An Electrochemical Synthesis of 2-Acetoxy-2-amino Acid and 3-Acetoxy-3-amino Acid Derivatives

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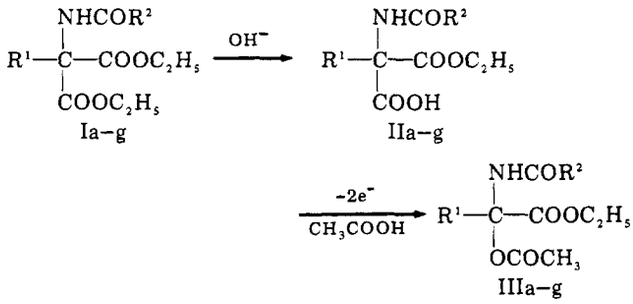
2-Acetoxy-2-amino acid derivatives, which are useful synthetic intermediates, have been synthesized in good yields by anodic oxidation of acylaminomalonic acid monoesters in acetic acid containing sodium acetate. This electrochemical method has been extended to a synthesis of 3-acetoxy-3-amino acid derivatives from 3-alkoxycarbonylalanine derivatives. The mechanism of these electrode reactions is also discussed.

Amino acids which contain a functional group in the 2 position, i.e., 2-hydroxy-2-amino acids,[1] 2-methoxy-2-amino acids,[2a-e] etc., have recently received much attention as useful synthetic intermediates for a preparation of a novel class of amino acids.[3a-c] Ben-Ishai et al.[4a-c] have shown the rich synthetic potentiality of 2-hydroxyglycinate and 2-methoxyglycinate which effectively react with a variety of nucleophiles under Lewis acid catalysts to afford physiologically important 2-substituted 2-amino acids. Most recently, the possible importance of 2-acetoxy-2-amino acid in amino acid chemistry has been recognized by Olsen et al.:[5] this amino acid is more susceptible to nucleophilic substitution under neutral or basic condition than are 2-hydroxy- and 2-methoxy-2-amino acids. Thus, from the viewpoint of the potential value as a synthetic intermediate[6a,b] for amidoalkylation, 2-acetoxy-2-amino acid is considered to be superior over 2-hydroxy- and 2-methoxy-2-amino acids. In spite of the superiority of the former amino acid, however, this amino acid has not been utilized as yet. Limited studies[5,7] of syntheses of 2-acetoxy-2-amino acid have indicated a synthetic difficulty of this amino acid in which the unstable *N,O*-acetal skeleton is involved. For example, *N*-acetyl-2-acetoxy-3-chloroalaninate was synthesized by the treatment of 2-acetamidoacrylate with *N*-chlorosuccinimide/HCl/LiOAc.[5] However, this method lacks versatility for a preparation of all types of 2-acetoxy-2-amino acids.

Recently, on the other hand, functionalization of the methine or methylene group attached to the acylamino group has been one of the interesting themes in synthetic chemistry in relationship to a synthesis of physiologically important natural products such as 7-methoxycephalosporin,[8] bicyclomycin,[9] ergotamine,[10a-c] etc., and excellent methods for the functionalization have been developed.[11a-c] In the previous communication from this laboratory,[12] the electrochemical method has been shown to be highly efficacious in functionalization at the 2 positions of *N*-acylamino acids, especially in the preparation of *N*-acyl-2-methoxy-2-amino acids. In the present paper, we wish to report a synthesis of 2-acetoxy-2-amino acid derivatives[13] by anodic oxidation of substituted and nonsubstituted acylaminomalonic acid monoesters. 3-Acetoxy-3-amino acid derivatives were synthesized in a similar way from 3-alkoxycarbonylalanine derivatives.

A synthesis of 2-acetoxy-2-amino acids (III) was carried out according to Scheme I. Monoesters (II) were prepared by the saponification of the one ester group of the corresponding acylaminomalonic acid diethyl esters (I) in ethanol–potassium hydroxide. The anodic oxidation of compounds II was carried out at 15–20 °C using graphite anode–graphite cathode in a nondivided cell. On electrolysis of monoesters IIa–e in acetic acid containing 0.25 molar equiv of sodium acetate to that of IIa–e, the corresponding *N*-acetyl-2-acetoxy-2-amino acid ethyl esters (IIIa–e) were obtained in 81–94% yield. The current efficiencies of these reactions were about 75%. The side reactions due to oxidation of the benzyl moieties[14] of

Scheme I



a, $R^1 = R^2 = CH_3$; b, $R^1 = C_2H_5$; $R^2 = CH_3$
c, $R^1 = (CH_2)_3CH_3$; $R^2 = CH_3$; d, $R^1 = CH_2Ph$; $R^2 = CH_3$
e, $R^1 = CH_2CH{=}CH_2$; $R^2 = CH_3$; f, $R^1 = H$; $R^2 = OCH_2Ph$
g, $R^1 = H$; $R^2 = CH_3$

monoester IId and the product IIId were not observed. Furthermore, the reduction of the products IIIa–e at the cathode which are sensitive to cathodic reduction[15] did not occur in this electrolysis system. The use of a larger amount of sodium acetate made the current efficiencies decrease: concurrent oxidation of acetate ion presumably took place. The electrolysis of *N*-benzyloxycarbonyl derivative IIf was carried out under the same condition as above to afford ethyl *N*-benzyloxycarbonyl-2-acetoxyglycinate (IIIf) in a good yield without appreciable oxidative cleavage of the benzyl group.[16] In the preparation of *N*-acetyl-2-acetoxyglycinate (IIIg), the potassium salt of monoester IIg was oxidized in acetic acid. The current efficiency of this electrode reaction was lower than those described above. The structural elucidation of these 2-acetoxy-2-amino acid derivatives was carried out based on IR, NMR, and mass spectra and elemental analyses. The yields and the characterizations of the products are summarized in Table I.

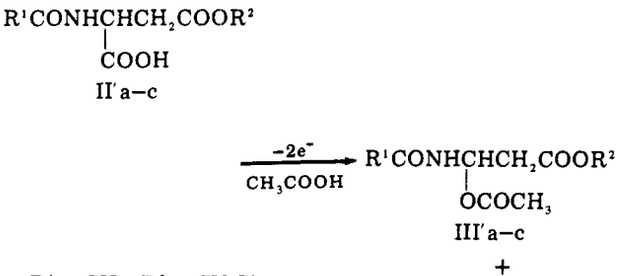
A facile elimination reaction to *N*-acyl-2,3-dehydroalaninate has been observed in *N*-acyl-2-methoxyalaninate[17] and *N*-acyl-2-chloroalaninate.[3a,18a,b] These 2-acetoxy 2-amino acid derivatives (IIIa–e) are so labile that a considerable amount of 2,3-dehydro-2-amino acid derivatives formed by elimination of acetic acid was detected on TLC on treating these amino acids with acetic acid at 50 °C. Accordingly, in the preparation of such unstable 2-acetoxy-2-amino acid derivatives, the electrolysis temperature was kept as low as possible, at least below 25 °C, and the workup procedure was also made carefully to avoid the formation of the dehydroamino acids.

The electrolysis of *N*-acyl-3-alkoxycarbonylalanine (II'a–c) was carried out at 5 °C in acetic acid–tetrahydrofuran (3:1) containing 0.33 molar equiv of sodium acetate to that of (II'a–c). *N*-Acetyl-3-benzyloxycarbonylalanine (II'a), *N*-benzoyl-3-methoxycarbonylalanine (II'b), and *N*,3-dibenzyloxycarbonylalanine (II'c) afforded the corresponding *N*-

Table I. Yields and Spectral Data

Registry no.	Compd	Yield %	IR, cm^{-1}	NMR ($CDCl_3$), δ
62183-00-0	IIIa	91	3300, 1765, 1740, 1670, 1550	1.28 9t, 3 H), 1.98 (s, 3 H), 2.03 (s, 3 H), 2.08 (s, 3 H), 4.26 (q, 2 H), 7.5 (broad s, 1 H)
62183-01-1	IIIb	81	3400, 1755, 1740, 1700, 1520	0.80 (t, 3 H), 1.28 (t, 3 H), 2.03 (s, 3 H), 2.08 (s, 3 H), 1.7–2.4 (m, 1 H), 2.7–3.3 (m, 1 H), 4.26 (q, 2 H), 7.13 (broad s, 1 H)
62183-02-2	IIIc	85	3300, 1750 (broad), 1680, 1510	0.7–1.6 (m, 7 H), 1.24 (t, 3 H), 2.02 (s, 3 H), 2.08 (s, 3 H), 2.4–3.2 (m, 2 H), 4.25 (q, 2 H), 7.1 (broad s, 1 H)
59223-92-6	IIId	94	33000,1770,1750, 1670, 1520	1.20 (t, 3 H), 1.94 (s, 3 H), 2.06 (s, 3 H), 3.26 and 4.30 (AB q, 2 H, J = 13.5 Hz), 4.18 (q, 2 H), 7.0–7.4 (m, 6 H, C_6H_5 + NH)
62183-03-3	IIIe	87	3400, 1755, 1740, 1705, 1540	1.28 (t, 3 H), 2.03 (s, 3 H), 2.09 (s, 3 H), 2.75 (m, 1 H), 3.80 (m, 1 H), 4.27 (q, 2 H), 5.0–6.0 (m, 3 H), 7.4 (broad s, 1 H)
62183-04-4	IIIf	87	3350, 1770, 1740, 1720, 1520	1.25 (t, 3 H), 2.09 (s, 3 H), 4.22 (q, 2 H), 5.25 (s, 2 H), 6.30 (broad s, 2 H, NH + CH), 7.36 (s, 5 H)
62183-05-5	IIIg	82	3300, 3100, 1765, 1740, 1550	1.30 (t, 3 H), 2.10 (s, 3 H), 2.12 (s, 3 H), 4.26 (q, 2 H), 6.40 (d, 1 H), 7.73 (broad d, 1 H)
62183-06-6	IIIh	79	3400, 1740, 1715	1.18 (t, 3 H), 1.88 (s, 3 H), 2.04 (s, 3 H), 3.11 (s, 3 H), 4.11 (q, 2 H), 5.11 (s, 2 H), 7.30 (s, 5 H)
62183-07-7	III'a	40	3300, 1750–1710 (broad), 1670	1.95 (s, 6 H), 2.87 (d, 2 H), 5.14 (s, 2 H), 6.60 (m, 1 H), 7.2–7.5 (m, 6 H, C_6H_5 + NH)
62183-08-8	III'b	54	3300, 1750–1730 (broad), 1655	2.05 (s, 3 H), 2.98 (m, 2 H), 3.77 (s, 3 H), 6.82 (m, 1 H), 7.2–8.0 (m, 5 H), 8.20 (broad d, 1 H)
62183-09-9	III'c	76	3340, 1735, 1720–1700 (broad)	2.05 (s, 3 H), 2.7–3.1 (m, 2 H), 5.10 (s, 2 H), 5.13 (s, 2 H), 6.4–6.6 (m, 1 H), 7.30 (s, 10 H), 10.42 (broad s, 1 H)

Scheme II



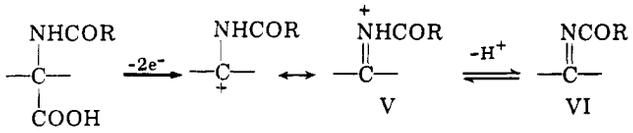
acyl-3-acetoxy-3-amino acid esters (III'a–c) in 40–76% yield. The spectral data of these 3-acetoxy-3-amino acids are shown in Table I. The amount of current passed with 2 Faradays/mol, which was insufficient to consume all the starting materials. A trace amount of products other than the 3-acetoxy-3-amino acid III'b were found on TLC of the electrolyzed solution. The products isolated by preparative TLC were assigned to be *trans*- and *cis*-*N*-acyl-2,3-dehydro-3-amino acids (IV'b) which were presumably formed by elimination of acetic acid from the acetoxyamino acid III'b but not by direct electrode reaction. The electrolysis at a temperature above 20 °C afforded a fair amount of the dehydroamino acid other than the acetoxyamino acid. *N*-Acyl-3-acetoxy-3-amino acids (III'a–c) obtained here are less stable to heat in acetic acid than *N*-acyl-2-acetoxy-2-amino acids (IIIa–e).

In anodic decarboxylation, it is well known that the possible product-forming intermediates are radical and carbonium ion: Kolbe-type reaction involves the former; Hofer–Moest reaction the latter.[19a–c] In these anodic oxidations reported here, no Kolbe dimers were observed. Furthermore, the current efficiencies were fairly good. The results suggest that the carbonium ion intermediate generated via a two-electron transfer is favored over the radical intermediate in these electrode reactions. If the radical intermediate formed by decarboxylation of the monoesters reacts with acetoxy radical, a lower current efficiency would be observed, because the lifetime of acetoxy radical, which is of the order of 10^{-10} s,[20] is too short to give such an efficiency. Furthermore, no elimination and rearrangement took place in these reactions. Thus, the presence of the acylamino group would lead to stabilization of the carbonium ion and allow the formation of only the acetoxy compound. A similar carbonium ion process stabilized by acylamino group has been documented in anodic replacement of carboxylate by methoxy group[12,21a,b] or acetoxy group.[21a] On the other hand, anodic oxidation of alkylated malonic acid monoesters makes the product distribution more complex owing to simultaneous occurrence of elimination, rearrangement, and Kolbe-type reactions.[22a,b]

It has recently been proposed that *N*-acylimine would be an intermediate rather than *N*-acylimmonium both in displacement reaction on 2-substituted *N*-acylalaninate[5,23] and

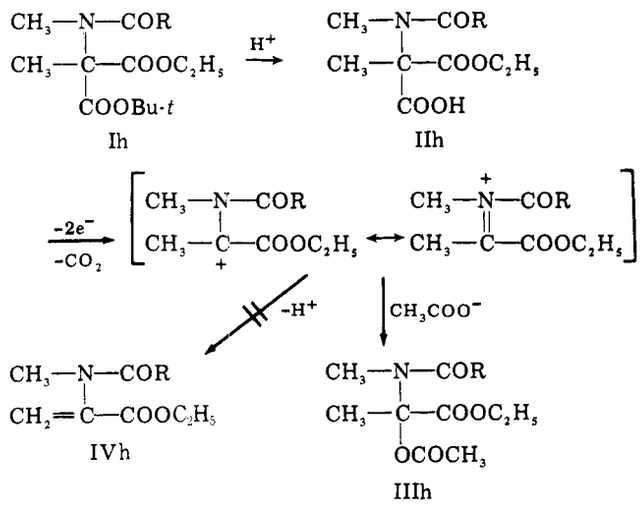
in electrophilic addition reaction[5,18b] to *N*-acyl-2,3-dehydroalaninate; the *N*-methyl analogue of *N*-acyl-2,3-dehydroalaninate, which cannot form *N*-acylimine, did not afford the corresponding 2-substituted alaninate but 2-substituted alaninate produced by Michael addition reaction.[5] The same intermediates, *N*-acylimmonium (V) and *N*-acylimine (VI),

Scheme III



are possible as an intermediate in this electrode reaction. In order to compare the electrode reaction with the electrophilic addition reaction as referenced above, methyl(*N*-methyl-*N*-benzyloxycarbonylamino)malonic acid monoethyl ester (IIh) was synthesized from diester Ih. Anodic oxidation of IIh

Scheme IV



was carried out in acetic acid–tetrahydrofuran (3:1) at 5 °C to afford only the corresponding acetoxy compound (IIIh) but not the elimination product (IVh). This result, which is in contrast with the addition reaction, indicates that the lifetime of the immonium ion (V) is long enough for it to be susceptible to nucleophilic attack of acetate ion, although the immonium ion (V) would be destabilized by inductive effect of the electron-withdrawing acyl group. It is, therefore, suggested that *N*-acylimmonium (V) may be involved in the anodic oxidation of monoesters II and II′. It has also been noted that anodic oxidation of *N,N*-dialkylformamides,[24a,b] trialkylamines,[25a,b] and *N,N*-dialkylcarbamates[26] in methanol proceeds through the immonium intermediates to afford the corresponding α-methoxylated products.

Experimental Section

Equipment. Melting points were measured using the Yamato melting point apparatus and were uncorrected. IR spectra were recorded on a Shimadzu IR-27G infrared spectrophotometer. NMR spectra were obtained using a Hitachi Perkin-Elmer R-20 high-resolution NMR spectrometer with tetramethylsilane as internal standard. The electrolyses were carried out by the use of a Hokuto Potentio-Galvanostat HA 104 (1A-55V) attached to a Hokuto HA-108A coulomb meter.

Preparation of Substituted Acylaminomalonic Acid Diesters (Ia–h). Compound Ig was recrystallized from ethanol–ethyl acetate. Compounds Ia–e were prepared by the reaction of Ig with the corresponding alkyl halides in ethanol containing sodium ethoxide. The yields of these reactions were usually good (70–95%). The physical constants of these compounds have appeared elsewhere.[27] The *N*-benzyloxycarbonyl derivative (If) was prepared according to the reported method.[28]

Compound Ih. *N*-Benzyloxycarbonylaminomalonic acid monoethyl ester (10.0 g) was dissolved in 150 mL of methylene chloride containing 1 mL of concentrated sulfuric acid. This solution was saturated with isobutene at 0 °C. The reaction mixture was allowed to stand overnight at room temperature, washed several times with 1% aqueous sodium bicarbonate and with water, then dried over magnesium sulfate. The solution was evaporated to dryness in vacuo and the resulting residue was purified on silica gel chromatography using chloroform–ethyl acetate (4:1) as eluate to afford 11.6 g (97%) of *N*-benzyloxycarbonylaminomalonic acid *tert*-butyl ethyl diester as a colorless syrup: IR (film) 3360 (NH), 1755, 1740, 1715 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.27 (t, 3 H), 1.47 (s, 9 H), 4.26 (q, 2 H), 5.90 (d, 1 H, J = 6 Hz), 5.16 (s, 2 H), 5.89 (broad d, 1 H), 7.39 (s, 5 H). Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.48; H, 6.86; N, 4.30. Anhydrous dimethylformamide (130 mL) was added to a mixture of the diester (11.0 g) obtained above and commercially available silver oxide (purchased from Nakarai Kagaku Co. Ltd.) (25 g). To this was added 40 mL of methyl iodide at 0 °C under vigorous stirring. The stirring was continued for 16 h at room temperature. The above procedure[29] was performed in a dark room. After the reaction was over, insoluble materials were filtered off and the filtrate was evaporated to dryness in vacuo. To the resulting residue was added 200 mL of ethyl acetate and insoluble materials were filtered off. The filtrate was washed five times with 50 mL of 10% aqueous sodium thiosulfate, washed with water, then dried over magnesium sulfate. The solution was evaporated to dryness in vacuo and the residue was purified on silica gel chromatography using chloroform–ethyl acetate (4:1) as eluate to afford 11.5 g (97%) of methyl(*N*-methyl-*N*-benzyloxycarbonylamino)malonic acid *tert*-butyl ethyl diester as a light yellow syrup: IR (film), 1750, 1731, 1708 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.23 (t, 3 H), 1.47 (s, 9 H), 1.71 (s, 3 H), 2.96 (s, 3 H), 4.28 (q, 2 H), 5.17 (s, 2 H), 7.35 (s, 5 H). Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.36; H, 7.37; N, 3.73.

Preparation of Monoesters (IIa–g) (General Procedure). Diester I (0.1 mol) was dissolved in 70 mL of ethanol. To this was added dropwise a solution of potassium hydroxide (0.12 mol) dissolved in 6 mL of water at 20–25 °C under vigorous stirring. The reaction mixture was allowed to stand for 1 week at the same temperature, and then the solvent was evaporated under reduced pressure below 35 °C. The residue was dissolved in 10–30 mL of water and the solution was washed with ethyl acetate. The aqueous layer was acidified to Congo red with 12 N hydrochloric acid at 0 °C. The acidified solution was shaken with five 100-mL portions of ethyl acetate, and the combined ethyl acetate layer was washed twice with 20 mL of water, dried over magnesium sulfate, then evaporated to dryness in vacuo below 30 °C. The resulting crystals were recrystallized with ethyl acetate-*n*-hexane. This procedure gave monoesters IIa–e,g in good yields. Analytical data are as follows.

Compound IIa (76% yield), mp 135–136 °C (lit.[30] mp 136–136.5 °C). Anal. Calcd for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.10; H, 6.51; N, 6.93.

Compound IIb (78% yield): mp 138–140 °C; NMR ($CDCl_3$ + Me_2SO-d_6) δ 0.82 (t, 3 H), 1.27 (t, 3 H), 2.05 (s, 3 H), 2.34 (q, 2 H), 4.24 (q, 2 H), 7.08 (broad s, 1 H), 11.10 (broad s, 1 H). Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.75; H, 6.86; N, 6.51.

Compound IIc (73% yield): mp 128–130 °C; NMR (Me_2SO-d_6) δ 0.7–1.5 (m, 7 H), 1.24 (t, 3 H), 2.02 (s, 3 H), 2.1–2.7 (m, 2 H), 4.19 (q, 2 H), 7.12 (s, 1 H). Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.86; H, 7.81; N, 5.71. Found: C, 53.50; H, 7.52; N, 5.74.

Compound IId (79% yield): mp 130–131 °C; NMR ($CDCl_3$ + Me_2SO-d_6) δ 1.28 (t, 3 H), 2.01 (s, 3 H), 3.59 (s, 2 H), 4.23 (q, 2 H), 6.8–7.5 (m, 6 H, C_6H_5 + NH), 11.65 (broad s, 1 H). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.01; H, 6.21; N, 5.09.

Compound IIe (82% yield), mp 123–124 °C (lit.[31] mp 121–122 °C). Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.39; H, 6.60; N, 6.11. Found: C, 52.15; H, 6.72; N, 6.21.

Compound IIf (78% yield): mp 65–67 °C; NMR (Me_2SO-d_6) δ 1.20 (t, 3 H), 4.15 (q, 2 H), 4.82 (d, 1 H), 5.08 (s, 2 H), 7.36 (s, 5 H), 8.03 (d, 1 H). Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 55.62; H, 5.41; N, 4.82.

In the case of monoester IIg, the following procedure was employed. Diethyl acetamidomalonate (Ig) was saponified as described above. The reaction mixture was evaporated to dryness in vacuo, and the resulting residue was triturated with acetone. The crystals were collected by filtration and used without purification.

Compound IIh. Compound Ih (8.0 g) was dissolved in 50 mL of 20% hydrogen chloride in dioxane and the reaction mixture was allowed to stand at room temperature for 4 h. The solvent was evaporated

under reduced pressure and the resulting residue was purified on silica gel chromatography with chloroform–ethyl acetate (1:1) as eluate to afford 3.3 g (49%) of IIh: mp 77–78 °C; IR (Nujol) 1760, 1736, 1569 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.19 (t, 3 H), 1.73 (s, 3 H), 3.12 (s, 3 H), 4.20 (q, 2 H), 5.18 (s, 2 H), 7.35 (s, 5 H), 9.1 (broad s, 1 H). Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.24; H, 6.19; N, 4.53. Found: C, 57.96; H, 6.27; N, 4.71.

Compounds II'a–c. Compounds II'a (mp 107–109 °C) and II'c (mp 93–95 °C) were prepared from 3-benzyloxycarbonyl-L-alanine, according to the known method.[32] Compound II'b (mp 125–126 °C) was synthesized from 3-methoxycarbonyl-L-alanine as reported previously.[33]

Reagent and Apparatus for Electrolysis. Acetic acid was purified as follows. Acetic acid (2 L) was refluxed with 70 mL of acetic anhydride for 5 h, and distilled under dried nitrogen gas (bp 115 °C). Special grade sodium acetate was purchased from Katayama Kagaku Co. Ltd., and used without further purification. The electrolysis cell used is an ordinary beaker which is 4 cm in diameter and 10 cm in height. A graphite anode (3 × 4 cm) was placed 1–3 mm apart from a graphite cathode in a nondivided cell.

Electrolysis. Method A. Monoester II (0.02 mol) and sodium acetate (0.005 mol) were dissolved in 50 mL of acetic acid. The solution was put in an electrolysis cell and electrolyzed at a constant current of 250 mA at 20–25 °C. The amount of current passed was 80 mFaradays. After the electrolysis was over, the electrolyzed solution was evaporated to dryness in vacuo below 30 °C. To the residue was added 50 mL of benzene and the mixture was evaporated to dryness in vacuo. This evaporation procedure was repeated at least five times until acetic acid was completely removed. The residue was extracted with ethyl acetate. The extract was washed once with water, dried over magnesium sulfate, then evaporated to dryness in vacuo. The resulting syrup was crystallized by standing at −30 °C in a refrigerator and the crystals were recrystallized from ethyl acetate–*n*-hexane.

Method B. Monoester II or II' (0.01 mol) and sodium acetate (0.0033 mol) were dissolved in a mixture of 30 mL of acetic acid and 10 mL of tetrahydrofuran. The electrolysis was carried out at a constant current of 125 mA at 5–7 °C. The reaction was discontinued when 20 mFaradays was passed. The electrolyzed solution was evaporated to dryness in vacuo below 15 °C, and the resulting residue was treated with benzene as described in method A. To the residue was added 20 mL of dry ethyl ether, and insoluble materials were filtered off. The filtrate was treated with 1 g of activated charcoal, and insoluble materials were filtered off. The treatment with activated charcoal was repeated three times. The filtrate was evaporated to dryness in vacuo. The resulting syrup was allowed to stand at −30 °C, and the crystals formed were collected by filtration. The acetoxyamino acids obtained by method A or method B should be stored below −30 °C; otherwise these decompose to the dehydroamino acids by elimination of acetic acid.

Compound IIIa. This compound was obtained by method A, mp 72–73 °C. Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.49; H, 7.09; N, 6.55.

Compound IIIb. Electrolysis of IIb by method A afforded this compound, mp 71–72 °C. Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.74; H, 7.39; N, 6.12.

Compound IIIc. This compound prepared by method A was resistant to crystallization, but analytical data support IIIc: colorless syrup; mass spectrum *m/e* 259 (M^+), 200 (M^+-$OCOCH_3$). Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.32; H, 8.22; N, 5.31.

Compound IIId. This compound was prepared by method A, mp 69–70 °C. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.35; H, 6.53; N, 4.74.

Compound IIIe. Treatment of IIe by method A gave this compound: mp 61–62 °C; mass spectrum *m/e* 243 (M^+), 184 ($M^+ - OCOCH_3$). Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 53.88; H, 7.02; N, 5.57.

Compound IIIf. After electrolysis by method A, the crude product was purified on silica gel chromatography with chloroform–ethyl acetate (3:1) as eluate to afford IIIf as a colorless syrup. Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.82; H, 5.94; N, 4.83.

Compound IIIg. The potassium salt of IIg was electrolyzed in acetic acid to afford IIIg: mp 61–62 °C; mass spectrum *m/e* 203 (M^+), 144 ($M^+ - OCOCH_3$). Anal. Calcd for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.28; H, 6.39; N, 6.94.

Compound IIIh. Method B was applied to this compound: mp −7 to −8 °C; mass spectrum *m/e* 295 (M^+), 236 ($M^+ - OCOCH_3$). Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.34; H, 6.55; N, 4.33. Found: C, 59.41; H, 6.57; N, 4.56.

Compounds III'a–c. These compounds were treated by method B. Compound III'a, mp 78–79 °C (from ethyl acetate–*n*-hexane). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02. Found: C, 60.11; H, 5.98; N, 5.11. Compound III'b, mp 88–89 °C (from ethyl acetate–*n*-hexane). Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.42; H, 5.74; N, 5.42.

Compound II'c was electrolyzed at 5 °C. The workup procedure was also performed below 10 °C to afford pure III'c as a colorless syrup which was confirmed by IR and NMR spectra (Table I). This compound is so unstable that the elemental analysis and mass spectrum did not show reasonable values. When this compound was allowed to stand at room temperature, the spot of this compound on TLC almost vanished to afford the elimination product IV'c.

Electrolysis of II'b at 25 °C. Compound II'b was electrolyzed in acetic acid–tetrahydrofuran (3:1) at 25 °C. Two spots, R_f 0.48 and 0.94, other than the acetoxyamino acid III'b (R_f 0.55) were observed on TLC using chloroform–acetic acid–methanol (95:5:3) as a developing solvent. The spots were isolated by preparative TLC and assigned to be the trans form of IV'b (R_f 0.48) and the cis form of IV'b (R_f 0.94). *trans*-IV'b: mp 137–139 °C; IR (Nujol) 3350, 1690, 1620 cm^{-1}; NMR ($CDCl_3$) δ 3.70 (s, 3 H), 5.70 (d, 1 H, J = 14 Hz), 7.2–8.0 (m, 5 H), 8.23 (dd, 1 H, J = 11, 14 Hz), 9.25 (broad d, 1 H, J = 11 Hz). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.45; H, 5.52; N, 6.55. *cis*-IV'b: mp 61–62 °C; IR (Nujol) 3330, 1700, 1685, 1630 cm^{-1}; NMR ($CDCl_3$) δ 3.78 (s, 3 H), 5.27 (d, 1 H, J = 9 Hz), 7.2–8.1 (m, 6 H), 11.0–12.0 (broad s, 1 H). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.53; H, 5.61; N, 6.54.

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Registry No.—Ia, 55166-91-1; Ib, 32819-24-2; Ic, 62183-10-2; Id, 3235-26-5; Ie, 14109-62-7; If, 3005-66-1; Ih, 62183-11-3; IIa, 59223-81-3; IIb, 59223-82-4; IIc, 62183-12-4; IId, 59223-84-6; IIe, 2584-73-8; IIf, 7682-49-7; IIg potassium salt, 62183-13-5; IIh, 62183-14-6; II'a, 10144-33-9; II'b, 39741-26-9; II'c, 62813-15-7; *trans*-IV'b, 62813-16-8; *cis*-IV'b, 62813-17-9; *N*-benzyloxycarbonylaminomalonic acid *tert*-butyl ethyl diester, 61016-16-8; isobutene, 115-11-7.

References and Notes

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Reaction of 2,3-Di(*p*-anisyl)-2,3-butanediol with Acetyl Bromide

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The reaction of *meso*-di(*p*-anisyl)-2,3-butanediol (**1**) with acetyl bromide in the presence of a small amount of *N*-phenyl-β-naphthylamine at room temperature is different from the literature,[1,2] and gives *cis*- and *trans*-2,3-di(*p*-anisyl)-2-butene (**6** and **2**) and 2-*p*-anisyl-3-methyl-6-methoxyindene (**5**) together with another isomeric butene, 2,3-di(*p*-anisyl)-1-butene (**7**) and pinacol rearrangement product, 3,3-di(*p*-anisyl)-2-butanone (**4**), but the yield of expected product, 2,3-di(*p*-anisyl)-1,3-butadiene (**3**), is very low. Addition of a small amount of HBr and KI promotes the formation of the butenes with simultaneous decrease in the content of the indene and the butanone. The time–conversion curves for the reaction of **1** and **4** with acetyl bromide were drawn and a mechanism involving dianisyl-3-methylallyl cation (**9**) is suggested.

2,3-Diaryl-1,3-butadiene was reported to be prepared by the dehydration of *meso*-2,3-diaryl-2,3-butanediol with acetyl bromide in the presence of a small amount of *N*-phenyl-β-naphthylamine.[1,2] In the course of our attempt to prepare 2,3-di(*p*-anisyl)-1,3-butadiene (**3**) according to this procedure, however, we found that by long duration of reaction the yield of butadiene **3** was very low and that *trans*-2,3-di(*p*-anisyl)-2-butene (**2**) and 2-*p*-anisyl-3-methyl-6-methoxyindene (**5**) were obtained together with a certain amount of 3,3-di(*p*-anisyl)-2-butanone (**4**) and other products. The easy formation of pinacolone **4** is anticipated under these acidic conditions, because the *p*-anisyl group has a high migratory aptitude in the pinacol rearrangement[3] and the substituted butadiene **3** can be converted to the substituted indene **5** by acid catalysts,[1] but the substituted butene **2** is an unexpected product. We tried to confirm the reaction products and to elucidate the mechanism for this abnormal formation of **2** and other products.

Results and Discussion

When the reaction of pinacol **1** with acetyl bromide in the presence of a little *N*-phenyl-β-naphthylamine was carried out at 0 °C for 2 h according to the literature procedure,[2] the main products were pinacolone **4** and indene **5** together with minor products such as butadiene **3** and butenes **2**, **6**, and **7**, as shown in Table I.

The products were identified by NMR, IR, and MS, and GLC products **2**, **3**, **4**, and **5** were isolated by column chromatography using silicic acid as an adsorbent and benzene–petroleum ether as an eluent. The yields of butenes **2**, **6**, and **7** were low after 2-h reaction at 0 °C (run 1), but at higher temperature (run 2), longer reaction time (run 3) or addition of KI and HBr (runs 4 and 6) caused an increase in the contents of the butenes with a simultaneous decrease in the content of pinacolone **4** and indene **5**. These results suggest that reducing agents such as HBr and HI promote the formation of butenes **2**, **6**, and **7**. Acetyl bromide which can give HBr by the reaction with pinacol **1** is effective in the butene formation and, as expected, acetyl chloride is also effective in the presence of KI (run 9).

Acetic anhydride as well as acetyl chloride as a diluent suppressed the butene formation (runs 7 and 8). The amine acts to increase the amount of butadiene **3** but decreases that of indene **5** (runs 10 and 11). Excess acetyl bromide tends to increase the amount of **5** and pinacolone **4**, but decreases those of other products (runs 2 and 5).

Figure 1 shows the time–conversion curves in the reaction of pinacol **1** with acetyl bromide. Figure 1 implies the initial formation and then gradual consumption of indene **5** and diene **3** to butenes **2**, **6**, and **7**. The total recovery decreases to 70%, probably because of the formation of tarry material; the decrease of indene **5** seems to be parallel to the decrease of whole products.

Since pinacol **1** under these acidic reaction condition can be converted to pinacolone **4** at an early stage of the reaction, the reaction of **4** with acetyl bromide was examined. On addition of acetyl bromide to the pinacolone, the same products and the similar time–conversion curve as Figure 1 were obtained, but the reaction with pinacolone **4** was much slower than pinacol **1**. Hence, the reaction of **1** to give butenes **2**, **6**, and **7** would not proceed mainly via pinacolone **4**. Also, addition to KI to the system of **4**–AcBr accelerated the reaction of pinacolone **4**, giving the butenes **2** and **6**.

Figure 1 might suggest a pathway **1** → **5** → **2**, **6**, and **7**, but it is less plausible, since the treatment of indene **5** with acetyl bromide alone, aqueous HBr, acetic anhydride, or acetyl