Lactone Carboxylic Acids. VIII.[1] A Synthesis of γ-Substituted α-Amino-butyrolactones from Ethyl γ-Substituted α-Hydroxyaminoaconates

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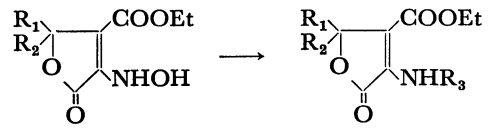
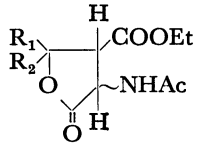
The conversion of α-hydroxyaminoaconates **1a** and **1b** to α-aminoaconates **2a** and **2c** was described, involving a novel reduction of the α-hydroxyamines on treatment with *p*-toluenesulfonyl chloridep–yridine in 62.1—89.5% yields. In the case of the reduction of **1b** *N*-tosyloxy derivative **11b** was isolated. α-Amino-γ-butyrolactones **3** and **4** could be obtained by hydrogenation of *N*-acetates of **2a** and **2c**. Ammonolysis of 2-hydroxy-2-butenolides **5a** and **7a** prepared from acid-hydrolysis of **1b** also gave α-aminobutyrolactones **6**, **8a**, **8b**, **9**, and **10**.

α-Amino-γ-butyrolactones have been used extensively for a variety of synthetic purposes,[2–8] above all in the field of antibiotics synthesis.[9] In this connection, neccessity of the α-aminobutyrolactones as a synthetic intermediate is increasing in recent years. Thus, many attempts have been made to obtain appropriate amino-lactones starting from α-halogenobutyrolactone,[2] 2-hydroxy-2-butenolide,[3] α-azidobutyrolactone,[4] 2-carboxy-2-butenolide,[5] α-cyanobutyrolactone,[6] β,γ-dihydroxy-α-amino acid,[7] and others.[8] We wish to report here a convenient synthetic method of γ-substituted α-amino-γ-butyrolactones and its derivatives. The procedure involves initial reduction of ethyl γ-substituted α-hydroxyaminoaconates **1a** and **1b** on treatment with *p*-toluenesulfonyl chloride–pyridine to form the corresponding α-aminoaconates **2a** and **2c** and the subsequent hydrogenation to form α-acetylamino-γ-butyrolactones **3** and **4**.



1a $R_1=R_2=Me$
1b R_1, $R_2=-(CH_2)_5-$

2a $R_1=R_2=Me$, $R_3=H$
2b $R_1=R_2=Me$, $R_3=Ac$
2c R_1, $R_2=-(CH_2)_5-$, $R_3=H$
2d R_1, $R_2=-(CH_2)_5-$, $R_3=Ac$



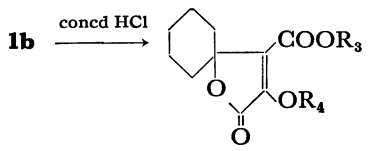
3a $R_1=R_2=Me$ (*trans*)
3b $R_1=R_2=Me$ (*cis*)
4a R_1, $R_2=-(CH_2)_5-$ (*trans*)
4b R_1, $R_2=-(CH_2)_5-$ (*cis*)

Nitrosation of β-ethoxycarbonyl-α-carboxy-γ-butyrolactones with an equimolar amount of sodium nitrite in acetic acid at —5—0 °C gave ethyl α-hydroxyamino-aconates **1a** and **1b** in excellent yields.[10] The infrared spectrum of **1b** showed characteristic bands at 3520 and 3460 cm^{-1} corresponding to NH and OH functions and a broad band at 1744 due to lactone and ester carbonyls. Reduction of **1a** and **1b** to the corresponding primary amines **2a** and **2c** were carried out on treatment with *p*-toluenesulfonyl chloride–pyridine at room temperature for 2 days to afford ethyl γ-substituted α-aminoaconates **2a** and **2c** in 62.1—89.5% yields. The infrared spectrum of **2c** exhibited two sharp bands at 3410 and 3320 cm^{-1} due to primary amine and bands at 1762 and 1692 corresponding to lactone and conjugated ester carbonyls.

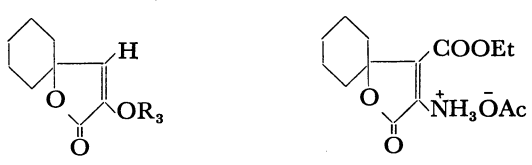
Acetylation of **2c** giving α-acetylaminoaconate **2d** and the subsequent hydrogenation in ethanol containing a small amount of acetic acid over platinum oxide at room temperature gave a mixture of the corresponding α-acetylamino-γ-butyrolactones **4a** and **4b** in quantitative yield. Separation of *cis* and *trans* isomers was accomplished by column chromatography over silica gel to afford 22.2% of **4a** and 77.5% of **4b**, respectively. In the similar manner, conversion of **2a** into the corresponding **3a** and **3b** *via* **2b** was achieved in quantitative yield.

The α-hydroxyaminoaconate **1b** underwent hydrolysis on treatment with concentrated hydrochloric acid at room temperature for 7 days to give ethyl α-hydroxy-aconate **5a** as a major product together with **5c** (3.6%). Spectral evidences and the formation of **5b** from **5a** support assignment of the structure of **5a**.

The α-hydroxybutenolides **5a** and **7a** are considered to be a good precursor for α-aminolactone synthesis.[3] Thus, treatment of **5a** with ammonium acetate at 110—120 °C for 6 h afforded **6** in 81.1% yield.



5a $R_3=Et$, $R_4=H$
5b $R_3=Et$, $R_4=Me$
5c $R_3=H$, $R_4=H$
5d $R_3=Me$, $R_4=Me$

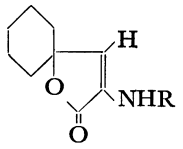


7a $R_3=H$
7b $R_3=Me$

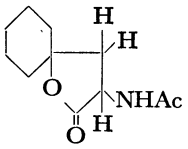
6

Acid-hydrolysis of **5a** under refluxing for 20 h afforded 2-hydroxy-2-butenolide **7a** in 79.6% yield. Ammonolysis of **7a** with 11.3 equivalents of ammonium

acetate at 104 °C for 30 min gave the α-aminobutenolide **8a** in 92.1% yield. However, in the ammonolysis reaction decrease of the amount of ammonium acetate to 7.6 equivalents provided the dimeric compound **10** as a minor product, whose structure was confirmed by spectral data and elemental analysis.



8a R=H
8b R=Ac



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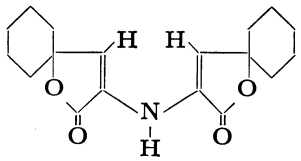

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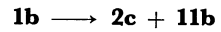
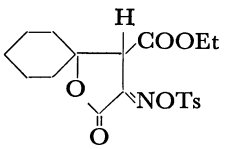
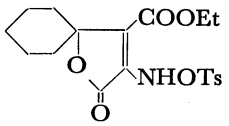
The conversion of **8a** into the α-aminobutyrolactone **9** *via* **8b** was carried out successfully. Treatment of **8a** with acetic anhydride in the presence of a catalytic amount of *p*-toluenesulfonic acid resulted in the acetate **8b** in 95.9% yield. The subsequent hydrogenation of **8b** in ethanol containing a trace of acetic acid over platinum oxide gave **9** in 95% yield.

From the reaction products of **1b** with *p*-tolenesulfonyl chloride–pyridine 7.1% of (tosyloxyamino)aconate **11b** was isolated. Similarly, when **1b** was treated with equimolar amount of butyllithium followed by treatment with *p*-toluenesulfonyl chloride, the reaction produced 26.4% of **11b** in addition to the formation of **2c** (68.7%). The conversion of the tosylate **11b** into **2c** could be carried out by stirring in pyridine at room temperature.



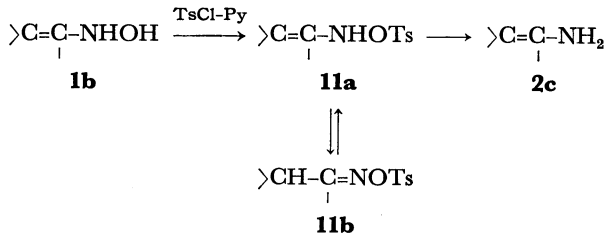


11b



11a

One possible pathway for the formation of **2c** and **11b** from **1b** may involve an unstable intermediate **11a**, a tautomer of **11b**. In the conversion of **11b** into **2c** the



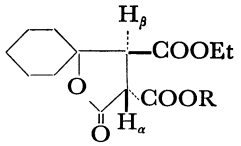
reaction may also proceed *via* the intermediate **11a**, which would provide **2c** promptly in contrast to the slow change of **11b** into **11a**.

Discrimination of *cis* and *trans* isomers of α-amino-β-ethoxycarbonylbutyrolactones **3** and **4** was accomplished by comparison with related compounds **12**,[11] **13**,[12] and **14**.[13] Aminobutyrolactones **3a** and **4a**, which were separated from hydrogenation products of **2b** and **2d** by column chromatography, have PMR coupling constants ($J_{\alpha,\beta}$) of 10.5 and 11.1 Hz respectively, indicating that structure of **3a** and **4a** should be assigned to the *trans* isomers. The butyrolactones **12** and **13**, which are considered to be thermodynamically favorable *trans* isomers, have coupling constants in the range of 10.0—13.0 Hz (Table 1).

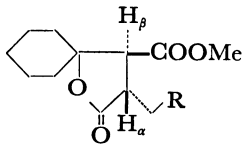
Table 1. Coupling constants between H_α and H_β of α,β-substituted butyrolactones

Compound	H_α (δ)		H_β (δ)	$J_{\alpha,\beta}$ (Hz)	
	cis	*trans*		*cis*	*trans*
3a	—	4.73	3.65	—	11.1
3b	5.29	—	3.43	7.5	—
4a	—	4.76	3.50	—	10.5
4b	5.25	—	3.46	7.5	—
12a	—	4.17	3.54	—	11.0
12b	—	3.96	3.39	—	11.5
12c	—	4.15	3.55	—	11.0
13a	—	3.47	3.04	—	12.8
13b	—	3.30	2.82	—	11.5
14	2.80	2.60[a]	3.07	7.0	11.0

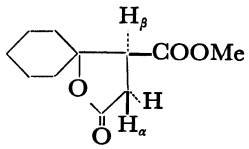
a) The coupling constant of geminal hydrogen atoms at the α position was 18.0 Hz.



12a R=H; **12b** R=Me
12c R=Et



13a R=CHO
13b R=HC=CH$_2$



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On the other hand, the isomers **3b** and **4b** have identical coupling constant ($J_{\alpha,\beta}$: 7.5 Hz), being assigned to the *cis* isomer based on the result observed in the resemble *cis* substituted cyclopentane system[14] and on the calculation from the Karplus equation.[15]

Experimental

Melting points and boiling points are uncorrected. NMR spectra were recorded on Hitachi R-24 and/or R-20 instruments. IR spectra were determined with a Hitachi EPI-S2, with only major absorptions being cited. Wako gel C-200 silica gel was used for elution chromatography. Elemental analysis was performed by Mr. Tsutomu Okamoto of our Laboratory.

γ,γ-Pentamethylene-β-ethoxycarbonyl-α-carboxy-γ-butyrolactone (12a). Hydrolysis of γ,γ-pentamethylene-α,β-diethoxycarbonyl-γ-butyrolactone (**12c**)[11] (8.9 g, 0.03 mol) with NaOH (3.42 g, 0.09 mol) in aqueous 20% EtOH (18 ml) afforded 7.1 g (87.5%) of **12a** as a white solid: mp 130.0—131.0 °C (from water); IR (neat) 3600—2200 (COOH),

1785, 1740 cm^{-1}; NMR (CCl_4) δ 1.32 (t, J=6.8 Hz, 3H, CH_3), 1.00—2.10 (m, 10H), 3.54 (d, J=11.0 Hz, 1H, H_β), 4.17 (d, J=11.0 Hz, 1H, H_α), 4.27 (q, J=7.0 Hz, 2H, CH_2O). Treatment of the acid with diazomethane gave the corresponding methyl ester **12b**: bp 82.0—86.0 °C/1 mmHg; IR (neat) 1790, 1742 cm^{-1}; NMR ($CDCl_3$) δ 1.29 (t, J=7.0 Hz, 3H, CH_3), 1.00—2.20 (m, 10H), 3.39 (d, J=11.5 Hz, 1H, H_β), 3.76 (s, 3H, CH_3O), 3.96 (d, J=11.5 Hz, 1H, H_α), 4.16 (q, J=7.0 Hz, CH_2O). Found: C, 59.26; H, 7.18%. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09%.

*Ethyl γ,γ-Pentamethylene-α-hydroxyaminoaconate (**1b**).* To a stirred solution of **12a** (5.0 g, 18.5 mmol) in AcOH (15 ml) a solution of $NaNO_2$ (1.28 g, 18.5 mmol) in water (3.0 ml) was added dropwise for 10 min at −5—0 °C. The mixture was stirred for 40 min at 5 °C and then diluted with water. After stirring for additional 40 min at 10 °C the organic phase was extracted with ether. The extracts were washed with water, with aqueous $NaHCO_3$, and with water and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded a light yellow oil which was triturated with a small amount of hexane–$CHCl_3$ (3: 1) to give 4.5 g (92%) of **1b** as white crystals: mp 61.5—62.0 °C (from hexane–$CHCl_3$); IR (Nujol) 3520, 3460, 1744, 1660, 1529 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (t, J=7.0 Hz, 3H, CH_3), 1.69 (s, 10H), 2.50—3.10 (broad, 2H, HO–N, 1/2H_2O), 3.81 (s, 1H, NH), 4.19 (q, J=7.0 Hz, 2H, CH_2O).

Found: C, 54.62; H, 6.89%. Calcd for $C_{12}H_{17}NO_5 \cdot 1/2H_2O$: C, 54.54; H, 6.86%.

*Ethyl γ,γ-Pentamethylene-α-aminoaconate (**2c**).* To a stirred solution of **1b** (96.0 mg, 0.36 mmol) in anhydrous pyridine (0.5 ml) *p*-toluenesulfonyl chloride (140 mg, 0.73 mmol) was added portionwise for 30 min. The mixture was stirred for additional 1 h at 0—5 °C under nitrogen and for 2 days at room temperature. After cooling in an ice bath the mixture was poured into 10% HCl and adjusted to pH 7 and extracted with ether. The extracts were washed with aqueous $NaHCO_3$ and with water, dried (Na_2SO_4), and concentrated. The residual oil was chromatographed over silica gel. The first comming elution from the column with CH_2Cl_2(*ca.* 5 ml) gave 10.5 mg (7.1%) of an oil. Upon standing for several days, the oily material bigan to crystallize to give white crystals **11b**, mp 115.0—116.0 °C (from hexane–benzene); IR (Nujol) 1792 (lactone C=O), 1759, 1635, 1596 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (t, J=7.0 Hz, 3H, CH_3), 0.70—2.20 (m, 11H), 2.46 (s, 3H, CH_3C=C), 4.35 (q, J=7.0 Hz, 2H, CH_2O), 7.34 (d, J=8.0 Hz, 2H, HC=C), 7.89 (d, J=8.0 Hz, 2H, HC=C). Found: C, 55.58; H, 5.49%. Calcd for $C_{19}H_{23}NO_7S$: C, 55.74; H, 5.66%.

The second elution with CH_2Cl_2 (*ca.* 20 ml) gave 54.0 mg (62.1%) of **2c**: mp 139.0—139.5 °C (from hexane–CH_2Cl_2); IR (Nujol) 3410, 3320, 1762, 1692, 1661 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (t, J=7.0 Hz, 3H, CH_3), 1.52—2.52 (m, 10H), 4.28 (q, J=7.0 Hz, 2H, CH_2O), 5.59 (broad s, 2H, NH_2). Found: C, 60.45; H, 6.99%. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16%.

The following elution with CH_2Cl_2–AcOEt (10: 1, *ca.* 10 ml) gave 3.0 mg (1.6%) of an amorphous, glassy solid: IR (neat) 3450—2700, 1775, 1731, 1650, 1590, 1563, 1497 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (t, J=7.0 Hz, 3H, CH_3), 1.00—2.50 (m, 10H), 2.40 (s, 3H, CH_3C=C), 4.30 (q, J=7.0 Hz, 2H, CH_2O), 5.50 (broad, 1H, NH), 7.00—7.46 (m, 5H, HC=C), 7.95 (d, J=8.0 Hz, 2H), 8.46 (d, J=6.0 Hz, 2H). Difficulty was encountered in obtaining a pure sample for elemental analysis by recrystallization.

In the similar manner, ethyl γ,γ-dimethyl-α-aminoaconate (**2a**) was obtained in 89.5% yield, mp 120.0 °C (lit,[10] mp 120.0 °C).

*Ethyl γ,γ-Pentamethylene-α-acetylaminoaconate (**2d**).* A mixture of **2c** (126 mg, 0.527 mmol), Ac_2O(1.0 ml) and anhydrous *p*-toluenesulfonic acid (9.0 mg, 0.05 mmol) was stirred for 18 h under nitrogen at room temperature. Upon cooling with an ice-bath the mixture was poured into water and the aqueous solution was adjusted to weak alkaline solution by addition of solid $NaHCO_3$ (1.0 g) and then extracted with ether. The extracts were washed with water, dried (Na_2SO_4) and concentrated. The residue was chromatographed over silica gel using CH_2Cl_2, giving 147.0 mg (99.2%) of **2d**: mp 118.0—119.0 °C (from hexane–CH_2Cl_2), IR (Nujol) 3310 (NH), 1746, 1725, 1668 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (t, J=7.0 Hz, 3H, CH_3), 1.49—2.01 (m, 10H), 2.19 (s, 3H, CH_3CO), 4.33 (q, J=7.0 Hz, 2H, CH_2O), 8.04 (broad, 1H, NH). Found: C, 59.85; H, 6.88%. Calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81%.

In the similar manner, ethyl γ,γ-dimethyl-α-acetylaminoaconate (**2b**) was obtained in 93.5% yield: mp 115.5—116.5 °C (from hexane–benzene); IR (Nujol) 3320 (NH), 1755, 1724, 1678 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (t, J=7.2 Hz, 3H, CH_3), 1.65 (s, 6H, *gem* CH_3), 2.22 (s, 3H, CH_3CO), 4.37 (q, J=7.2 Hz, CH_2O), 8.18 (broad, 1H, NH). Found: C, 54.90; H, 6.30%. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27%.

*γ,γ-Pentamethylene-β-ethoxycarbonyl-α-acetylamino-γ-butyrolactones (**4a** and **4b**).* Hydrogenation of **2d** (102 mg, 0.36 mmol) was carried out in ethanol (1 ml) containing one drop of AcOH in the presence of platinum oxide (25 mg) for 43 h until 8 ml of hydrogen gas was absorbed. The catalyst was filtered off and washed with ethanol. The filtrate was concentrated under reduced pressure to give 106 mg of a light yellow oil, which was chromatographed over silica gel. Elution of the column with 10—30 ml of benzene–AcOEt (3: 2) gave 79.6 mg (77.5%) of **4b** (*cis*); mp 116.5—117.0 °C (from hexane–CH_2Cl_2): IR (Nujol) 3250 (NH), 3050, 1780, 1736, 1643 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (t, J=7.5 Hz, 3H, CH_3), 1.40—1.95 (m, 10H), 2.03 (s, 3H, CH_3CO), 3.46 (d, J=7.5 Hz, 1H. H_β), 4.23 (q, J=7.0 Hz, 2H, CH_2O), 5.25 (q, J=7.5 Hz, J=7.0 Hz, 1H, H_α), 6.65 (d, J=7.0 Hz, 1H, NH). Found: C, 59.31; H, 7.38%. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47%.

Following elution of the column with 30—40 ml of benzene–AcOEt (3: 2) gave 22.8 mg (22.2%) of **4a** (*trans*): mp 147.5—148.0 °C (from hexane–CH_2Cl_2); IR (Nujol) 3280 (NH), 3080, 1783, 1732, 1658 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (t, J=7.0 Hz, 3H, CH_3), 1.40—1.95 (m, 10H), 2.01 (s, 3H, CH_3CO), 3.50 (d, J=10.5 Hz, 1H, H_β), 4.22 (q, J=7.0 Hz, 2H, CH_2O); 4.76 (q, J=10.5 Hz, J=7.0 Hz, 1H, H_α), 6.86 (d, J=7.0 Hz, 1H, NH). Found: C, 59.07; H, 7.50%. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47%.

In the similar manner, γ,γ-dimethyl-β-ethoxycarbonyl-α-acetylamino-γ-butyrolactones (**3a** and **3b**) were obtained in quantitative yield. Analytical samples of **3a** and **3b** were obtained by preparative glpc (3a/3b: 1/1.1; Column SE-30, 3 m×4 mm, carrier gas H_2 27 ml/min at 160 °C). **3a** (*trans*, glpc retention time 3.2 min): IR (neat) 3290 (NH), 1790, 1738, 1661 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (t, J=7.1 Hz, 3H, CH_3), 1.33 (s, 6H, *gem* CH_3), 2.05 (s, CH_3CO), 3.65 (d, J=11.1 Hz, 1H, H_β), 4.25 (q, J=7.1 Hz, 2H, CH_2O), 4.73 (q, J=11.1 Hz, 1H, H_α), 6.74 (d, J=6.8 Hz, 1H, NH). Found: C, 54.33; H, 6.98%. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04%.

The compound **3b** (*cis*, glpc retention time 9.0 min): IR (neat) 3310 (NH), 1797, 1736, 1668 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (t, J=7.1 Hz, 3H, CH_3), 1.49, 1.59 (each s, 6H, *gem* CH_3), 3.43 (d, J=7.5 Hz, 1H, H_β), 4.22 (q, J=7.1 Hz, 2H, CH_2O), 5.29 (t, J=7.5 Hz, 1H, H_α), 6.33 (d, J=7.5 Hz, 1H, NH). Found: C, 54.34; H, 7.14%. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04%.

Ethyl γ,γ-Pentamethylene-α-hydroxyaconate (5a). A mixture of **1b** (1.0 g, 3.78 mmol) in concd HCl (25 ml) was allowed to stand for 7 days at room temperature. The precipitate was collected by filtration. The precipitate was taken up in CH_2Cl_2 and the solution was washed with water, dried (Na_2SO_4), and concentrated to give 607 mg (66.8%) of **5a**: mp 118.0—119.0 °C (from hexane–CH_2Cl_2) (lit.[16] mp 119.0—119.5 °C); IR (Nujol) 3235 (OH), 1753, 1713, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.39 (t, J=7.0 Hz, 3H, CH_3), 1.52—2.36 (m, 10H), 4.35 (q, J=7.0 Hz, 2H, CH_2O), 8.84 (broad s, 1H, OH).

The filtrate was concentrated and extracted with ether. The extracts were washed with water, dried (Na_2SO_4), and concentrated to give 188 mg of an oily material, which was triturated with hexane–CH_2Cl_2 (3: 1) to give 29 mg (3.6%) of **5c**: mp 119.0—119.5 °C (decomp.); IR (Nujol) 3450—2100 (COOH), 1762, 1705, 1680, 1630 cm^{-1}. During recrystallization partial decarboxylation of **5c** was encountered. Thus, the crude acid **5c** (10.0 mg, 0.047 mmol) was treated with excess amount of diazomethane in ether for 30 min at 0—5 °C and then the solvent was evaporated. The residue was chromatographed over silica gel using CH_2Cl_2, which eluted 10.8 mg (95.4%) of **5d**: mp 64.5—65.0 °C (from hexane–CH_2Cl_2); IR (Nujol) 1755, 1698, 1642 cm^{-1}; NMR (CCl_4) δ 1.00—2.70 (m, 10H), 3.79 (s, 3H, CH_3O), 4.19 (s, 3H, CH_3O). Found: C, 60.08; H, 6.66%. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71%.

From the residual filtrate 60 mg (6.6%) of **5a** was recovered along with 74 mg (7.4%) of **1b**.

Ethyl γ,γ-Pentamethylene-α-methoxyaconate (5b). The α-hydroxyaconate **5a** (100 mg, 0.42 mmol) was treated with an excess amount of diazomethane in ether for 30 min at 0—5 °C and then the solvent was evaporated. The residue was chromatographed over silica gel using hexane–CH_2Cl_2 (1: 1), which eluted 100 mg (94.5%) of **5b**: mp 84.5—85.0 °C (from hexane–CH_2Cl_2); IR (Nujol) 1763, 1700, 1646 cm^{-1}; NMR (CCl_4) δ 1.32 (t, J=7.0 Hz, 3H, CH_3), 1.48—2.40 (m, 10H), 4.12 (s, 3H, CH_3O), 4.18 (q, J=7.0 Hz, 2H, CH_2O). Found: C, 61.38; H, 7.08%. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14%.

4,4-Pentemethylene-3-ethoxycarbonyl-2-ammonio-2-butenolide Acetate (6). A mixture of **5a** (100 mg, 0.416 mmol) and $AcONH_4$ (32.0 mg, 0.416 mmol) was allowed to stand at 110—120 °C under nitrogen for 6 h, and then the resulting white solid was sublimed at 110—120 °C to afford 101 mg (81.1%) of **6**: IR (Nujol) 3220 (NH), 1756, 1682, 1568 (COO^-) cm^{-1}; NMR ($CDCl_3$) δ 1.40 (t, J=7.0 Hz, 3H, CH_3), 1.56—2.10 (m, 10H). 2.15 (s, 3H, CH_3CO), 4.40 (q, J=7.0 Hz, 2H, CH_2O), 6.30—8.00 (broad, 3H, NH_3^+). Found: C, 56.21; H, 7.13%. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07%.

Hydrolysis of 5a. A solution of **5a** (510 mg, 2.12 mmol) in EtOH (4 ml) and concd HCl (12 ml) was stirred for 20 h at 90 °C. The mixture was cooled and filtered with suction. The filtrate was concentrated and extracted with ether. The extracts were washed with aqueous $NaHCO_3$ and water and dried (Na_2SO_4). Removal of the solvent gave 284 mg (79.6%) of **7a**: mp 132.5—133.5 °C (from hexane–CH_2Cl_2)(lit.[16] 136—137 °C); IR (Nujol) 3185 (OH), 1748, 1644 cm^{-1}; NMR ($CDCl_3$) δ 1.64 (broad s, 10H), 5.51—6.81 (broad s, 1H, OH), 6.24 (s, 1H, H_β).

The alkaline solution was acidified to pH 3 with 10% HCl and extracted with ether. After usual work-up, there was obtained 38.0 mg (8.4%) of **5c**: mp 119.0—119.5 °C.

γ,γ-Pentamethylene-α-methoxybutenolide (7b). The α-hydroxybutenolide **7a** (20.0 mg, 0.119 mmol) was treated with an excess amount of diazomethane in ether at 0—5 °C for 30 min. After work-up as an usual manner, there was obtained 21.0 mg (96.8%) of **7b**: mp 73.0—73.5 °C (from hexane–CH_2Cl_2); IR (Nujol) 1770, 1690, 1655 cm^{-1}; NMR (CCl_4) δ 1.64 (s, 10H), 3.29 (s, 3H, CH_3O), 6.15 (s, 1H, H_β). Found: C, 65.73; H, 7.83%. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74%.

4,4-Pentamethylene-2-amino-2-butenolide (8a) and its dimer (10). *Procedure A*: A mixture of **7a** (84.1 mg, 0.50 mmol) and $AcONH_4$ (436 mg, 5.65 mmol) was heated for 30 min at 104 °C under nitrogen. The mixture was taken up in $CHCl_3$ and the $CHCl_3$ solution was washed with aqueous $NaHCO_3$, and with water, and dried (Na_2SO_4). Removal of the solvent gave 80 mg of **8a** as a solid. Purification was achieved by chromatography over silica gel using hexane–CH_2Cl_2 to give 77.0 mg (92.1%) of **8a**: mp 139.0—139.5 °C (from hexane–CH_2Cl_2); IR (Nujol) 3420, 3320 (NH), 1740, 1670, 1608 cm^{-1}; NMR ($CDCl_3$) δ 1.62 (s, 10H), 3.75 (broad, 2H, NH), 6.01 (s, 1H, H_β). Found: C, 64.54; H, 7.95%. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84%.

Procedure B: A mixture of **7a** (172 mg, 1.02 mmol) and $AcONH_4$ (598 mg, 7.76 mmol) was heated to 100 °C for 30 min under nitrogen. After work-up as described above, there was obtained 126 mg (73.7%) of **8a**; mp 139.0—139.5 °C, 12 mg (7.4%) of **10**; mp 187.5—188.5 °C (from hexane–CH_2Cl_2), and 12 mg (7.0%) of the starting material **7a**.

The spectral data together with the result of elemental analysis of **10** are as follows: IR (Nujol) 3380 (NH), 3100, 1770, 1745, 1665 cm^{-1}; NMR ($CDCl_3$) δ 1.70 (s, 20H), 6.19 (s, 2H, H_β), 6.63 (broad s, 1H, NH). Found: C, 68.21; H, 7.30%. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30%.

4,4-Pentamethylene-2-acetylamino-2-butenolide (8b). A mixture of **8a** (25.0 mg, 0.15 mmol), Ac_2O (0.5 ml), and *p*-toluenesulfonic acid (2.5 mg, 0.015 mmol) was stirred under nitrogen for 13 h at room temperature. After work-up as an usual manner, there was obtained 30 mg (95.9%) of **8b**: mp 136.0—137.0 °C (from hexane–CH_2Cl_2); IR (Nujol) 3310 (NH), 1770, 1740, 1693, 1655 cm^{-1}; NMR ($CDCl_3$) δ 1.69 (s, 10H), 2.21 (s, 3H, CH_3CO), 7.53 (s, 1H, H_β), 8.09 (broad s, 1H, NH). Found: C, 63.32; H, 7.19%. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23%.

γ,γ-Pentamethylene-α-acetylamino-γ-butyrolactone (9). Hydrogenation of **8b** (25.0 mg, 0.12 mmol) was carried out in EtOH (0.5 ml) containing AcOH (0.01 ml) in the presence of platinum oxide (5.0 mg) for 38 h at room temperature until 3 ml of hydrogen gas was absorbed. The catalyst was filtered off and washed with EtOH. The combined filtrates were concentrated. The residual oil (31 mg) was cooled at 0—5 °C and triturated with ether to give 24.0 mg (95.0%) of **9** as a white crystal: mp 134.5—135.0 °C (from hexane–CH_2Cl_2); IR (Nujol) 3280 (NH), 3090, 1775, 1655 cm^{-1}; NMR ($CDCl_3$) δ 1.30—1.90 (broad s, 10H), 2.03 (s, 3H, CH_3CO), 2.24 (m, 2H, H_β), 4.80 (m, 1H, H_α), 6.89 (d, J=7.0 Hz, 1H, NH). Found: C, 62.60; H, 8.11%. Calcd. for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11%.

Reaction of 1b with p-Toluenesulfonyl Chloride–Butyllithium. To a THF solution (1.0 ml) of **1b** (66.2 mg, 0.25 mmol) 1.1 M butyllithium in ether (0.25 ml, 0.275 mmol) was added at −78 °C under nitrogen. After stirring for 30 min at −78 °C *p*-toluenesulfonyl chloride (50.0 mg, 0.26 mmol) was added. The mixture was allowed to warm slowly to room temperature during 2 h and stirring was continued for additional 3 h. The mixture was poured into 1.0 ml of ice-cooled diluted HCl and extracted with $CHCl_3$. The extracts were washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel. Elution of the column with benzene (2—3 ml) gave 27.1 mg (26.4%) of **11b**. Following elution with benzene–AcOEt (30: 1, 10 ml) gave 41.2 mg (68.7%) of **2c**. The structure of both **11b** and **2c** were identified spectroscopically in comparison with authentic samples.

Reaction of 11b with Pyridine. A solution of **11b** (10.0 mg, 0.024 mmol) in pyridine (0.5 ml) was heated to 110 °C in

a sealed tube for 15 h. The mixture was concentrated *in vacuo* and the residue was chromatographed over silica gel using benzene to give 4.7 mg (80%) of **2c**. IR and NMR spectra were identical with those of authentic sample.

Alternative Procedure: A solution of **11b** (13.5 mg, 0.033 mmol) in pyridine (0.5 ml) was stirred at room temperature under nitrogen for 2 days. The mixture was worked up in the same manner as described above to give 3.3 mg (41.9%) of **2c** and 6.3 mg (46.7%) of **11b** (recovered).

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