The Photo-induced Alkylation of Glycine Residues in Dipeptides

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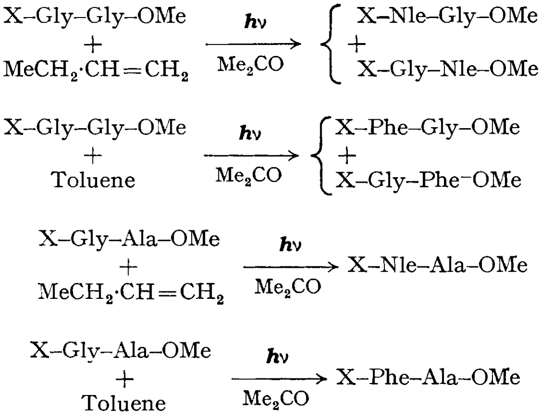
THE light- and free-radical-induced alkylation of glycine derivatives with olefins and toluene leading to the corresponding branched amino-acids has been reported.[1] We report the photochemical acetone-initiated conversion of glycine residues in dipeptides into residues of leucine, norleucine, or phenylalanine by reactions of the dipeptides with isobutene, but-1-ene, or toluene, respectively. The reactions leading to 1 : 1 adducts can be summarized as follows:



$$\begin{array}{c}\text{X–Gly–Gly–OMe}\\+\\\text{MeCH}_2\cdot\text{CH}=\text{CH}_2\end{array}\xrightarrow[\text{Me}_2\text{CO}]{h\nu}\left\{\begin{array}{l}\text{X–Nle–Gly–OMe}\\+\\\text{X–Gly–Nle–OMe}\end{array}\right.$$

$$\begin{array}{c}\text{X–Gly–Gly–OMe}\\+\\\text{Toluene}\end{array}\xrightarrow[\text{Me}_2\text{CO}]{h\nu}\left\{\begin{array}{l}\text{X–Phe–Gly–OMe}\\+\\\text{X–Gly–Phe–OMe}\end{array}\right.$$

$$\begin{array}{c}\text{X–Gly–Ala–OMe}\\+\\\text{MeCH}_2\cdot\text{CH}=\text{CH}_2\end{array}\xrightarrow[\text{Me}_2\text{CO}]{h\nu}\text{X–Nle–Ala–OMe}$$

$$\begin{array}{c}\text{X–Gly–Ala–OMe}\\+\\\text{Toluene}\end{array}\xrightarrow[\text{Me}_2\text{CO}]{h\nu}\text{X–Phe–Ala–OMe}$$

[X† = Acetyl (Ac) or Trifluoroacetyl (Tfa).]

The reactions studied and the results obtained are summarized in the Table.

Reactions were effected by irradiation of a solution of the *N*-Ac- or *N*-Tfa-dipeptide methyl ester (4—6 g.) in t-butyl alcohol (40 ml.) and acetone (10 ml.) while bubbling but-1-ene or isobutene through the reaction mixture, and by irradiation of the dipeptide derivative in toluene–acetone mixtures. The progress of the reactions was followed by acid hydrolysis of samples and analysis on an Amino-acid Analyzer. Products were isolated by chromatography on silica gel and the 1 : 1 adducts were characterized by direct comparison with authentic samples, by standard procedures, including retention times in v.p.c.[2] Low-molecular-weight telomers (mostly 2 : 1 adducts) were also formed, and isolated by the same chromatographic procedure. These were characterized by elemental analyses, mass spectral determinations, and hydrolysis to the constituent amino-acids. In glycylglycine derivatives two 1 : 1 adducts have been obtained by conversion of either of the two glycine residues into the corresponding branched amino-acid. In glycylalanine derivatives only the glycine residue was converted into a branched amino-acid, and thus the reaction seems to be selective for glycine in glycylalanine dipeptides. The telomeric products formed in the reactions of glycylalanine dipeptides result from conversion of a glycine residue into a C_{10}-α-amino-acid, as shown by n.m.r.; *e.g.* acid hydrolysis of one dipeptide led to alanine and a C_{10}-α-amino-acid. Some unsaturation present in the products from the reactions of

† The abbreviations for amino-acid residues and protecting groups used are those suggested by IUPAC and IUB which are reported in *Biochemistry*, 1966, **5**, 2485.

Alkylation products of glycine dipeptides (initiated photochemically by acetone)[a]

Deptide derivative	Substrate	1 : 1 Adduct	Yield[b] (%)
Ac–Gly–Gly–OMe	Toluene	Ac–Phe–Gly–OMe 52%[c] Ac–Gly–Phe–OMe 48%[c]	52[d]
Tfa–Gly–Gly–OMe	Toluene	Tfa–Phe–Gly–OMe 43%[c] Tfa–Gly–Phe–OMe 57%[c]	61[d]
Tfa–Gly–Gly–OMe	But-1-ene	Tfa–Nle–Gly–OMe 55%[c] Tfa–Gly–Nle–OMe 45%[c]	30,[d] 53[e]
Ac–Gly–Ala–OMe	Toluene	Ac–Phe–Ala–OMe	22[d]
Tfa–Gly–Ala–OMe	Toluene	Tfa–Phe–Ala–OMe	32[d]
Ac–Gly–Ala–OMe	But-1-ene	Ac–Nle–Ala–OMe	22,[d] 32[e]
Tfa–Gly–L–Ala–OMe	But-1-ene	Tfa–Nle–L–Ala–OMe	27,[d] 60[e]
Tfa–Gly–Ala–OMe	Isobutene	Tfa–Leu–Ala–OMe	12,[d] 40[e]

[a] Hanovia 200 w lamps with Corex filters and Hanovia 450 w lamps with Pyrex filters were used for reactions with toluene and butenes, respectively; [b] Yields are based on consumed starting dipeptide. Conversions ranged from 30—50%; [c] In the 1 : 1 adduct mixture reported; [d] Yield of 1 : 1 adduct based on consumed starting dipeptide; [e] Yield of newly formed dipeptides, including telomers, based on consumed starting dipeptide.

but-1-ene and isobutene was "removed" by catalytic hydrogenation of the product mixture.

The reaction of Tfa–Gly–L-Ala–OMe with but-1-ene led to an optically active Tfa–Nle–L-Ala–OMe as well as to an optically active telomeric mixture, which was shown to result from conversion of the glycine residue into a C_{10}-α-amino-acid in the dipeptide. Furthermore, the recovered Tfa–Gly–L-Ala–OMe from the reaction mixture showed the same rotation as the starting dipeptide. These results indicate that under the above reaction conditions the alanine residue in dipeptides undergoes racemization to a very low degree, if at all; this presents additional support for the selectivity of the reaction.

The preferential reactivity of glycine residues in the presence of alanine in these reactions, as well as the possible asymmetric induction, are now being examined with higher peptides.

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[2] *Cf.* F. Weygand, A. Prox, L. Schmidhammer, and W. Koenig, *Angew. Chem. Internat. Edn.*, 1963, **2**, 183.