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A NEW SYNTHESIS OF 2-ALKOXY-AND 2-ACETOXY-2-AMINO ACIDS BY ANODIC OXIDATION

Hiroshi Horikawa, Tameo Iwasaki, Kazuo Matsumoto, and Muneji Miyoshi
Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd.,
16-89, Kashima-3-chome, Yodogawa-ku, Osaka, Japan

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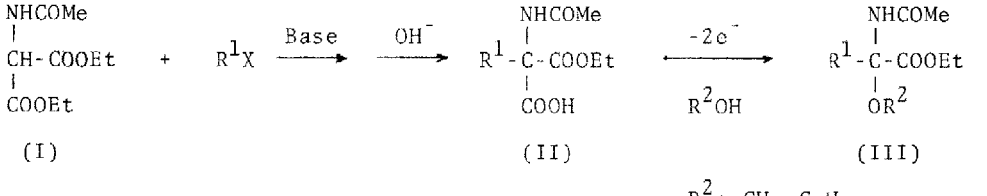
2-Alkoxy-2-amino acids[1] and 2-acetoxy-2-amino acids are known as structural elements of naturally occurring Ergot Alkaloids such as Ergotamines[2a-c] which are physiologically important. However, only a few synthetic methods of these amino acids have hitherto been reported, owing to their poor stability to heat, acid etc.. These have been prepared: by heating 2-benzylideneoxazole-5-ones with alcohols[3a,b]; by treating 2-acylaminoacrylate with alcohols containing hydrogen chloride,[4a,b] or with alcohols and mercury (II) acetate, followed by demercuration with sodium borohydride[5]; by the conversion of 2-methylthio-2-amino acids to 2-methoxy-2-amino acids.[6a,b] These methods are rather unsatisfactory in the product yields and/or in the tedious procedures for the preparation of the starting materials.

In the present communication, we wish to report a new synthesis of 2-alkoxy- and 2-acetoxy-2-amino acids (III) by anodic oxidation of 2-ethoxycarbonyl-2-acetamidoacetic acid derivatives (II) which are easily prepared by the reaction of diethyl 2-acetamidomalonate (I) with alkyl halides, followed by saponification of the one ester groups.



A general electrolysis procedure for a preparation of 2-methoxy-2-amino acid derivatives [R_2:CH_3 in compound (III)] is as follows. Compound (II) (0.1 mole) was dissolved in 30 ml of methanol, to which sodium salt of compound (II) (0.0005 mole) was added. The solution was electrolyzed at 15-20°C using 2 cm^2 of carbon anode which was placed 0.5 cm apart from carbon cathode. An electro-

Table

Compound(III) R^1	R^2	Yield(%)	Mp.(°C)	Compound(III) R^1	R^2	Yield(%)	Mp.(°C)
H	CH_3	89	Syrup [a]	$PhCH_2$	C_2H_5	79	102-104
CH_3	CH_3	97	40-42	CH_3	$(CH_3)_2CH$	80	71-73 [c]
C_2H_5	CH_3	91	80-81	$CH_2=CHCH_2$	CH_3	83	Syrup [d]
$(CH_3)_2CH$	CH_3 [b]	85	81-82	$PhCH_2$	$COCH_3$	85	Syrup [e]
$PhCH_2$	CH_3	96	97-98				

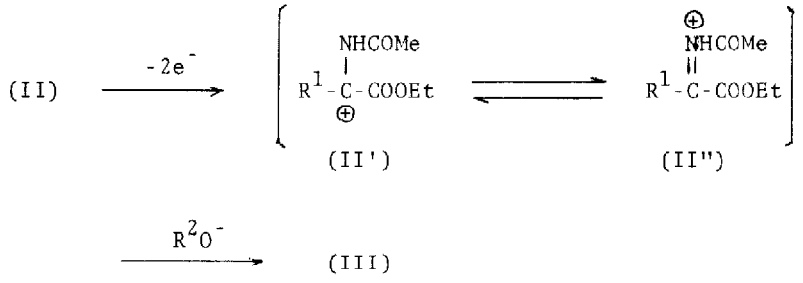
a) nmr in $CDCl_3$ (TMS as internal standard), δ 1.33(t,3H), 2.12(s,3H), 3.39(s, 3H), 4.28(q,2H), 5.57(d,1H), 6.9-7.4(broad d,1H). b) Methyl ester c) Electrolysis current was 50mA. d) nmr in $CDCl_3$, δ 1.33(t,3H), 2.09(s,3H), 2.4-3.3(m, 2H), 3.30(s,3H), 4.26(q,2H), 4.9-6.0(m,3H), 6.9(broad s,1H). e) nmr in $CDCl_3$, δ 1.23(t,3H), 1.99(s,3H), 2.10(s,3H), 3.25 and 4.29(AB q,2H,J=13Hz), 4.16(q,2H), 7.2(m,6H).

lysis current was maintained at 250 mA during the electrolysis. After the theoretical amount of current (130 min. as a two-electron transfer) was passed, the electrolyzed solution was neutralized with acetic acid. The solution was evaporated to dryness in vacuo, the residue was dissolved in ethyl acetate, then the ethyl acetate solution was washed with a small amount of water. The ethyl acetate layer was dried over $MgSO_4$, and the solution was evaporated to dryness in vacuo to afford compound(III) (R^2:CH_3) which was pure enough for elemental analysis without further purification. The electrolyses in ethanol and isopropanol also proceeded to afford 2-ethoxy derivative [R^2:C_2H_5 in compound (III)] and 2-isopropoxy derivative [R^2:-$CH(CH_3)_2$ in compound (III)] respectively. 2-Acetoxy derivative [R^2:$COCH_3$ in compound (III)] was similarly prepared by anodic oxidation of compound(II) in AcOH-AcONa. The structural elucidation was carried out by NMR and mass spectra, and elemental analysis. For example, ethyl N-acetyl-2-methoxyphenylalaninate had m.p. 97-98°C. NMR, IR, and mass spectra, and elemental analysis are as follows: NMR in $CDCl_3$, δ 1.33 (t, 3H, J=7 Hz), 2.04 (s, 3H), 3.22 and 3.88(AB q, 2H, J=13 Hz), 3.30 (s, 3H), 4.26 (q, 2H, J=7 Hz), 6.4-6.6 (broad s, 1H), 7.23 (s, 5H); IR (nujol), 3300, 1740, 1675, 1530 cm^{-1}; mass spectrum, m/e 265 (M^+); elemental analysis, found: C, 63.11; H, 6.99; N, 5.28. $C_{14}H_{19}O_4N$ requires: C, 63.38; H, 7.22; N, 5.28.

The yields were satisfactorily good in all cases with quantitative current efficiencies as listed in Table. In these reactions, rearrangement and elimination were not observed. Furthermore, no Kolbe dimer was detected at all.

The use of Pt anode gave almost the same results as those in carbon anode. However, the alkoxylation did not proceed at all in the presence of ClO_4^- or BF_4^-, the starting material being completely recovered from the electrolytic solution. The cyclic voltagram in this system indicated that the solvent was oxidized at more cathodic potential than the oxidation potential of the substrate.

The detailed mechanism of the electrode reaction is uncertain. However, carbonium ion (II') route via a two-electron transfer would be favored over radical route[7] which involves the recombination of the alkoxy or acetoxy radical, a short-lived radical, with the radical generated by an electron transfer to the substrate (II). If the reaction proceeds via the radical route, a lower current efficiency would be observed than that obtained in the present study.[8]



Thus, the carbonium ion (II'), which would be stabilized as immonium ion (II"),[9] would react with nucleophile to give the product (III).

This electrochemical synthesis will serve as a useful method for preparing 2-alkoxy- and 2-acetoxy-2-amino acids in high yields from the common starting materials. Furthermore, 2-alkoxy- and 2-acetoxy-2-amino acids are attractive as synthetic intermediates of unusual amino acids.[6a, 10a-d]

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References and Footnotes

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