Oxidative Dehydrodimerization of *N*-Acyl α-Amino-acids: Synthesis of Novel Di-αα′-amino-acid Derivatives

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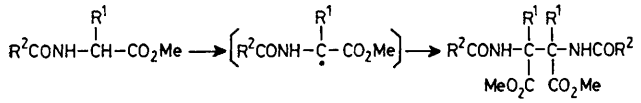
Summary The action of photochemically produced t-butoxyl radicals on *N*-acylated α-amino-acid derivatives in benzene causes dehydrodimerization at the α-position to form novel di-αα′-amino-acid derivatives, the structures of which have been established by spectral data and optical resolution.

IN order to synthesize optically active functionalized corrinoid chromophores, we have investigated the C–C coupling reactions of *N*-acyl α-amino-acids as a route to the A–D ring components. Only a few amides (by thermal decomposition of di-t-butyl peroxide)[1] and pyrrolidone itself (by u.v. irradiation in acetone: *e.g.* with triplet acetone)[2] have been reported to give dehydrodimerization products. Here we present an easy dehydrodimerization of methyl esters of *N*-acyl α-amino-acids (I) with photochemically induced t-butoxyl radicals giving di-αα′-amino-acid derivatives (II) in satisfactory yields (Scheme 1) and present evidence for their structural characterization by optical resolution.



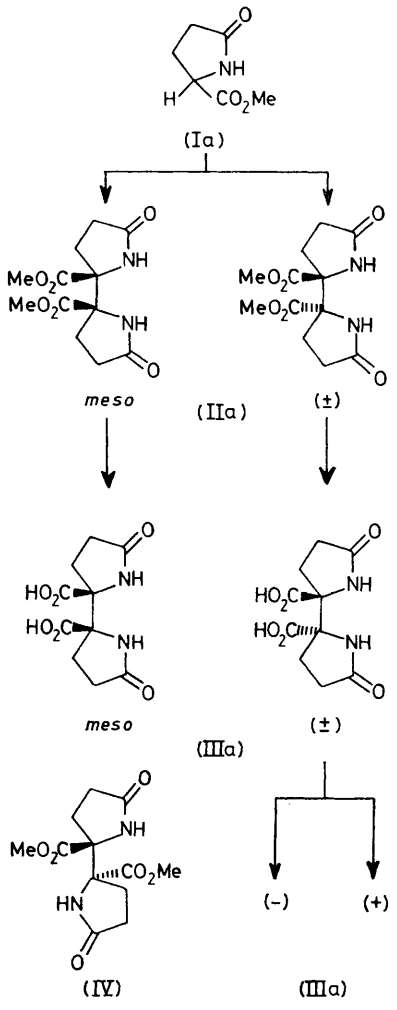
(I) (II)

a; $R^1R^2 = -[CH_2]_2-$
b; $R^1 = H$, $R^2 = Me$

SCHEME 1

Thus, irradiation (low-pressure Hg lamp, 120 W, quartz reactor) of racemic methyl pyroglutamate (Ia) in benzene, in the presence of di-t-butyl peroxide (1 mol. equiv.) for 48 h at room temperature under argon gave a *ca.* 1:1 diastereomeric mixture of dimethyl di-αα′-pyroglutamate (IIa) (m.p. 190—210 °C) in 64% yield† (separation by chromatography on silica gel) together with recovery of (Ia) (15%). Careful fractional recrystallization of (IIa) from methanol and methanol–acetone afforded the (±)-isomer (m.p. 216 °C) and the *meso*-isomer (m.p. 224 °C).

The structure of these dimers was established by elemental analysis, their mass spectra (*m/e*: 284), and other spectral data.‡ In the n.m.r. spectrum ($CDCl_3$) the disappearance of a proton (δ 4·2—4·4) at the α-position of the starting (Ia) and the presence of NH protons [δ 6·56, 2H for the (±)-isomer: δ 6·78, 2H for *meso*], CO_2Me protons (δ 3·74, 6H for both isomers), and ring CH_2 protons (δ 2·0—2·6, 8H for both isomers) indicated that the dimerization did occur at the α-position. Further, the dimers showed characteristic i.r. bands (KBr): ν_{NH} [3230 cm^{-1} for (±)-(IIa); 3150 and 3070 cm^{-1} for *meso*-(IIa)], lactam ν_{CO} (1690 cm^{-1} for both isomers), and ester ν_{CO} [1755 and 1740 cm^{-1} for (±)-(IIa) and 1740 cm^{-1} for *meso*-(IIa)]. In addition, the structure§ of the diastereomers (±)-(IIa) and *meso*-(IIa) was rigorously



SCHEME 2

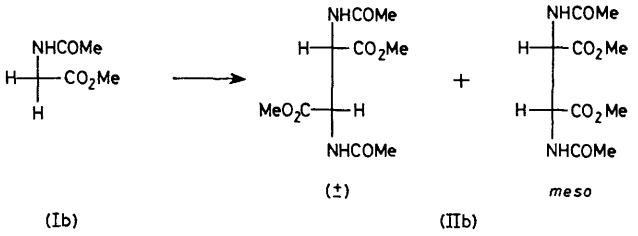
† Both thermal dehydrodimerization of (Ia) with di-t-butyl peroxide (150 °C in trichlorobenzene) and irradiation (high-pressure Hg lamp, 450 W, quartz reactor) of (Ia) in acetone for a prolonged time gave only a small amount of dimer (IIa). This indicates that the t-butoxyl radical might be more effective in S_H2 reactivity (see ref. 3) than triplet acetone towards the α-amino-acid derivatives (Ia).

‡ All new compounds were characterized by satisfactory analytical and spectral data.

§ The structures of the diastereomers of (IIa,b) was also assumed from their n.m.r. spectra with the chiral shift reagent $Eu(TFA\text{-}Cam)_3$ (for examples, see J. L. Green, jun., and P. B. Shevlin, *Chem. Comm.*, 1971, 1092; M. Kainosho, K. Ajisaka, W. H. Pirkle, and S. D. Beare, *J. Amer. Chem. Soc.*, 1972, **94**, 5924).

proved by attempted optical resolution of the products of base hydrolysis, the di-acids (±)- and *meso*-(IIIa), with brucine and quinine. Although the salt of *meso*-(IIIa) with quinine was not resolved, (±)-(IIIa) was resolved with brucine into two enantiomers (+)-(IIIa) ($[\alpha]_D^{30}$ +5·63°) and (−)-(IIIa) ($[\alpha]_D^{30}$ −6·50°) (*c* 1·6 in 1·3% aq. KOH solution for both enantiomers). Though the details of the stereochemistry remain unsolved, from n.m.r. spectroscopic evidence and consideration of steric requirements the stereochemistry of the (±)-isomer is assumed to be *syn-trans* and that of the *meso*-isomer *anti-trans* (IV) (Scheme 2).

Under the same conditions, methyl *N*-acetylglycinate (Ib) gave a *ca.* 1:1 diastereomeric mixture of dimethyl di-αα′-glycinate (IIb) (m.p. 115—130 °C) in 51%. (IIb) was also separated by repeated recrystallization from CH_2Cl_2–hexane into two diastereomers,§ the (±)-isomer (m.p. 137 °C) and the *meso*-isomer (m.p. 193 °C) (Scheme 3).



SCHEME 3

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[1] L. Friedman and H. Schecter, *Tetrahedron Letters*, 1961, 283.
[2] M. Pesaro, I. Felner-Caboga, and A. Eschenmoser, *Chimia* (*Switz.*), 1965, 566; J. Sinnreich and D. Elad, *Tetrahedron*, 1968, **24**, 4509.
[3] See, for example, A. G. Davies and B. P. Roberts in 'Free Radicals,' ed. J. K. Kochi, Wiley, New York, 1973.