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# THE REACTION OF BENZYLOXYCARBONYLGLUTAMIC ANHYDRIDE WITH DIAZOMETHANE

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Diazoketones derived from the γ-carboxy groups of partially protected L-glutamic acids are of interest as derivatives of the antitumor antibiotic 6-diazo-5-oxo-L-norleucine[1] and as intermediates in side chain elaboration sequences.[2] We have recently been interested (in the second connection) in the chloroketone 1 which we prepared unambiguously through the diazoketone 2 obtained from benzyloxycarbonyl-α-methyl-L-glutamate[3] by treatment of its mixed ethyl carbonic anhydride with diazomethane. The procedure was troublesome, however, as the diazoketone 2 prepared in this way was an oil which resisted all attempts at crystallisation even after complete chromatographic removal of the benzyloxycarbonyl-L-pyroglutamic acid methyl ester[4] and benzyloxycarbonyl-L-glutamic acid dimethyl ester[5] by-products. We therefore examined the preparation reported for this diazoketone by Balenovic and his colleagues,[6] as they had described the isolation of a crystalline product - in poor yield but by very simple manipulations without chromatography - after treating benzyloxycarbonyl-L-glutamic anhydride with diazomethane. We were able to obtain the crystalline diazoketone described by them using their procedure without difficulty but treatment of this material with hydrogen chloride gave not 1 but an isomeric chloroketone. It appeared therefore that the previously described crystalline diazoketone was in fact 3, not 2, and this was confirmed by unambiguous synthesis: treatment of the mixed ethyl carbonic anhydride of benzyloxycarbonyl-γ-methyl-L-glutamate[7] with diazomethane gave the easily crystallised diazoketone 3 which was identical in every respect with that obtained according to Balenovic and his colleagues. Chromatography of the liquors remaining after crystallisation of 3 from the mixture produced by treating benzyloxycarbonyl-L-glutamic anhydride with diazomethane revealed that 2 was also present, together with many other components. The erroneous assignment of structure 2 to their crystalline diazoketone by Balenovic and his colleagues was based on the fact that it gave on Wolff rearrangement in methanol a diester (thought to be 5, actually 6) which apparently yielded L-α-aminoadipic acid - identified by chromatography - on hydrolysis. We have repeated this degradation and find that although the amino acid produced has mobility in several systems which is similar to authentic L-α-aminoadipic acid, it is not identical to it and furthermore stains slightly differently with ninhydrin: the analogous reactions starting with the oily diazoketone 2, on the other hand, gave an amino acid which was chromotographically indistinguishable from L-α-aminoadipic acid in several systems and which responded in exactly the same way towards ninhydrin.

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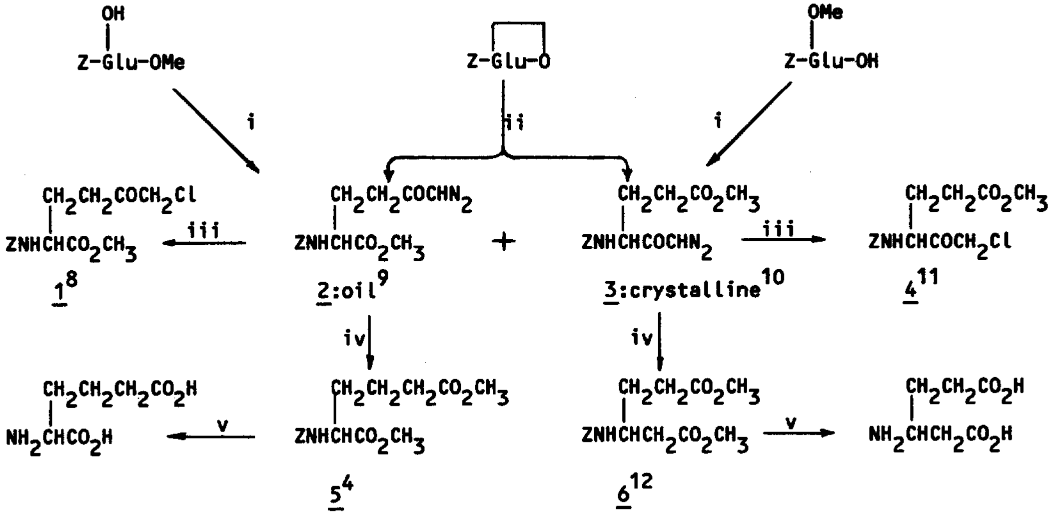

Conditions: i, 1 equ. EtOCOCl/1 equ. $Et_3N$/-15°/THF/10min, then excess $CH_2N_2/Et_2O$;
ii, excess $CH_2N_2/Et_2O$;iii, $HCl/Et_2O$;iv,$Ag_2O$/MeOH;v,aq. HCl.

SCHEME[13]

References and notes

1. H.A. DeWald and A.M. Moore, *J. Am. Chem. Soc.*, **80**, 3941 (1958)
2. W. Bloemhoff and K.E.T. Kerling, *Rec. Trav. Chim*, **94**, 182 (1975).
3. D. I. Marlborough and H.N. Rydon, *J. Chem. Soc. Perkin Trans. 1*, 1 (1972).
4. Obtained as an oil and characterised by n.m.r.
5. Obtained as an oil which crystallised on standing 6 months: mp 39-41°, $[\alpha]_D^{20}$ -1.8 (*c* 1,in $CHCl_3$).
6. W. Bregant, D. Francetic and K. Balenovic, *Bulletin Scientifique, Conseil des Academies des Sciences et des Beaux-Arts de la RSF de Yougoslavie, Section A*, **11** (10-12), 24 (1966); *Chemical Abstracts*, **67**, 73846y (1967).
7. M. Goodman,E.E. Schmitt and D.A. Yphantis, *J. Am. Chem. Soc.*, **84**, 1283 (1962).
8. mp 64-65°, $[\alpha]_D^{20}$ - 21.6° (*c* 1,in MeOH).
9. $[\alpha]_D^{20}$-7.5°(*c* 1,in EtOAc).
10. mp 111-112.5°, $[\alpha]_D^{20}$-28.6°(*c* 1,in EtOAc); lit.[6] mp (for supposed 2) 105-107°, $[\alpha]_D^{20}$-28.5°(*c* 1.128, in EtOAc).
11. mp 96-99°, $[\alpha]_D^{20}$+14.3°(*c* 1, in $CHCl_3$).
12. mp 76-78°, $[\alpha]_D^{20}$-14.2°(*c* 1, in MeOH): lit.[6] mp (for supposed 5) 75-77°, $[\alpha]_D^{20}$-9.1° (*c* 1.1, in MeOH).
13. Satisfactory elemental analyses and spectra were obtained for 1-4 and 6.