Serendipitous Synthesis of *N*-Tetrachlorophthaloyldehydroalanine Methyl Ester, a Michael Acceptor which is a Potential Precursor of γ-Carboxyglutamic Acid†

J. Chem. Research (S), 1998, 806–807†

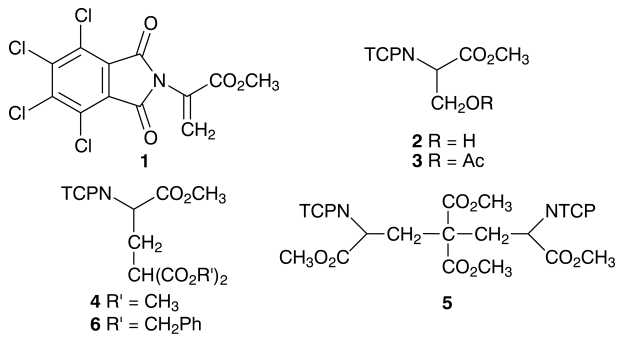
Mireille Caillard, Andrew Emm, Aneurin Jones, Thomas Matthews and J. Michael Williams*

Chemistry Department, University of Wales Swansea, Singleton Park, Swansea, UK SA2 8PP

An attempt to synthesise a new protected serine derivative led to the isolation of *N*-tetrachlorophthaloyldehydroalanine methyl ester, which underwent Michael addition of dialkyl malonates to form γ-carboxyglutamic acid derivatives.

The primary alcohol group in serine derivatives with *N*-alkoxycarbonyl protecting groups has been found to have diminished nucleophilic reactivity. This has been attributed[1] to intramolecular hydrogen bonding of the hydroxy oxygen atom to the nitrogen-bound hydrogen atom. In a search for serine derivatives in which such hydrogen bonding was not possible we attempted to prepare the *N*-tetrachlorophthaloyl derivative of serine methyl ester since this protecting group can be removed under mild conditions with 1,2-diaminoethane[2] or sodium borohydride followed by slightly acidic conditions (pH 5).[3]

Formation of the phthalimide derivative is a two-step process involving first the formation of the phthalamide and then a cyclisation effected by acetic anhydride. The reaction conditions of Fraser-Reid[2] gave a crystalline compound which proved to be the dehydroalanine derivative **1**. Two other products, namely the desired serine derivative **2** and the corresponding acetate **3**, were also formed in proportions that depended on the reaction conditions. Increasing the amount of acetic anhydride and the reaction temperature favoured alkene formation. The acetate **3** clearly readily undergoes β-elimination. Substituting acetic acid for pyridine as the solvent avoided alkene formation. It was not possible to optimise the conditions to form only the serine derivative **2**, but this could be obtained by deacetylating a mixture of **2** and **3**. Acid-catalysed methanolysis was the best method for this deacetylation; sodium methoxide as catalyst caused elimination.



[TCPN = tetrachlorophthalimido]

The alkene **1** is cross-conjugated, but it was anticipated that the nitrogen lone pair was unlikely to be delocalised onto the alkene, and hence deactivate the alkene towards nucleophilic attack, because of the effect of the two imide carbonyl groups. This was supported by MOPAC 93[4] AM1 calculations[5] (data not shown) which suggested that the preferred conformer had the plane of the aromatic bicyclic ring system at right angles to the alkene plane. That alkene **1** was a good substrate for Michael additions was shown by its reaction with the sodium salt of dimethyl malonate, which gave a mixture of the adduct **4** and the 4,4-dimethoxycarbonylheptanedioate derivative **5** resulting from addition of **4** to **1**. Increasing the malonate/Michael acceptor ratio and adding **1** to a solution of malonate decreased the amount of the byproduct **5**. It was not possible to obtain the product **4** pure by recrystallisation and almost identical TLC mobilities precluded chromatography. The pure product was isolated by sublimation. Michael addition of dibenzyl malonate was more successful, the desired γ-carboxyglutamic acid derivative **6** being isolated (22% yield, not optimised) from the crude product by column chromatography.

Experimental

N-*Tetrachlorophthaloyldehydroalanine Methyl Ester*.—A suspension of DL-serine methyl ester hydrochloride (6.0 g), tetrachlorophthalic anhydride (12.2 g) and triethylamine (5.9 ml) in dichloromethane (120 ml) was stirred at room temperature overnight. The dichloromethane was evaporated under reduced pressure and dry pyridine (100 ml) followed by acetic anhydride (8.1 ml) were added. The mixture was stirred at 70 °C for 24 h. The resultant orange–brown suspension was evaporated under reduced pressure to remove most of the pyridine and the remaining mixture was partitioned between dichloromethane (300 ml) and aqueous 2 M HCl (200 ml). Solid at the interface was removed by filtration. The dichloromethane layer was washed successively with more 2 M HCl (100 ml), saturated aqueous sodium hydrogencarbonate and water, and then dried ($MgSO_4$) and evaporated. Recrystallisation of the product from acetone–water (1:2) gave light-tan crystals, 7.46 g (52%), mp 173–174 °C; δ_H ($CDCl_3$) 6.74 and 6.03 (each 1 H, s, C=CH_2), 3.83 (3 H, s, OCH_3); δ_C 162.12, 161.67 (C=O), 140.71, 130.29, 128.47, 127.33 (Ar*C* + *C*=CH_2), 129.33 (C=*C*H_2), 53.09 (OCH_3); *m*/*z* (EI) 369‡ (M^+), 366.89410, $C_{12}H_5Cl_4NO_4$ requires 366.89727; (CI) 387‡ $(M + NH_4)^+$.

O-*Acetyl*-N-*tetrachlorophthaloylserine Methyl Ester*.—A mixture of L-serine methyl ester hydrochloride (2.0 g), anhydrous sodium acetate (1.16 g) and tetrachlorophthalic anhydride (4.04 g) in glacial acetic acid (80 ml) was stirred at 95 °C for 2 h. The solution was then allowed to cool, acetic anhydride (5.36 ml) was added and the mixture was heated at 95 °C for a further 24 h. The cooled reaction mixture contains some solid sodium chloride (which may be filtered off), and the product was then precipitated by pouring the mixture into cold water (800 ml). Filtration, thorough washing with water and drying, *in vacuo* over P_2O_5, gave the crude product, 4.32 g (79%, calculated as acetate) which was shown by NMR to contain mainly the acetate **3** with some serine derivative **2** and a trace of alkene **1**. Recrystallisation from methanol gave the pure acetate (3.16 g), mp 170–172 °C: δ_H ($CDCl_3$) 5.19 (1 H, dd, *J* 4.2, 10.1 Hz, CH), 4.91 (1 H, dd, *J* 4.2, 11.9 Hz, *H*CH), 4.60 (1 H, dd, *J* 10.1, 11.9 Hz, HC*H*), 3.80 (3 H, s, OCH_3), 2.00 (3 H, s, $OCOCH_3$); *m*/*z* (CI) 447‡ $(M + NH_4)^+$.

*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

‡Most intense ion; the isotopic pattern expected for four chlorine atoms was observed.

N-*Tetrachlorophthaloylserine Methyl Ester*.—To a suspension of the crude product (1.5 g) from the preceding experiment in dry methanol (300 ml) was added methanolic hydrogen chloride (150 ml, prepared from thionyl chloride 3 ml), and the mixture was boiled for 10 min. Evaporation under reduced pressure then gave the pure alcohol **2** (1.27 g), mp 177–179 °C; δ_H ($CDCl_3$) 5.04 (1 H, t, *J* 5.4 Hz, C*H*CH_2), 4.22 (2 H, d, *J* 5.4 Hz, CHCH_2), 3.81 (3 H, s, OCH_3), 2.93 (1 H, br s, OH); *m*/*z* (CI) 405‡ (M^++NH_4), 388‡ $(M + H)^+$.

Michael Addition of Dimethyl Malonate to N-*Tetrachlorophthaloyldehydroalanine Methyl Ester*.—Methanolic sodium methoxide (6 ml containing 10.8 mg of sodium) was added to stirred dry THF (10 ml) under nitrogen followed by dimethyl malonate (2.84 g) with stirring. After 5 min dry *N*-tetrachlorophthaloyl dehydroalanine methyl ester (2.0 g) was added and the mixture was stirred overnight. The resulting crude product was filtered off and washed with diethyl ether to give 1.98 g, mp 136–138 °C. NMR analysis (data below) showed the presence of a by-product **5** (ratio of **4** to **5** was 86/14), and recrystallisation from $CHCl_3$–light petroleum (bp 60–80 °C) and from acetone–ethanol–water did not remove the by-product. The pure product **4** was obtained by sublimation at 135 °C at 0.01 mbar; mp 143–144 °C; δ_H ($CDCl_3$) 4.98 (1 H, dd, *J* 5.0, 10.3 Hz, CH_2C*H*N), 3.77, 3.76, 3.69 (3 × 3 H, 3 s, 3 $COOCH_3$), 3.45 (1 H, dd, *J* 6.3, 8.7 Hz, COC*H*CO), 2.95 (1 H, oct, *J* 5.0, 8.7, 14.7 Hz, HC*H*), 2.71 (1 H, oct, *J* 6.3, 10.3, 14.7 Hz, *H*CH); *m*/*z* (EI) 502‡ $(M + H)^+$, 498.94088, $C_{17}H_{13}Cl_4NO_8$ 498.93953; (CI) 519‡ $(M + NH_4)^+$. Data for by-product **5**: δ_H ($CDCl_3$) 5.01 (2 H, dd, *J* 3.7, 9.8 Hz, CH_2CHN), 3.51, 3.78 (2 × 6 H, 2 s, $COOCH_3$), 3.0 (2 H, m, overlapping); *m*/*z* (EI) 871‡ $(M + H)^+$; (CI) 888‡ $(M + NH_4)^+$; a probe temperature of 600 °C was necessary in order to obtain these ions (using a product rich in compound **5**).

Michael Addition of Dibenzyl Malonate of N-*Tetrachlorophthaloyldehydroalanine Methyl Ester*.—Dibenzyl malonate (0.81 ml) was added to sodium hydride (80%, 0.122 g) under nitrogen and the mixture was stirred for 5 min. A solution of the alkene **1** (1.0 g) in dry THF (3 ml) was added and the mixture was stirred overnight. After 2 d the reaction mixture was evaporated to dryness and the residue partitioned between dichloromethane (20 ml) and water (20 ml). The organic layer was washed with 2 M HCl (10 ml) and water, dried ($MgSO_4$) and evaporated to give the crude product (1.71 g). Flash chromatography with hexane–ethyl acetate (5:1) as solvent gave the product (396 mg, mp 107–111 °C), which was recrystallised from hexane–ethyl acetate to give the pure adduct **6** (265 mg, mp 114–115 °C); δ_H ($CDCl_3$) 7.2–7.3 (10 H, m, ArH), 5.13 (2 H, q, *J* 12.2 Hz, $PhCH_2$), 5.05 (2 H, q, *J* 12.2 Hz, $PhCH_2$), 5.01 (1 H, dd, *J* 4.8, 10.5 Hz, CH_2C*H*N), 3.75 (3 H, s, OCH_3), 3.51 (1 H, dd, *J* 6.2, 8.5 Hz, COC*H*CO), 2.99 (1 H, oct, *J* 4.8, 8.5, 14.8 Hz, HC*H*), 2.77 (1 H, oct, *J* 6.3, 10.5, 14.8 Hz, *H*CH); δ_C 168.04, 167.83, 162.72 (C=O), 140.53, 134.90, 134.82, 130.00 (Ar*C*), 128.5–128.1 (Ar*C*H), 67.72, 67.59 (Ph*C*H_2), 53.26 (CH_3), 50.61 and 50.00 (*C*H), 27.61 (CH_2); *m*/*z* (CI) 671‡ $(M + NH_4)^+$.

Received, 17th August 1998; Accepted, 3rd September 1998
Paper E/8/06463F

References

1 L. Szabo, Y. Li and R. Polt, *Tetrahedron Lett*., 1991, **32**, 585; R. Polt, L. Szabo, J. Treiberg, Y. Li and V. J. Hruby, *J. Am. Chem. Soc*., 1992, **114**, 10249.
2 J. S. Debenham, R. Madsen, C. Roberts and B. Fraser-Reid, *J. Am. Chem. Soc*., 1995, **117**, 3302.
3 J. C. Castro-Palomino and R. R. Schmidt, *Tetrahedron Lett*., 1995, **36**, 5343.
4 J. J. P. Stewart and Fujitsu Limited, Tokyo, Japan (copyright, Fujitsu Limited, 1993); obtained from QCPE, Department of Chemistry, Indiana University, Bloomington, Indiana 47405, USA.
5 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc*., 1985, **107**, 3902.

‡See footnote on p. 806.