Optishift Pmr Spectroscopic Studies on some Quinoxaline Amino Esters and Dipeptides

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Optishift pmr spectral measurements on a series of *N*-(2-quinoxaloyl)α-amino esters and the C_3-CH_3 analogues indicate that their L-isomers are optically pure. Such measurements also show that the Eu atom in $Eu(tfc)_3$ preferentially complexes with the amide carbonyl. Similar optishift pmr studies on model quinoxaline-dipeptide esters reveal that the amino-terminal α-amino acid suffers appreciable racemization during the coupling process with triphenylphosphite-pyridine, whereas no detectable racemization is observed with diphenylphosphoryl azide. A Bystrov's model is suggested for the quinoxaline-dipeptide-Eu complexes studied. The benzylic protons of phenylalanine and the isopropyl methyls in their quinoxaline derivatives show signal splitting due to diastereotopy in the presence of $Eu(tfc)_3$.

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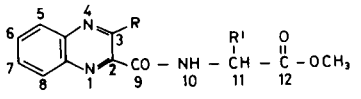
Introduction.

Direct determination of enantiomeric composition (optical purity) of chiral molecules can be achieved by pmr spectroscopy using a chiral reference such as chiral solvents (Pirkle's method) (1) or chiral lanthanide shift reagents (LSR) (2). Recently we have reported on the syntheses and chiroptical properties of some *N*-(3-methyl-2-quinoxaloyl) L-α-amino esters (I, **1b-4b**) (3). Also, the validity of the LSR method for optical purity determination of compound **3b** of this series has been noted (3). In the present work we wish to report the results of further optishift pmr measurements, using tris-[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium, $Eu(tfc)_3$, on compounds I (**1b-4b**) (3), the *N*-(2-quinoxaloyl) analogues I (**1a-4a**) (4) and model quinoxaline-dipeptides IV (**9** and **10**).



I

No.	R'	No.	R'
1	CH_3	3	ph
2	$CH(CH_3)_2$	4	CH_2 ph

a: R = H; b: R = CH_3

Results and Discussion.

1. Quinoxaline Amino Esters (I).

(a) Optical Purity Determination.

The results of the optishift pmr spectral data indicate that the presumed L-isomers (**1-4**) are optically pure. In each case, the $O{=}\overset{1}{C}\text{-}OCH_3$ protons in the L-isomers, **1-4**, give rise to a singlet before and after LSR addition as displayed in representative spectra in Figures (1A, 1B and 2A, 2B). However, this signal of the methyl ester protons is resolved into two diastereotopic singlets of almost the same intensity in the racemates of these compounds (Figures 1C and 2C).

Similarly, each of the C_3-H protons (**1a-4a**), as well as the C_3-CH_3 protons in the L-enantiomers (**1b-4b**), give rise to a singlet before and after the addition of LSR (Figures 1A, 1B and 2A, 2B). However, each of these

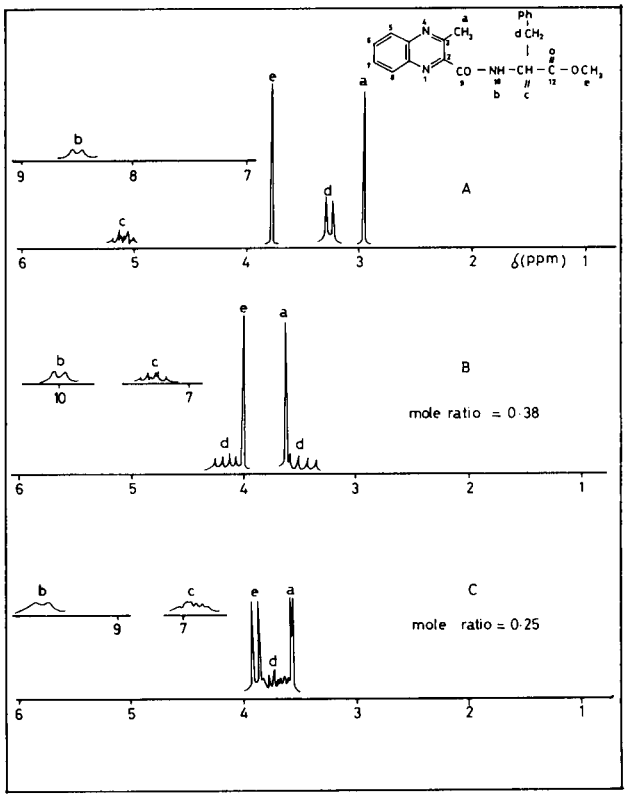


Figure 1

singlets is resolved into two singlets in the case of the racemates of these compounds (**1-4**) after the addition of $Eu(tfc)_3$ (Figures 1C and 2C).

It is worth noting that in each of the racemates of **3b** and **4b**, the methyl ester protons' signal is resolved into two singlets at [LSR]/[Substrate] ratios ($\leqslant$ 0.21 and 0.058 respectively), much lower than those observed for the C_3-CH_3 signals ($\leqslant$ 0.52 and 0.11 respectively).

The C_3-H proton signal in the racemates of each of the aromatic derivatives (**3a** and **4a**), is resolved into two singlets at [LSR]/[Substrate] ratios ($\leqslant$ 0.13 and 0.14 respectively), much less than those observed for the **DL**-aliphatic compounds (**1a** and **2a**) where these ratios are $\leqslant$ 0.23 and 0.24, respectively.

Except for **3a** and **3b** (3), the C_{11}-H methine proton of the chiral center is not as suitable a measure as the methyl ester and the C_3-H or C_3-CH_3 protons for optical purity determination of compounds I. This is due to the incompletely resolved multiplets observed for the C_{11}-H in the racemates (**1**, **2** and **4**) after the addition of LSR (Figures 1C and 2C).

The multiplicity of the NH protons in the racemates, **1-4**, after the addition of LSR could not be determined due to the excessive signal broadening (Figures 1 and 2).

It can, therefore, be concluded that the methyl ester and C_3-CH_3 or C_3-H proton signals are convenient criteria (probes) for the estimation of the enantiomeric composition of these chiral quinoxaline derivatives I.

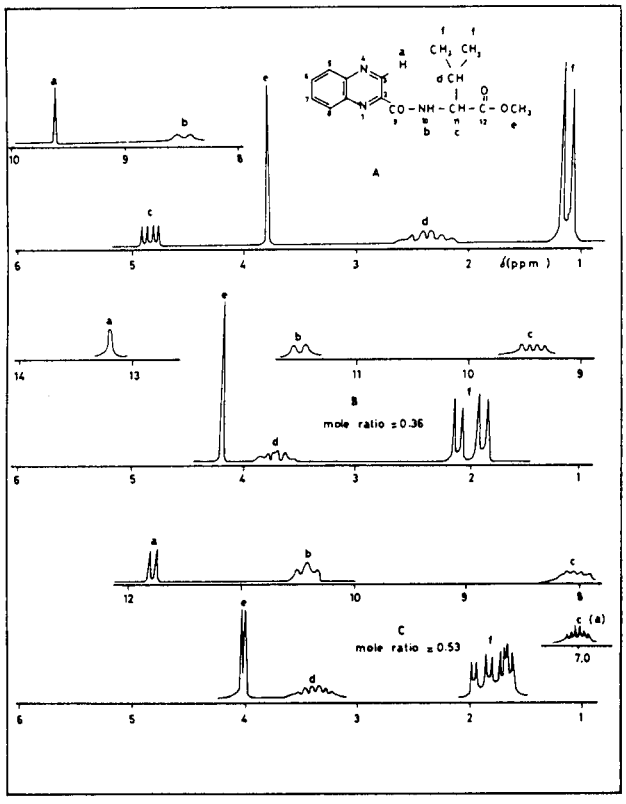


Figure 2

(b) Induced Shifts and Prochiral Groups' Nonequivalence.

The change in the induced shifts, $\Delta\delta$, with varying [LSR]/[Substrate] ratio for the different types of protons in the **L**-isomers (I, **1-4**) was studied. The $\Delta\delta$ values were computed for 1:1 mole ratio using the least-square analysis method (Table II). Zero order correlations were 0.99 in all cases. From these data the following conclusions can be drawn. (i) The C_3-CH_3 as well as the C_3-H proton signals usually show larger $\Delta\delta$ values than those of the methyl ester signals. This is also true for the -NH proton signal which shows a larger $\Delta\delta$ than the methyl ester signals. This indicates that the C_9-amide carbonyl is preferred over the C_{12}-ester carbonyl as the site of complexation with the Eu atom of $Eu(tfc)_3$. This is in agreement with previous data on related systems (2,5). (ii) The C_{11}-H methine proton show maximum $\Delta\delta$ values in each case. This might indicate that this proton is closer than others to the Eu atom in the complex, and is in a favourable position leading to a large induced shift. (iii) The $\Delta\delta$ values for the various protons are dependent on the nature of both R and R'. In compounds **1a-4a**, the values for protons, other than those of the ester methyl, are usually higher than those of the C_3-CH_3 analogues **1b-4b**. This might be attributed to the steric effect of the C_3-CH_3 group which probably forces the Eu atom to approach the amide carbonyl from the less favourable direction. (iv) Lanthanide shift reagents have been reported to remove the incidental isochrony of geminal groups which are intrinsically anisochronous due to their diastereotropy. Similar results are noticed here. The benzylic protons of **4a** and **4b** show incidental isochrony and appear as a doublet in the absence of the chiral LSR (Figure 1A). The differences in the chemical shifts of the two diastereotopic protons is too small to give resolved signals. However, the addition of LSR to the **L**-isomer leads to the separation of this doublet into two AB quartets (Figure 1B). This portion of the spectrum fits very well a computed ABX system (J_{AB} = 16 Hz; J_{AX} = -6 Hz; J_{BX} = -6 Hz). The isopropyl methyls in the valine derivatives **2a** and **2b** show incidental isochrony, too, and appear as a doublet in the absence of LSR (Figure 2A). However, the addition of LSR increases the chemical shift difference of these geminal methyl groups again, and thus they appear as two doublets in the **L**-isomer (Figure 2B). Correspondingly, they appear as four doublets in the **DL**-compounds (Figure 2C).

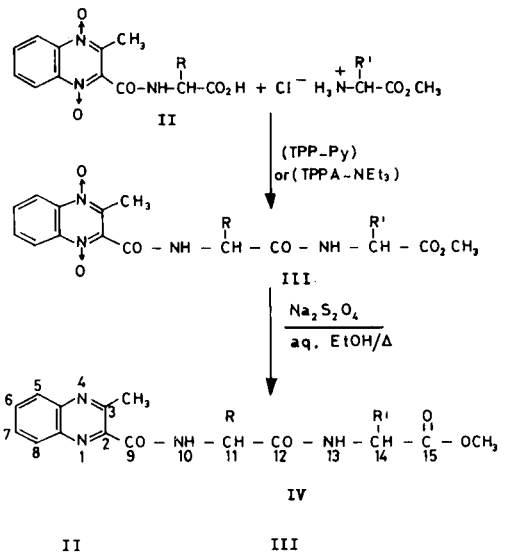
2. Quinoxaline-dipeptides (IV).

(a) Synthesis.

The *N*-(3-methyl-2-quinoxaloyl)glycyl-**L**-phenylalanine methyl ester, **9**, and **L**-phenylalanylglycine analogue, **10**, have been prepared as outlined in Scheme 1.

The coupling of compound II with the appropriate **L**-α-amino ester hydrochloride was effected by using either diphenylphosphoryl azide (DPPA) (7) or triphenyl phos-

Scheme 1



II		III			IV		
No.	R	No.	R	R'	No.	R	R'
5	H	7	H	CH_2Ph	9	H	CH_2Ph
6	CH_2Ph	8	CH_2Ph	H	10	CH_2Ph	H

phite-pyridine (TPP-Py) (8) as coupling reagents. Sodium dithionite reduction (3,9) of the produced dipeptide-1,4-dioxide derivatives (III, **7** and **8**), leads to the desired quinoxaline dipeptides (IV, **9** and **10**).

(b) Optical Purity.

The optical purity of the dipeptide derivatives, **9** and **10** was determined by the same LSR technique: The proton resonances used for this purpose (C_3-CH_3 and methyl ester) are similar to those discussed above for the simple quinoxaline-amino ester (I, **1b-4b**).

In compound **9**, the DL-isomer shows two singlets for each of the C_3-CH_3 and methyl ester, while the L-isomer (obtained by either method) shows one singlet for each, after the LSR additions. This agrees with the expectation that the added chiral α-amino ester does not suffer racemization under the coupling conditions employed. Similarly, the dipeptide derivative, **10**, prepared by the DPPA method, is also optically pure (Figure 3A, B and C). This indicates that the amino terminal amino acid does not suffer detectable racemization in the DPPA method, which agrees with literature reports that the use of DPPA in peptide synthesis avoids racemization (7).

Table I

Physical Data for Compounds I-IV

No. (a)	Yield %	M.p. °C	Crystallization Solvent (b)	$[\alpha]_{578}^{20}$	Formula	Analyses (%) Calcd. C	H	N	Found C	H	N
L-1a	80	112-113	C + P	+82.3°	$C_{13}H_{13}N_3O_3$	60.22	5.05	16.21	60.44	4.93	16.26
DL-1a	78	89-90	C + P			60.22	5.05	16.21	60.29	5.15	16.35
L-2a	85	88-89	C + P	+75.7°	$C_{15}H_{17}N_3O_3$	62.70	5.96	14.63	62.80	5.90	14.52
DL-2a	85	77-78	C + P			62.70	5.96	14.63	62.70	5.86	14.67
L-3a	95	124-125	E + W	-32.6°	$C_{18}H_{15}N_3O_3$	67.28	4.71	13.08	67.74	4.74	13.21
D-3a	94	124-125	C + P	+32.4°		67.28	4.71	13.08	67.25	4.57	13.11
DL-3a	92	114-115	M + W			67.28	4.71	13.08	67.93	4.71	13.26
L-4a	93	70-71	E + W	+24.7°	$C_{19}H_{17}N_3O_3$	68.05	5.11	12.53	67.89	5.00	12.38
DL-4a	90	120-121	C + P								
DL-1b	79	103	E + W		$C_{14}H_{15}N_3O_3$	61.53	5.54	15.38	61.42	5.48	15.27
L-2b	70	101-102	P	+73.2°	$C_{16}H_{19}N_3O_3$	63.77	6.36	13.94	63.90	6.43	13.86
DL-2b	72	95-96	P			63.77	6.36	13.94	63.89	6.41	13.87
DL-3b	90	108	M + W								
DL-4b	87	142	M + W								
5	82	220-221 dec.	M		$C_{12}H_{11}N_3O_5$	51.99	4.00	15.16	51.86	4.07	14.97
L-7	72	174-175 dec.	C + P	+78.2°	$C_{22}H_{22}N_4O_6$	60.27	5.06	12.78	60.40	5.08	12.64
L-8	80	189-190	C + P	-173.2°	$C_{22}H_{22}N_4O_6$	60.27	5.06	12.78	61.15	5.13	12.64
L-9	84	147-148	C + P	+48.4°	$C_{22}H_{22}N_4O_4$	65.01	5.46	13.79	64.90	5.49	13.94
DL-9	95	142-143	C + P								
L-10	88	184-185	C + P	+82.2°	$C_{22}H_{22}N_4O_4$	65.01	5.46	13.79	65.14	5.53	13.92
DL-10	96	163-164	C + P								

(a) The L-compounds **1b, 3b, 4b** and **6** were reported elsewhere (3). The DL-compounds **4a, 3b, 4b, 9** and **10** were obtained *via* racemization of the respective L-isomers. (b) C, chloroform; E, ethanol; M, methanol; P, petroleum ether (b.p. 60-80°); W, water.

Table II

The Chemical Shifts (a), δ (ppm) and the Induced Chemical Shifts, Δδ (ppm), Referred to 1:1 Mole Ratio of $Eu(tfc)_3$/Substrate, for the Different Protons of the L-Isomers of Compounds I

No.	N_{10}-H	C_{11}-H	-OCH_3	R	R'
1a	δ 8.47, 8.55 (d)	4.90 $(m)_c$	3.81 (s)	9.61 (s)	CH_3: 1.57, 1.66 (d)
	Δδ 5.90 ± 0.39	8.11 ± 0.70	0.56 ± 0.02	6.19 ± 0.44	2.12 ± 0.16
1b	δ 8.49, 8.58 (d)	4.82 $(m)_c$	3.79 (s)	2.96 (s)	CH_3: 1.54, 1.63 (d)
	Δδ 5.66 ± 0.56	8.46 ± 0.64	1.54 ± 0.20	3.15 ± 0.13	2.58 ± 0.17
2a	δ 8.47, 8.55 (d)	4.84 $(q)_c$	3.81 (s)	9.64 (s)	$CH(CH_3)_2$: 2.37 $(m)_c$; 1.04, 1.14 (d)
	Δδ 7.88 ± 0.26	12.16 ± 0.44	1.02 ± 0.04	9.95 ± 0.10	3.77 ± 0.31; 2.42 ± 0.00
2b	δ 8.48, 8.58 (d)	4.74 $(q)_c$	3.78 (s)	2.97 (s)	$CH(CH_3)_2$: 2.32 $(m)_c$, 1.00, 1.10 (d)
	Δδ 4.94 ± 0.27	8.58 ± 0.57	3.14 ± 0.18	1.75 ± 0.14	2.86 ± 0.20; 1.68 ± 0.02
3a	δ 8.82, 8.94 (d)	5.81, 5.93 (d)	3.81 (s)	9.63 (s)	Ph: 7.43 (s)
	Δδ 4.40 ± 0.31	6.25 ± 0.46	0.32 ± 0.01	3.91 ± 0.30	(b)
D-3a	Δδ 4.03 ± 0.34	5.65 ± 0.58	0.22 ± 0.02	3.22 ± 0.28	Ph: (b)
3b	δ 8.97, 9.09 (d)	5.78, 5.90 (d)	3.82 (s)	2.95 (s)	Ph: 7.47 (s)
	Δδ 2.64 ± 0.09	3.48 ± 0.14	0.38 ± 0.03	0.91 ± 0.04	(b)
4a	δ 8.37, 8.47 (d)	5.15 $(m)_c$	3.76 (s)	9.63 (s)	CH_2-Ph: 3.26, 3.33 (d); 7.25 (s)
	Δδ 5.48 ± 0.16	6.20 ± 0.51	0.37 ± 0.03	5.36 ± 0.14	2.07 ± 0.13; (b)
4b	δ 8.46, 8.55 (d)	5.11 $(m)_c$	3.79 (s)	2.93 (s)	CH_2-Ph: 3.26, 3.33 (d); 7.30 (s)
	Δδ 3.27 ± 0.23	5.14 ± 0.08	0.55 ± 0.01	1.51 ± 0.08	1.42 ± 0.16; (b)

(a) Solvent: deuteriochloroform; signals described as (s) = singlet, (d) = doublet, $(q)_c$ = center of quartet, $(m)_c$ = center of multiplet; H_5 and H_8 (8.01-8.17 ppm); H_6 and H_7 (7.78-7.87 ppm). Numbering of carbons are shown in structural formula I. (b) Δδ not calculated.

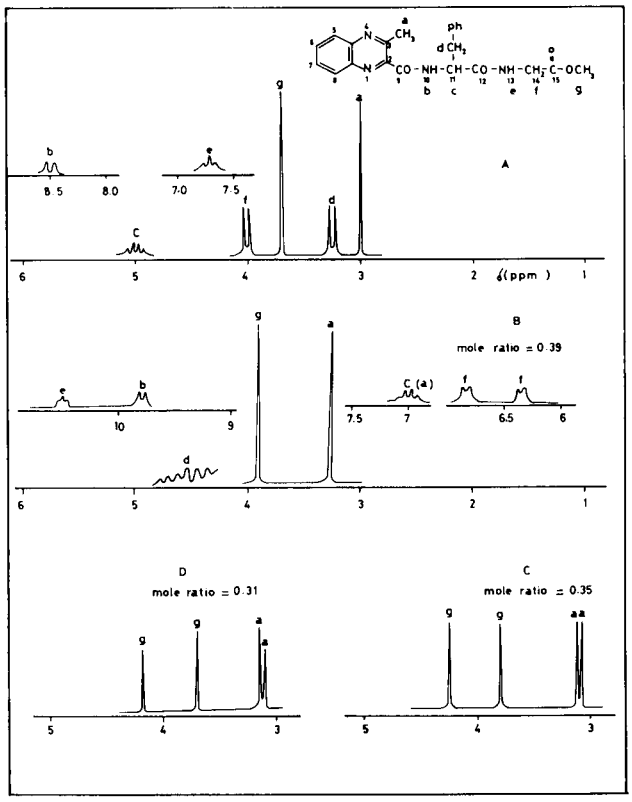


Figure 3

The TPP-Py method has been reported to lead to little (less than 5%) or no racemization when the carbobenzoxy group is the amino protecting group in peptide synthesis (8). However, the TPP-Py method leads to considerable racemization of the chiral center of the amino terminal acid in the produced dipeptide, **8**, and hence in **10**. The degree of racemization was calculated from both the C_3-CH_3 and the methyl ester signal peak areas (integration) to be about 80% (Figure 3D).

(c) Induced Shifts and Prochiral Groups' Nonequivalence.

The δ and Δδ values for the various protons in the dipeptides **9** and **10** are shown in Table III, from which the following conclusions are made. (i) The N_{13}-H in **9** shows a larger Δδ value than the N_{10}-H. (ii) The C_{11}-methylene protons in **9** show a Δδ value approximately equal to that of the C_{14}-methine proton.

These results might be explained by assuming that the Eu-complex of this dipeptide exists in a Bystrov's model (10) (Figure 4). In this complex, the N_{13}-H is intramolecularly hydrogen-bonded to the C_9-carbonyl oxygen, a fact that explains its larger shift compared to that of the N_{10}-H. The Eu atom preferably complexes with the C_{12}-carbonyl oxygen and lies below the plane of the hydrogen-bonded ring and is nearly equidistant from the C_{11}-methylene and the C_{14}-methine protons.

The Δδ values in **10** can be explained on similar lines.

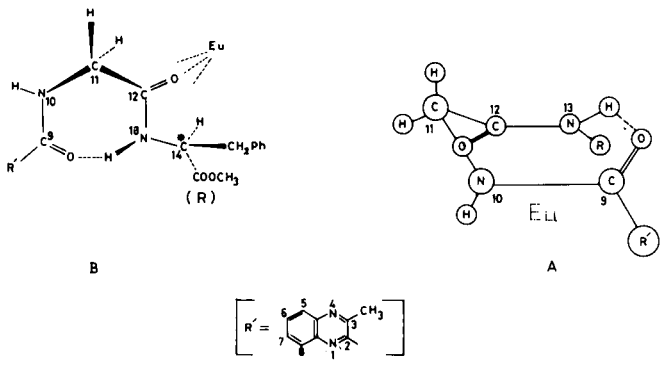


Figure 4

It is worth noting that the $\Delta\delta$ for the C_3-CH_3 protons in **10** (0.61) is much less than that in **4b** (1.51, Table II). This might be considered as a support to the assumed sites of complexation of Eu with the C_{12}- and the C_9-carbonyl oxygens respectively. (iii) In both **9** and **10**, the methylene protons of the glycine residue, as well as the benzylic protons show incidental isochrony before the addition of the LSR. However, after the addition of LSR, the former appear as two doublets, while the latter appears as two partially overlapped AB quartets of an ABX system (Figure 3B).

(d) Primary Structure.

The δ value of the N_{10}-H proton is larger than that of the N_{13}-H in both **9** and **10** (Table III). This indicates that the NH- proton of the amino terminal residue appears at a higher δ value than the NH- of the carboxy terminal, irrespective of the nature of the amino acid. Also, the methylene protons of the glycine residue in **9** show higher δ value than those in **10**. The phenyl protons' signal of the phenylalanine residue in **10** also has a larger value than that in **9** (Table III). Thus the signals of the various protons belonging to an amino terminal amino acid appear at larger δ value than those of the corresponding protons of the same, but carboxy terminal amino acid. This might be attributed to the presence of the quinoxaline group (which exerts the observed deshielding effect on the nearby protons). It seems, therefore, possible to determine the amino acid sequence of a dipeptide from the pmr spectrum of its *N*-quinoxaloyl derivative. This generalization is being further tested in several dipeptide analogues of IV.

EXPERIMENTAL

L-α-Amino acids and the respective methyl ester hydrochlorides are Biochemical Grades (Merck or Fluka) and were used without further purification. 2-Quinoxaloyl chloride, diphenylphosphoryl azide and $Eu(tfc)_3$ were purchased from Aldrich. Melting points were determined on a Gallenkamp capillary melting point apparatus and are uncorrected. Optical rotations were taken on a Perkin Elmer 141 polarimeter in chloroform (c, 1-2). Optishift pmr spectra were recorded on a Bruker HFX-90 or on a Varian T-60A

Table III

δ Values (ppm) and Δδ Values (a), Referred to 1:1 Mole Ratio of $Eu(tfc)_3$/Substrate, for the Different Protons (a) of the L-Isomers of Compounds IV

No.		N_{10}-H	N_{13}-H	C_{11}-H	C_{14}-H	C_3-CH_3	-OCH_3	R	R′
9	δ	8.53, 8.60, 8.67 (t)	6.72, 6.79 (d)	4.13, 4.20 (d)	4.92 (m)$_c$	3.03 (s)	3.69 (s)	R = H (see C_{11}-H)	CH_2-Ph: 3.09, 3.16 (d); 7.09 (s)
	Δδ	5.77 ± 0.43	8.56 ± 0.60	8.40 ± 0.48	9.44 ± 0.60	3.55 ± 0.28	0.76 ± 0.07		3.97 ± 0.26; (b)
10	δ	8.54, 8.62 (d)	6.71, 6.78, 6.85 (t)	4.96 (m)$_c$	3.98, 4.05 (d)	2.99 (s)	3.67 (s)	CH_2-Ph: 3.22, 3.30 (d); 7.27 (s)	R′ = H (see C_{14}-H)
	Δδ	3.00 ± 0.14	9.06 ± 0.18	6.82 ± 0.30	5.47 ± 0.50	0.62 ± 0.05	0.61 ± 0.01	2.94 ± 0.17; (b)	

(a) Numbering of carbons are shown in Scheme 1. (t) = triplet; see also footnote (a), Table II. (b) See Footnote (b), Table II.

spectrometer for solutions in deuteriochloroform with TMS as internal standard. Usually spectra were determined at 4 different mole ratios (0.1-0.5 of LSR to substrate) for each L-isomer. Elemental analyses were performed by Dr. F. Pascher (Bonn).

General Procedures of Syntheses.

Quinoxaline-α-amino Acid Derivatives (Table I).

The *N*-(2-quinoxaloyl)α-amino esters (L-isomers of **1a-4a**, DL of **1a-3a**) were obtained by quinoxaloylation of the corresponding α-amino acids in alkaline medium (4a), followed by esterification with diazomethane etherate (4b). Compounds **L-2b**, **DL-2b** and **DL-1b** were obtained by the general procedure previously described (3) for **1b**, **3b** and **4b**.

The synthesis of **5** followed the literature procedure reported (3) for **6** and other related α-amino acid derivatives (II). Here, compound **5** crystallized out as its triethylammonium salt. Acidification of an aqueous solution of the latter with 6*N* hydrochloric acid yielded the free acid, **5**, as shining yellow scales.

Quinoxaline-dipeptide 1,4-Dioxides (II, **7** and **8**, Table I).

(a) The Triphenyl Phosphite-pyridine (TPP-Py) Method (8).

To a solution of triphenyl phosphite (Merck, 0.075 mole) in pyridine (100 ml.) was added a solution of compound **5** or **6** (0.05 mole), and the α-amino ester hydrochloride (0.05 mole) in pyridine (~ 100 ml.). The resulting mixture was stirred for 2-3 days at room temperature. Pyridine was then evaporated *in vacuo* (below 30°), and the viscous residue was taken up in ethyl acetate (or in chloroform). The organic layer was washed successively with 2*N* hydrochloric acid, saturated aqueous sodium bicarbonate and water (2 x 30 ml.) in each case), dried (sodium sulfate), and the solvent was evaporated. Trituration of the residue with methanol, followed by addition of ether (~ 150 ml.) yielded the required dipeptide derivatives as yellow solids. The latter were purified on preparative thick layer plates (tlc) (20 x 20 cm, 2 mm thickness) using Silica Gel (60 PF_{254}, Merck) as the adsorbent and chloroform/ethanol (95:5 v/v) as the developing solvent mixture.

(b) The Diphenylphosphoryl Azide (DPPA) Method (7).

To a stirred mixture of **5** or **6** (0.05 mole) and the appropriate α-amino ester hydrochloride (0.06 mole) in dimethylformamide (~ 50 ml.) was added DPPA (0.06 mole) in dimethylformamide (~ 20 ml.) at zero to -5°, followed by the addition of triethylamine (0.12 mole). The mixture was stirred at zero to -5° for 3-5 hours, and at room temperature overnight. Dilution of the reaction mixture with cold water led to the separation of the required dipeptide derivative as a yellow oil which solidified upon cooling. The product can also be conveniently isolated by extraction with chloroform (or ethyl acetate), and purified on preparative tlc plates.

Quinoxaline-dipeptides (IV, **9** and **10**, Table I).

These compounds were obtained by sodium dithionite reduction of the corresponding 1,4-dioxide analogues, **7** and **8**, following established procedures (3,9), and were purified on preparative tlc plates.

Racemization.

The racemates of the aromatic derivatives **3b**, **4b**, **4a**, **9** and **10** (Table I) were obtained by the following procedure.

A solution of the L-isomer (0.01 mole) in methanol-triethylamine solvent mixture (~ 150 ml., 1:1 v/v) was refluxed for 3-4 days. The solvent was then distilled off, and the solid residue was crystallized from the appropriate solvent.

Under these conditions, the L-alanine derivative, **1b**, undergoes incomplete racemization (53%, as calculated from the optishift-pmr spectral data). This might be due to the decreased acidity of the chiral methine proton compared to that of the aromatic analogues. However, the L-valine derivative, **2b**, showed no detectable racemization, probably due to the added steric effect of the isopropyl group.

Acknowledgment.

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