cm$^{-1}$.

$^1$H-N.M.R. (CDCl$_3$): $\delta$=2.5 (m, 8H); 5.45 (m, 2H); 10.90 ppm (s, 2H).

**4-Oxobutanoic Acid (1a):**

Ozone-enriched oxygen (~5% enrichment) is passed through a solution of the diacid **5** (0.86 g, 0.005 mol) in ethyl acetate (20 ml) at $-78\,°C$ (15 min). Excess of ozone is removed under a stream of nitrogen and a solution of triphenylphosphine (1.3 g, 0.005 mol) in ethyl acetate (20 ml) is added to the above solution at $-78\,°C$. The solution is allowed to reach room temperature and after 30 min **1a** is extracted with distilled water (3 × 10 ml). The aqueous solution is titrated enzymatically using Gabase as described[5]. The concentration of **1a** is determined as 0.23 molar. Pure **1a** can be recovered by distillation; yield: 0.612 g (60%); b.p. 90–92 °C/0.05 torr (Ref.[3], b.p. 90–91 °C/0.05 torr).

| | | | | |
|---|---|---|---|---|
| $C_4H_6O_3$ | calc. | C 47.06 | H 5.92 | |
| (102.1) | found | 47.40 | 5.80 | |

I.R. and $^1$H-N.M.R. ($CDCl_3$) spectra were in accord with reported values[5], whereas in $D_2O$ no trace of the aldehyde hydrogen could be found in the N.M.R. spectrum[4].

**2,4-Dinitrophenylhydrazone of 1a:**
A solution of **1a** (51 mg, 0.5 mmol) in water (2 ml) is treated with a solution of 2,4-dinitrophenylhydrazine (0.1 g) in acetic acid (2 ml) and the precipitate is filtered off. An additional purification is achieved by treatment of the ethyl acetate solution of the formed phenylhydrazone with a solution of sodium hydrogen carbonate, in which the derivative is soluble. Precipitation with 1 normal hydrochloric acid and recrystallization from methanol affords an analytically pure sample; m.p. 202–203 °C (Ref.[9], m.p. 203 °C).

| | | | | |
|---|---|---|---|---|
| $C_{10}H_{10}N_4O_6$ | calc. | C 42.55 | H 3.54 | N 19.85 |
| (186.2) | found | 42.25 | 3.60 | 20.00 |

$^1$H-N.M.R. (DMSO-$d_6$): $\delta$=2.65 (m, 4H); 7.90 (d, 1H); 8.2 (m, 1H); 8.45 (dd, 1H); 8.85 ppm (d, 1H).

**Methyl 4-Oxobutanoate:**
A 0.42 molar aqueous solution of **1a** (20 ml, 8.4 mmol) is liophylized (−30 °C/0.005 torr, 12 h), the resultant oil (0.86 g) is dissolved in dry methanol (5 ml), and treated with excess ethereal diazomethane solution (19 ml of 0.45 molar solution, 8.55 mmol). Evaporation of the solvents leaves a colourless oil (0.96 g) which is distilled; yield: 0.82 g (84%); b.p. 76–78 °C/15 torr (Ref.[10], b.p. 76.5–77 °C/15 torr).

| | | | | |
|---|---|---|---|---|
| $C_5H_8O_3$ | calc. | C 51.72 | H 6.94 | |
| (116.2) | found | 52.00 | 7.05 | |

I.R. (neat): $\nu$= 1740, 1720 cm$^{-1}$.

$^1$H-N.M.R. ($CDCl_3$): $\delta$=2.7 (m, 4H); 3.70 (s, 3H); 9.70 ppm (s, 1H).

The 2,4-dinitrophenylhydrazone is prepared as described above; m.p. 131–133 °C (Ref.[10], m.p. 133–133.5 °C).

$^1$H-N.M.R. (DMSO-$d_6$): $\delta$=2.65 (m, 4H); 3.70 (s, 3H); 7.70 (d, 1H); 8.1 (m, 1H); 8.30 (dd, 1H); 8.75 ppm (d, 1H).

**Ethyl 4,4-Diethoxybutanoate:**
A 0.42 molar aqueous solution of **1a** (6 ml, 2.5 mmol) is treated as described above. The resultant colourless oil is dissolved in dry ethanol (5 ml) and treated with hydrogen chloride gas at room temperature. The solvent is evaporated under a stream of nitrogen at reduced pressure to leave a colourless residue consisting of equimolar amounts of ethyl 4,4-diethoxybutanoate and the semi-acetal of the ethyl ester of **1a** (either open or cyclic form) according to the $^1$H-N.M.R. spectrum of a $CDCl_3$ solution. Addition of $D_2O$ to this solution results in the appearance of a signal for an aldehydic hydrogen atom, probably arising from the facile hydrolysis of the cyclic form[3].

$^1$H-N.M.R. ($CDCl_3$/$D_2O$): $\delta$= 1.25 (t); 1.95 (m); 2.3–2.8 (m); 3.6 (m); 4.20 (q); 4.60 (t); 5.55 ppm (m).

*We thank Ministero della Pubblica Istruzione for financial support.*

Received: September 23, 1982
(Revised form: November 16, 1982)

1 E. Roberts, R. Hammerschlag, in: *Basic Neurochemistry*, R. W. Albers, G. J. Siegel, R. Katzman, B. W. Agranoff, Eds., Little Brown and Co., Boston, 1972, p. 131–165.

2 H. Laborit, in: *Progress in Neurobiology* Vol. 1, Part 4, G. A. Kerkut, J. W. Phillis, Eds., Pergamon Press, Oxford, 1973, p. 255–274.

3 C. G. Wermuth, *J. Org. Chem.* **44**, 2406 (1979).

4 See, e.g. N. M. Tsybina, T. V. Protopopova, S. G. Rozenberg, A. I. Talygina, A. P. Skoldinov, *Zh. Org. Khim.* **7**, 253 (1971); *C. A.* **74**, 124652 (1971).

5 E. Santaniello, A. Manzocchi, *Analyt. Biochem.* **108**, 190 (1980).

6 P. Yates, E. G. Lewards, P. H. McCabe, *Can. J. Chem.* **50**, 1548 (1972).

7 A. Barco, S. Benetti, G. P. Pollini, R. Taddia, *Org. Prep. Proc. Int.* **6**, 217 (1974).

8 See, e.g. M. E. Jung, K. Shishido, H. L. Davis, *J. Org. Chem.* **47**, 891 (1982).

9 H. Kondo, H. Suzuki, *Ber. Dtsch. Chem. Ges.* **69**, 2459 (1936).

10 W. F. Gresham, R. E. Brooks, *U. S. Patent* 2497303 (1950); *C. A.* **44**, 4492 (1950).