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CONVENIENT SYNTHESIS AND REACTION OF VARIOUS KINDS OF α-DEHYDROGLUTAMIC ACID DERIVATIVES

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Summary: Various conversions of methyl γ-methyl-α-(N-benzyloxycarbonyl)-α-dehydroglutamate, derived by the condensation of methyl γ-methyl-α-oxoglutarate with benzyl carbamate, gave the corresponding five more different and interesting α-dehydroglutamic acid and a quasi-pyrodehydroglutamic acid derivatives.

In the course of the synthesis of dehydrooligopeptides, which are very important material and substrate for both the pharmacological study[1] and the asymmetric hydrogenation,[2] we reported so far useful synthesis and coupling[3,4] of α-dehydroamino acid (DHA) derivatives.[5-7] Up to the present, however, only the synthesis of the neutral DHA, which seems to originate from aliphatic and aromatic α-amino acid such as Thr, Leu, and Phe, has been reported.[8,9]

In this paper, we wish to report the convenient synthesis and tranformation of various interesting α-dehydroglutamic acid (ΔGlu) derivatives, which are also supposed to originate from the proteingenic acidic α-amino acid.

According to the method reported previously,[7] methyl γ-methyl-α-oxoglutarate (2; 680 mmol), derived by the esterification of α-oxoglutaric acid (1) with MeOH by the usual method, was condensed with benzyl carbamate (750 mmol) in dry benzene (500 ml) in the presence of $POCl_3$ (160 mmol) under reflux for 10 h to give methyl γ-methyl-α-(N-benzyloxycarbonyl)-α-dehydroglutamate [3; Cbz-ΔGlu(Me)-OMe] in a good yield.

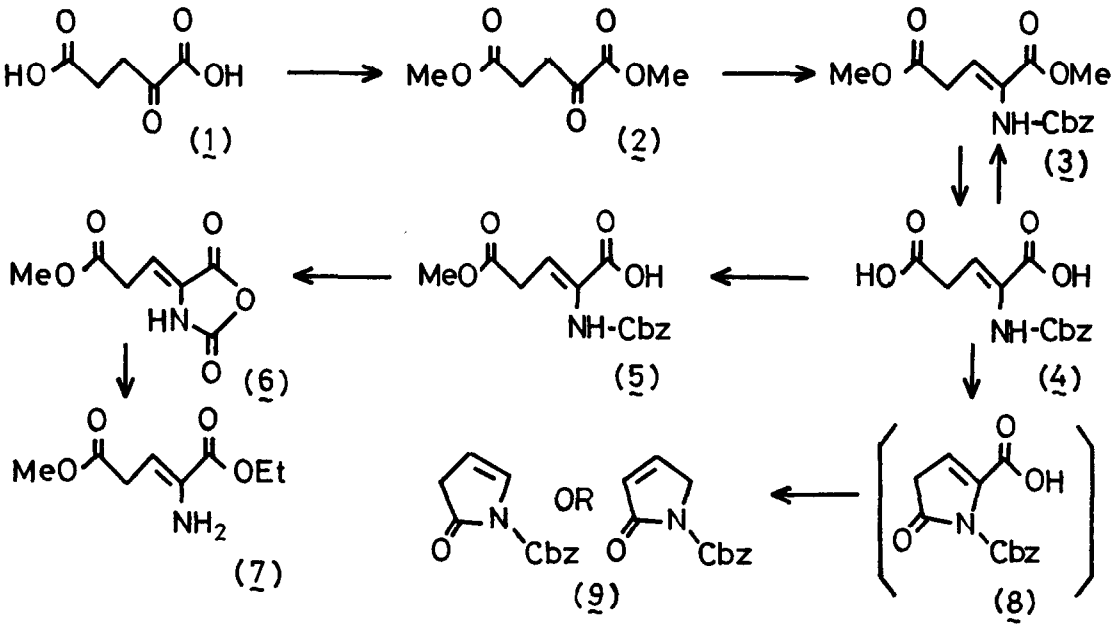
On the other hand, since it was found that the synthesis of the dicarboxylic acid of 3 (4) by the direct condensation of 1 with benzyl carbamate was unsuccessful, 3 was attempted to hydrolyze under several conditions. The hydrolysis of 3 (20 mmol) with $LiOH.H_2O$ (44 mmol) in 40% MeOH solution (80 ml) under cooling for 3 h was achieved to give Cbz-ΔGlu-OH (4) in ca. a 90% yield. As a result, the procedure was found to be superior to the other hydrolysis of 3 with NaOH or $Ba(OH)_2$, by which the yield of 4 was less than 30%.

Judging from the structural characteristic of 4, as in the case of free glutamic acid, it is also anticipated that, besides the formation of two kinds of half esters, the possible three types of intramolecular cyclization will take

place between the appropriate two of α-, γ-carboxyl, and α-Cbz-amino groups respectively.

First, in order to obtain N-carboxy α-dehydroglutamic acid anhydride (ΔGlu-NCA) by the cyclization between γ-carboxyl and Cbz-amino groups, the treatment of 4 with $SOCl_2$ was performed according to the procedure reported.[7] Unfortunately, however, it was found that the desired ΔNCA could not be synthesized but only a few kinds of structurally ambiguous products were obtained as a mixture. Therefore, to avoid the undesirable reactions, in the first place, the selective protection of each of carboxyl groups in 4 was thoroughly pursued. As a result, the esterification of 4 (18 mmol) with MeOH (100 ml) in excess ethyl ether (ca. 500 ml) in the presence of $SOCl_2$ (22 mmol) at room temperature overnight proceeded to give only a γ-ester, Cbz-ΔGlu(Me)-OH (5) in a fairly good yield, whereas the similar treatment of 4 in the absence of ether gave only a dimethyl ester (3) quantitatively. The subsequent cyclization between α-carboxyl and α-Cbz groups of 5 (6.8 mmol) with excess $SOCl_2$ (130 mmol) in acetyl chloride (3 ml) was carried out to give the expected ΔGlu(Me)-NCA (6), which was further treated with excess EtOH (10 ml) to give first N-deprotected ΔGlu(Me)-OEt (7) in a good yield.

Next, to examine whether or not the dehydration between γ- and α-carboxyl or α-amino and γ-carboxyl groups occurs, 4 was subjected to the dehydration with several reagents such as acetic anhydride or dicyclohexylcarbodiimide (DCC). The reaction of 4 (6 mmol) with acetic anhydride (30 ml) at 60 °C for 3 h proceeded smoothly to give decarboxylated pyrrolin-5-one derivative [9; $C_{12}H_{11}NO_3$, yield

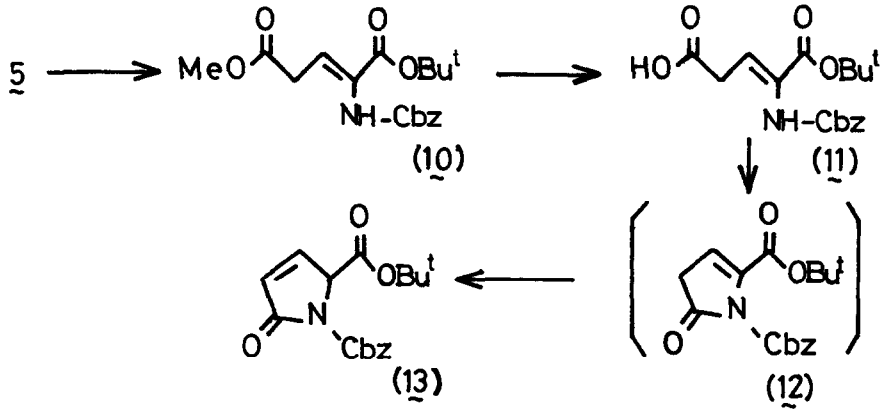


Scheme 1.

95%, colorless needles from isopropyl ether, mp 89-90 °C. IR (KBr): 1765, 1685 (C=O), 1650 (C=C) cm^{-1}. NMR ($CDCl_3$): δ 7.36 (m, 6H, C_6H_5 + 1H, 2-H), 6.15 (dt, 1H, J=6.2 Hz, J=2.2 Hz, 3-H), 4.42 (dd, 2H, 4-H)], insstead of the expected pyro-ΔGlu-OH (6) and acid anhydride of 4. On the other hand, in the case of DCC, the similar treatment of 4 was worked up to give 9 in a poor yield. Because it is difficult to determine the configurational structure of 9 to be either 2- or 3-pyrrolin-5-one from the above spectral data alone, the another synthetic method for pyro-dehydroglutamic acid ester was investigated, as shown in Scheme 2.

Further esterification of 5 (70 mmol) with enough isobutene in CH_2Cl_2 (50 ml) in the presence of a drop of concentrated H_2SO_4 in a sealed tube for 48 h at room temperature gave Cbz-ΔGlu(Me)-OBu^t (10), which (50 mmol) was then selectively hydrolyzed with LiOH (55 mmol) in MeOH (13 ml) to give γ-deblocked Cbz-ΔGlu-OBu^t (11) in a good yield. Similarly, 11 was cyclized with acetic anhydride (15 ml) for 3 h to give t-butyl pyrrolin-5-one-2-carboxylate [13; $C_{17}H_{19}NO_5$, yield 65%, colorless prisms from benzene, mp 86.5-87.5 °C. IR (KBr): 1780, 1745 (COO), 1690 (C=O), 1590 (C=C) cm^{-1}. NMR ($CDCl_3$): δ 7.10 (dd, 1H, J=6.0 Hz, J=2.0 Hz, 4-H), 6.20 (dd, 1H, J=6.0 Hz, J=2.0 Hz, 3-H), 5.10 (dd, 1H, J=2.0 Hz, J=2.0 Hz, 2-H)].

Based on the ^{1}H-NMR spectral data obtained above, it was found that the



Scheme 2.

spectral pattern of 9 and 13 was very similar to that of 3-pyrrolin-5-one derivatives,[10] which chemical shifts and the coupling constants were presented by Vasvari-Decreczy et al.[11] Accordingly, from the above results and fact, it was concluded that the position of the double bond in pyrrolinones thus obtained was located at 3-position, instead of 2-position. In addition, it was supposed that the shift of the double bond in ring from 2- to 3-position took place during or after the cyclization.

The yields, melting points, and the spectral data of 3-7, 10, and 11 are summarized in Table 1.

Table 1. ΔGlu derivatives

Compd. No.	Yield (%)	mp °C	IR spectrum, cm^{-1} in KBr				NMR spectrum, δ in $CDCl_3$			
			NH	C=O		C=C	-CH=	(J_{Hz})	$-CH_2CH=$	-NH- $-NH_2$
3	70 quant[a]	81-82[b]	3250	1730	1700	1665	6.76t	(7.0)	3.32d	6.60s
4	89	146-147[c]	3250	1710	1690	1655	6.50t	(7.0)	3.19d	8.72s[f]
5	80	129-130[d]	3250	1730	1690	1660	6.82t	(7.5)	3.26d	6.76bs
6	95	101-102[b]	3250	1860	1770	1670	5.81t	(7.5)	3.39d	8.89bs
7	49	syrup	3450 3350	1730	1700	1650	5.70t	(7.0)	3.15d	(2.30bs)
10	75	syrup	3300	1730	1720	1660	6.65t	(7.0)	3.31d	6.60bs
11	87	73-75[e]	3300	1740	1720	1640	6.65t	(7.0)	3.29d	6.76bs

a) Yield from 4. b) Colorless needles from chloroform. c) Colorless needles from ethyl acetate-chloroform. d) Colorless needles from benzene. e) Colorless prisms from hexane. f) Measured in DMSO-d_6.

Moreover, it is note-worthy that the one-pot coupling of 6 with α-amino acid or peptide and the new synthesis of other proteingenic basic DHA from 11 have been successful. The results will be reported and discussed elsewhere.

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