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RACEMISATION DURING PEPTIDE SYNTHETIC WORK - II[+]
BASE-CATALYSED RACEMISATION OF ACTIVE DERIVATIVES OF PHTHALOYL AMINO-ACIDS

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It was previously reported that active derivatives of N-carbobenzoxy amino-acids with a suitable substituent in the beta position racemise if triethylamine is present.[1]

It has now been found that active derivatives of phthaloyl amino-acids racemise much more readily than the corresponding active derivatives of carbobenzoxy amino-acids. The racemisation conditions and results are summarised in Table I.

Since no enolizable N-H bond is present in derivatives of phthaloyl amino-acids, the results of base-catalysed racemisation can only be explained by assuming that initial ionisation of the hydrogen on the asymetric carbon atom, leading in the first place to the carbanion /I/, is followed by electron shift which destroy the asymetry.

The following possible mechanisms involving electron migrations are likely to be operating.

[+]Part I: Tetrahedron Letters No. 14 925, (1963).

T A B L E I

All experiments carried out at 22.5°C ± 0.5°

A - 2% acetone solution containing in 100 ml 1.2 ml of N/Et/$_3$; P - 2% pyridine solution

No	Compound	L-isomer		Time within optical rotation decreases to zero or near constant value	Isolated racemate or near racemised product		
					Yield	analytical sample	
		m.p. °C	$[\alpha]_D$ c=2.0 acetone		% /crude/	m.p. °C	$[\alpha]_D$ c=2.0 acetone
1	Phth-Ala.ONp (CN)	152-156 [a]	-98.2	A 2.5 min. P 6 min.	89 70	141-142.5 141-142.5	0.0 0.0
2	Phth-Ala.OMe (CN)	119-120 [b]	-13.0	P 3.5 days	86	119-120	0.0
3	Phth-Asp.O	223-225	-77.8	A 2 min.	on further standing at room temp. the triethylammonium salt of racemic phthaloyl aspartic acid readily crystallized		
4	Phth-Asp.ONp (ONp)	96-97	-74.0	A 50 min. P 90 min.		163-164.5 163-164.5	0.0 0.0
5	Phth-Asp.ONp (OBz)	133-134	-78.4	A 90 min. P 2.5 hrs	88 96	116-117 116-117	0.0 0.0

T A B L E I - continued

6	Phth-Glu(ONp).ONp	147-148	-125.2	A 8 hrs P 3.5 days		124-125.5 124-125.5	0.0 0.0
7	Phth-Phe.ONp	177-178	-212.0	A 28 hrs P 15 days	93 79	155-156 154-156	0.0 -5.2
8	Phth-Ala.ONp	119-120[c]	-103.1	A 24 hrs	95	129-130	0.0
9	Phth-Leu.ONp	87-88[d]	-92.0	A 6.5 days	88	124	0.0

Symbols according to M.Goodman and G.W.Kenner, Adv.Protein Chem., 12, 465 /1957/

All m.p. are uncorrected; for all new compounds satisfactory nitrogen analyses have been obtained; All optically active p-nitrophenyl esters have been obtained by the dicyclohexylcarbodiimide /DCC/ method;[3]

a/ with some softening at 143-145; it seems probable that this product may contain some racemate;

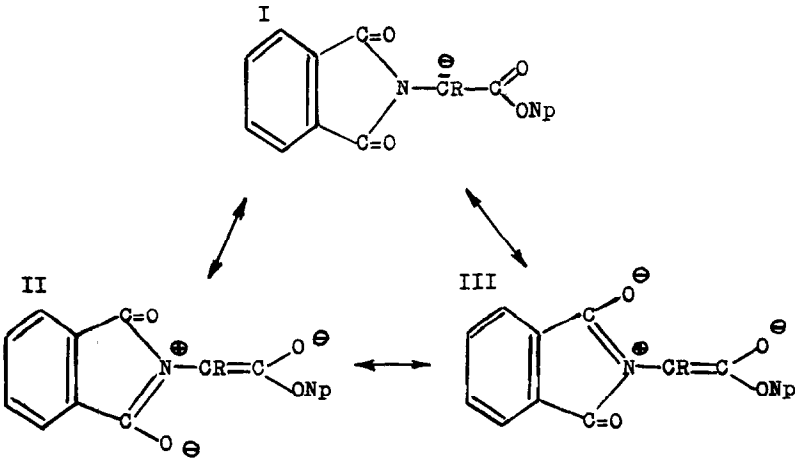
b/ may be partially racemised; obtained in the presence of tributylamine by simultaneous dehydration and esterification of phthaloyl-L-asparagine;[4]

c/ literature[5] m.p. 127 and $[\alpha]_D$ -92 /c=5 dioxane/ obtainable by mixed anhydride method; our lower melting product obtained by DCC method[3] is higher laevorotatory, $[\alpha]_D$ -115.4 /c=5 dioxane/;

d/ literature[5] m.p. 82 obtainable by mixed anhydride method; literature[6] m.p. 86-88 by DCC method;

If a suitable group is linked to the beta-carbon, the resulting carbanion /I/ may be considerably stabilised by contribution of the structures in which the negative charge on the alpha-carbon atom is conjugated with π-electrons of beta substituent. This possibility was already discussed to account for base-catalysed racemisation of active derivatives of carbobenzoxy amino-acids.[1,2]

But in addition, apart from this possibility, the loss of optical activity for derivatives of phthaloyl amino-acids may be explained by postulating the formation of the contributing enol-like structures /II,III/ in which stabilising conjugation involves the benzene ring, one carbonyl bond and two enolic double bonds, the second one being formed within the phthalimide moiety.



The both suggested stabilising effects are likely to lower the energy content of the carbanion /I/ and thus to facilitate ionisation and racemisation. The most rapid racemisation is observed for derivatives which, apart from enol-like structures, are capable of involving an additional stabilising effect with π-electrons of beta substituent.

Recently an excellent method for phthaloylation of amino-acids has been reported.[7] Thus phthaloyl protecting group, which has since its introduction been of little use, is becoming increasingly popular in peptide synthesis.[6] In our opinion it is time to warn against too great reliance upon such amino-protection. The danger of some racemisation seems a very real one. The degree of racemisation during peptide bond-forming reactions will be dependent upon relative rates of ionisation and coupling. This accounts for attempted stepvise elongation of the peptide chain using p-nitrophenyl esters of phthaloyl amino-acids[6] instead of carbobenzoxy amino-acids[3] especially if triethylamine would be present[3,8] or the coupling reaction would be carried out in pyridine.[8]

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