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Synthesis and Polymerization of γ-Ethyl-L-Glutamate Derivatives of Nucleic Acid Bases

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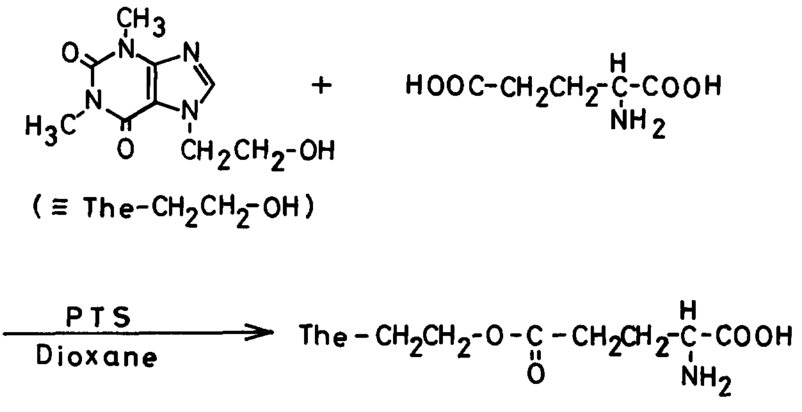
Summary

γ-Ethyl-L-glutamate derivatives having pendant nucleic acid bases, that is, uracil, adenine and theophylline were synthesized. The γ-ethyl-L-glutamate having theophylline moiety was polymerized by using the N-carboxyamino acid anhydride (NCA) method.

In a series of our previous papers, monomers and their polymers containing pendant nucleic acid bases have been reported (TAKEMOTO 1976). Particularly, the preparation of active amino acid derivatives of the nucleic acid bases appears to be attractive. In this connection, monomers and polymers of L-lysine derivatives having such bases were prepared recently (ISHIKAWA et al. 1978; Idem 1978), while the β-alanine type polymers were prepared by the hydrogen-transfer polymerization technique from acryloylaminomethyl derivatives of nucleic acid bases (KONDO et al. 1979). The present report deals with a convenient synthesis of the nucleic acid base substituted L-glutamic acid derivatives and the polymerization of the theophylline derivative by the NCA method.

γ-[2-(7-theophyllinyl)ethyl]-L-glutamate (TLG, 1) was first obtained by esterification of L-glutamic acid with 7-β-hydroxyethyltheophylline which was prepared by the reaction of theophylline with ethylene carbonate (UEDA et al. 1968). The esterification was performed in the presence of *p*-toluenesulfonic acid (PTS) at 100-110°C in dioxane solution for 10 hrs, and water formed was removed by azeotropic distillation with dioxane. After the neutralization by using triethylamine, the mixture was condensed in vacuo and the residue was recrystallized from aqueous ethanol to afford colorless needles in a 20 % yield; mp 160 - 161°C. ANAL. Calcd. for $C_{14}H_{19}N_5O_6$: C, 47.59 %; H, 5.42 %; N 19.82 %. Found: C, 47.41 %; H, 5.40 %; N 19.64 %. UV (H_2O): λ_{max}

274 nm. NMR (D_2O): δ 2.06 (q, 2H), 2.48 (t, 2H), 3.26 (s, 3H), 3.46 (s, 3H), 3.70 (t, 1H), 4,50, 4,53 (t, 4H), 8.00 (s, 1H).



$$HOOC\text{-}CH_2CH_2\text{-}\overset{H}{\underset{NH_2}{C}}\text{-}COOH$$

$$The\text{-}CH_2CH_2\text{-}O\text{-}\underset{O}{\overset{\|}{C}}\text{-}CH_2CH_2\text{-}\overset{H}{\underset{NH_2}{C}}\text{-}COOH$$

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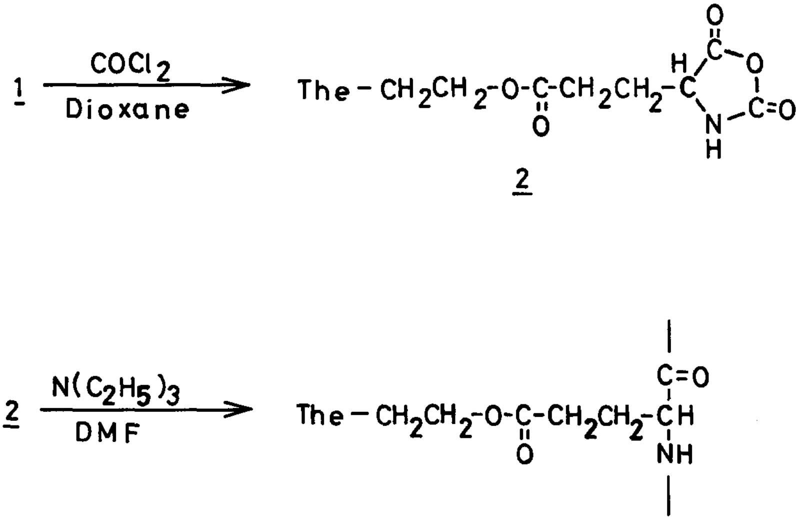
It is evident from the peaks based on α-CH and γ-CH_2 groups of the NMR spectra that the esterification in question took place preferentially on γ-carboxyl group as seen for benzyl and methyl esterifications. The esterification of L-glutamic acid can be thus regarded as a convenient method to obtain optically active amino acids having nucleic acid bases. In a similar way, L-glutamic acid was esterified by the reaction with hydroxyethyl derivatives of uracil and adenine (UEDA et al. 1968), which afforded the corresponding monomers. They were recrystallized from aqueous ethanol to give colorless needles in a 16 and 43 % yield, respectively; mp 152 - 153, and 162 - 163°C, respectively.

The amino acid 1 was polymerized by the NCA method. The N-carboxyamino acid anhydride of TLG (TLG-NCA) was prepared by passing phosgene gas into anhydrous dioxane solution dispersed with TLG at 60°C for 2.5 hrs. After excess phosgene and dioxane were removed, the residue was dissolved again in dioxane and reprecipitated by adding petroleum ether. The reprecipitation was repeated thrice to give colorless crystal in a 75 % yield; IR (KBr): 1850 and 1780 cm^{-1} (-CO-O-CO- stretching vibration). TLG-NCA was soluble in dioxane and DMF, but insoluble in common organic solvents.

TLG-NCA was polymerized with triethylamine as an initiator. The polymerization was carried out at 20°C for 2 days in DMF solution, and was completed further by keeping at 100°C for 2.5 hrs. After DMF



was evaporated in vacuo, the residue was dissolved in a small amount of DMF and reprecipitated by using a large amount of diethyl ether to give a colorless precipitate in a 72 % conversion. IR (KBr): 1730, 1710, 1670 and 1660 cm^{-1}. NMR (CF_3COOH): δ 2.24 (q, 2H), 2.58 (t, 2H), 3.40 (s, 3H), 3.60 (s, 3H), 4.36 (t, 1H), 4.60 (s, 2H), 4.75 (s, 2H), 8.02 (broad, 1H), 8.68 (s, 1H). UV (H_2O): λ_{max} 274 nm. $[\eta]$ = 0.03 dl/g at 25°C in DMF.

The polymer obtained was soluble in dioxane, DMF and water. From the viscometric data, the polymer obtained appears to be oligomeric.

Further studies to find the preferable polymerization conditions systematically, as well as on the polymerization of other L-glutamic acid derivatives are now in progress.

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