A Convenient Synthesis of γ-Ethoxy-γ-butyrolactone and of Succinic Semialdehyde

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Saponification of the diethyl acetal of diethyl formylsuccinate (**6**) yields the corresponding diacid (**7**). This compound undergoes a thermal decarboxylation with elimination of ethanol by a concerted mechanism and yields γ-ethoxybutyrolactone (**2**) via the cyclization of the intermediate γ-ethoxyvinylacetic acid (**10**). The γ-ethoxybutyrolactone is a stable protected form of succinic semialdehyde (**1**) (SSA), allowing its preparation when required. In chloroform solution SSA is in 2 to 1 equilibrium with its γ-hydroxylactone form (ring–chain tautomerism).

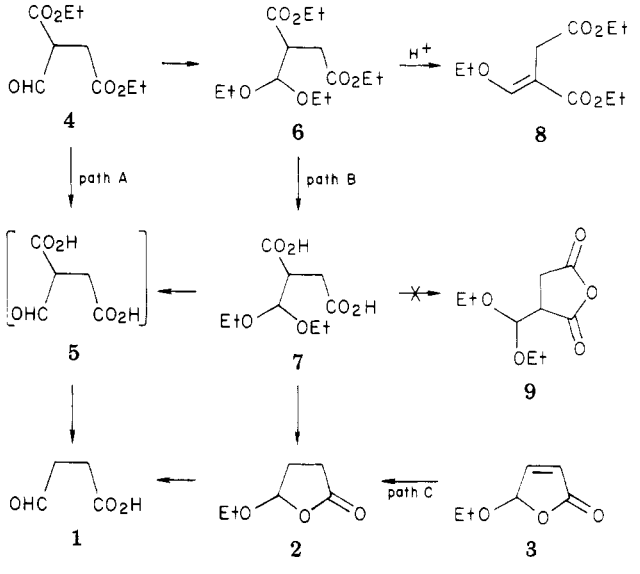
Succinic semialdehyde (SSA) (**1**) is produced by transamination of γ-aminobutyric acid (GABA) in a neural metabolic route known as the GABA shunt; it so constitutes the link between GABA and γ-hydroxybutyric acid and is of considerable interest in neurochemistry and central pharmacology.[1-6] This compound is, however, very unstable: the free aldehyde polymerizes rapidly, mainly into the corresponding solid trioxane,[7] and the sodium salt, even when freeze dried, leads to colored aldol products. Thus there is a need for a form in which SSA can be preserved and which would allow its preparation when needed. We suggest the use of γ-ethoxybutyrolactone (**2**) for this purpose. Indeed, as shown by Schenck,[8] this substance is immediately hydrolyzed into SSA and ethanol by simple boiling in water. In a kinetic study Fife[9] confirmed that the hydrolysis is facile even at neutral pH (in water at 30 °C, k_{obsd} (min^{-1}) is 0.0207 at pH 6.01 and 0.0218 at pH 7.51, with a constant ionic strength μ = 0.25 M) and most likely proceeds through an S_N1-type reaction in which the carboxylic anion acts as leaving group.

But γ-ethoxybutyrolactone is not readily available and one of the best syntheses of this lactone consists in the hydrogenation of γ-ethoxybutenolide (**3**) (path C, Scheme I) obtained through a rather capricious photochemical reaction.[10-12] We report here a convenient and original synthesis of this compound which was developed during our investigations on γ-hydroxybutyric acid and SSA.[13]

The classical synthesis of SSA proposed by Carriere[14] proceeds via acid hydrolysis of diethyl formylsuccinate (**4**), followed by decarboxylation (path A, Scheme I). This process has the disadvantages that the yields are low and that the operating conditions induce polymerization of SSA. We thought that it would be possible to improve this reaction by protecting the aldehyde function by diethyl acetal formation. Alkaline saponification followed by acid hydrolysis of **7** should then give the unstable aldehydo acid **5** which would undergo a spontaneous decarboxylation to SSA.

Diethyl formylsuccinate (**4**) was prepared according to Carriere[14] with slight modifications. Alkaline saponification of the diethyl acetal **6**, which was prepared by the orthoformate method,[15] led to the oily free diacid **7**. Purification of this compound was attempted by vacuum distillation in the hopes of converting it to its anhydride, **9**. In fact, we observed decarboxylation and collected first ethanol and then a colorless, mobile liquid. Spectral

Scheme I



Scheme II

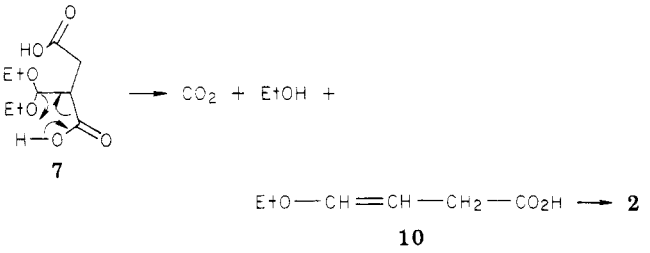


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Table I. 90-MHz ^{1}H NMR Spectra ($CDCl_3$/Me_4Si, 30 °C) of Freshly Distilled Succinic Semialdehyde (1a ⇄ 1b)

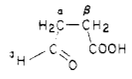
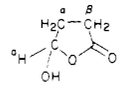
	$^{\alpha}CH_2$-$^{\beta}CH_2$	^aH	$^3J_{a_{H-H\alpha}}$
	AA′BB′	singlet	no coupling with $^{\alpha}CH_2$
1a	~2.65	9.7	0
	ABCD	multiplet	coupled with $^{\alpha}CH_2$
1b	~2.40	5.83	0

Table II. Aspect of H^a Signals (90-MHz ^{1}H NMR 30 °C) of Succinaldehyde in Various Solvents

	^aH-1a	^aH-1b	1a/1b
$CDCl_3$	9.7	5.83	2/1
toluene-d_8	9.1	5.1	2/1
benzene-d_6	coalesced; very broad signal ~8.2 ppm		

analysis showed it to be γ-ethoxybutyrolactone (**2**) (path B, Scheme I).

This unexpected reaction was eminently advantageous, and we propose the following mechanism for it: a concerted six-center electronic transfer of the dicarboxylic diethyl acetal **7** leads first to γ-ethoxyvinylacetic acid (**10**), ethanol, and carbon dioxide. The β,γ-ethylenic acid then cyclizes, in the usual way, into γ-ethoxybutyrolactone.

To our knowledge this behavior of β,β-diethoxy acids has not been previously mentioned. The suggested mechanism can be compared with other cyclic electron transfer reactions like the thermal decarboxylation of glycidic acids or β-halogeno acids.[16] It is noteworthy that diethyl acetal formation and the alkaline saponification can be carried out in a one-pot reaction giving a 72% yield based on formylsuccinate. A solution of SSA in water, suitable for most purposes, is obtained by passing a rapid stream of steam through a mixture of γ-ethoxybutyrolactone and water until a homogeneous phase is obtained (under these conditions the liberated ethanol is removed by steam distillation).

Pure succinic semialdehyde can be obtained by vacuum distillation of this solution. The infrared spectrum (CCl_4) of this compound shows, in addition to the acidic and aldehydic bands at 1720 and 1750 cm^{-1}, a lactonic carbonyl band at 1780 cm^{-1} which suggests **1a** ⇄ **1b** equilibrium (Table I). The 90-MHz ^{1}H NMR spectrum is consistent with this equilibrium which is more rapid than polymerization or formation of trioxane. Characteristic proton chemical shifts, obtained in $DCCl_3$, are given in Table I. Aldehydo acid **1a** and hydroxylactone **1b** are easily distinguished by using H^a signals. It was observed that the rate of exchange depends strongly on the nature of the solvent (Table II).

The fact that transfer of saturation occurs from irradiated H^a at 9.7 ppm to nonirradiated H^a at 5.8 ppm indicated that the rate is faster than the relaxation time.

Experimental Section

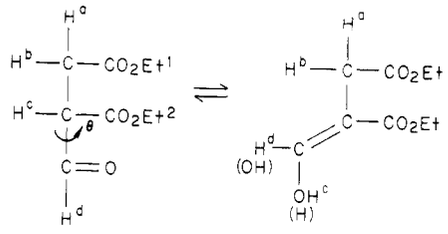
All boiling points are uncorrected. ^{1}H NMR spectra were recorded at 90 MHz on a Brucker WH90 instrument and at 250 MHz on a Cameca 250 instrument operating in the FT mode; δ values are relative to Me_4Si. IR spectra were recorded on a Beckman Acculab 4 spectrometer.

Diethyl Formylsuccinate (4). (a) Sodium Ethanolate. In a 5-L round-bottomed flask, fitted with an efficient fractionating column, were placed commercial absolute ethanol (900 mL) and toluene (1200 mL). The small amount of water present in the mixture was removed by distillation of the ternary azeotrope (74.5 °C). After slight cooling of the mixture, the column was replaced by a reflux condenser, and 55.2 g (2.4 g-atoms) of sodium cuttings was added portionwise. Again the reflux condenser was replaced by the column, and the alcohol and the toluene were rapidly distilled (binary azeotrope, 76.4 °C). At the end, sodium ethanolate crystallized in the flask and the vapor temperature reached 85 °C. Only then was the distillation stopped.

(b) Diethyl Formylsuccinate. To the above prepared sodium ethanolate was added portionwise, with stirring and cooling in an ice bath, a mixture of 348 g (334 mL, 2 mol) of diethyl succinate and 178 g (193 mL, 2.4. mol) of ethyl formate. The mixture was kept at room temperature for 48 h. After this time about 500 g of crushed ice was added, followed by sufficient 10 N H_2SO_4 to ensure acidification. The water layer was removed and washed with ether and the ether layer was pooled with the toluene solution. The combined organic layers were washed to neutrality with a 10% solution of potassium bicarbonate, followed by water. The solution was dried on anhydrous $MgSO_4$, filtered, and distilled.

After the solvents, a head fraction, containing essentially unreacted diethyl succinate, passed at 104–120 °C (14 mmHg). The diethyl formylsuccinate distilled at 95–105 °C (1 mmHg) (362 g, 82%).

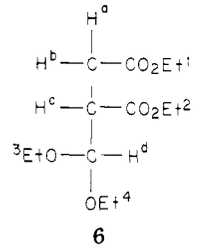
IR and NMR spectra are consistent with compound **4** but as a mixture of the two species **4a** (aldehyde form) and **4b** (enolic form). IR (CCl_4): ν(CO) ester 5.75 (**4a**, **4b**), ν(CO) conjugated



4a **4b**

ester 5.95 (**4b**), ν(CC) conjugated 6.15 (**4b**). 250-MHz ^{1}H NMR (CCl_4/Me_4Si): **4a**, δ ~1 (dt, 6 H); ABX system, δ 2.16 (2 H, AB, ^2J = −16 Hz), 2.85 (1 H, X, $J_{AX} + J_{BX}$ = 12 Hz); δ 3.18 (dq, 4 H) 3.28 (dq, 4 H), 7.6 (s, 1 H, no coupling with H^c, perhaps because the dihedral angle θ is near 90° or because the exchange rate **4a** ⇄ **4b** is fast enough to erase the splitting). **4b**, δ ~1 (dt, 6 H), 2.28 (s, 2 H), 3.18 (dq, 4 H), 3.28 (dq, 4 H), 5.44 (d, 1 H, ^3J = 13 Hz), 8.86 (d, 1 H, ^3J = 13 Hz).

Diethyl Formylsuccinate Diethyl Acetal (6). In a 250-mL



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Claisen flask fitted with a short Vigreux column were placed 40.4 g (36.2 mL, 0.20 mol) of diethyl formylsuccinate, 31.15 g (34.7 mL, 0.218 mol) of ethyl orthoformate, 60 mL of absolute ethanol, and 0.5 g of *p*-toluenesulfonic acid.

The mixture was heated on a water bath so as to distill approximately 16 mL of ethyl formate (at 56–60 °C) over a period of 3 h.

After this time, it was neutralized with a slight excess of triethanolamine (0.5 mL). The alcohol was evaporated and the residue was distilled under reduced pressure. Overheating is to be avoided because of enol ether formation. After a head fraction of about 7 mL (57–85 °C (0.01 mmHg)) the main product was collected at 87–88 °C (0.01 mmHg) (44.5 g, 80%). IR (CCl_4): ν(CO) 5.75 μm. 250-MHz ^{1}H NMR (CCl_4/Me_4Si): **6**, δ 1.15 (dt, 6 H), 1.25 (dt, 6 H); ABXK system, δ 2.52 (2 H, AB, ^2J = −16 Hz), 3.04 (1 H, X, $^3J_{XK}$ = 5 Hz), 4.6 (1 H, K, $^3J_{XK}$ = 5 Hz); δ 3.45 (q,

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2 H), 3.62 (q, 2 H), 4.1 (m, 4 H).

γ-Ethoxybutyrolactone 2. A mixture of 53.3 g (0.2 mol) of diethyl formylsuccinate diethyl acetal and 34 g (~ 0.48 mol) of potassium hydroxide pellets, dissolved in 420 mL of 95% ethanol, was refluxed for 2 h. The alcohol was then evaporated under reduced pressure. The residual potassium salt was dissolved in 70 mL of water. The aqueous phase was washed two times with 40 mL of ether to eliminate neutral byproducts, acidified with 10 N H_2SO_4, and extracted three times with ether. The pooled ether extracts were washed twice with saturated brine (see note), dried over $MgSO_4$, and evaporated.

The residue was placed in a Claisen flask fitted with a short Vigreux column and the distillation was performed under reduced pressure, by use of a water pump. At 100–110 °C the decarboxylation and the ethanol elimination began, allowing only a moderate vacuum. Finally the lactone distilled at 102–103 °C (14 mmHg); yield 19.3 g, 74%.

Note: If washing of the combined ethereal layers was omitted, traces of sulfuric acid present in the mixture caused the formation of ethyl β-formylpropionate (5–10%, bp 83–85 °C (12 mmHg) ν(C=O) 1725 cm^{-1}, ν(C–H) in CHO 1720 cm^{-1}). IR (CCl_4): ν(CO) 5.6 μm. 250-MHz ^1H NMR (CCl_4/Me_4Si): **2**, ABX_3 system, δ 1.12 (t, 3 H), 3.64 (2 H, AB $\Delta\nu$(AB) >50 Hz); δ 2.0 (m, 1 H), 2.25 (m, 2 H), 2.50 (m, 1 H), 5.34 (m, 1 H).

One-Pot Procedure for the Preparation of γ-Ethoxybutyrolactone (2). The isolation of diethyl formylsuccinate diethyl acetal can be omitted. Initially the procedure is as indicated for the synthesis of diethyl formylsuccinate diethyl acetal, starting on a 0.2-mol scale. When all the ethyl formate has distilled, the distillate is allowed to cool and 34 g (~0.48 mol) of potassium hydroxide pellets in 420 mL of 95% ethanol is added. The mixture is refluxed for 2 h. The procedure then continues as indicated for the γ-ethoxybutyrolactone. The yield is 18.7 g (72%).

Succinic Semialdehyde (1). To 6.5 g (0.05 mol) of γ-ethoxybutyrolactone was added 13 mL of distilled water. After this solution was heated to boiling, a rapid stream of steam was passed through the mixture for 1–2 min. The solution was transferred to a distillation flask fitted with a short column and the water was first distilled under reduced pressure. After a high vacuum was obtained, the succinic semialdehyde distilled as a white viscous oil at 91–92 °C (0.05 mmHg). The yield was 3.3 g (65%).

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Registry No. **1a**, 692-29-5; **1b**, 50768-69-9; **2**, 932-85-4; **4a**, 5472-38-8; **4b**, 14273-44-0; **6**, 70145-29-8; **7**, 70145-30-1; **8**, 70145-31-2; sodium ethanolate, 141-52-6; diethyl succinate, 123-25-1; ethyl formate, 109-94-4.

Stereoselective Synthesis of Alkenes and Alkenyl Sulfides from Alkenyl Halides Using Palladium and Ruthenium Catalysts

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Alkenyl halides react with organolithium compounds, such as alkyl, aryl, and heterocyclic lithiums, in the presence of zerovalent palladium compounds to form alkenes stereoselectively under both stoichiometric and catalytic conditions. Alkenyl halides also are easily converted to the corresponding alkenyl sulfides stereoselectively upon treatment with thiolate anions in the presence of the same palladium catalyst. These reactions occur readily at 80 °C and the yields are generally good to excellent.

The difficulty of nucleophilic substitution at an sp^2 carbon atom by conventional organic techniques is overcome by using transition metals.[1] Carbon–carbon bond formation by cross-coupling of alkenyl halides with either Grignard reagents or organolithium compounds is one of the attractive and important pathways for the synthesis of alkenes. The stoichiometric process for synthesis of alkenes by the reaction of alkenyl halides with organocuprates[2] has been replaced by catalytic processes.[3] Iron,[4,5] nickel,[6,7] and copper catalysts[8] are most efficient for cross-coupling between alkenyl halides and Grignard reagents. The scope of the nickel-catalyzed reaction has been verified by many successful applications,[9] and its mechanism has been clarified.[10] However, the nickel catalysts are unfortunately not applicable to the reaction

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