Synthesis of Peptides containing 1,2,3,4-Tetrahydroquinoline-2-carboxylic Acid. Part 2.[1] Crystal and Molecular Structure of a 1*H*,3*H*,5*H*-Oxazolo[3,4-*a*]quinolin-3-one Derivative obtained from a Linear Tripeptide

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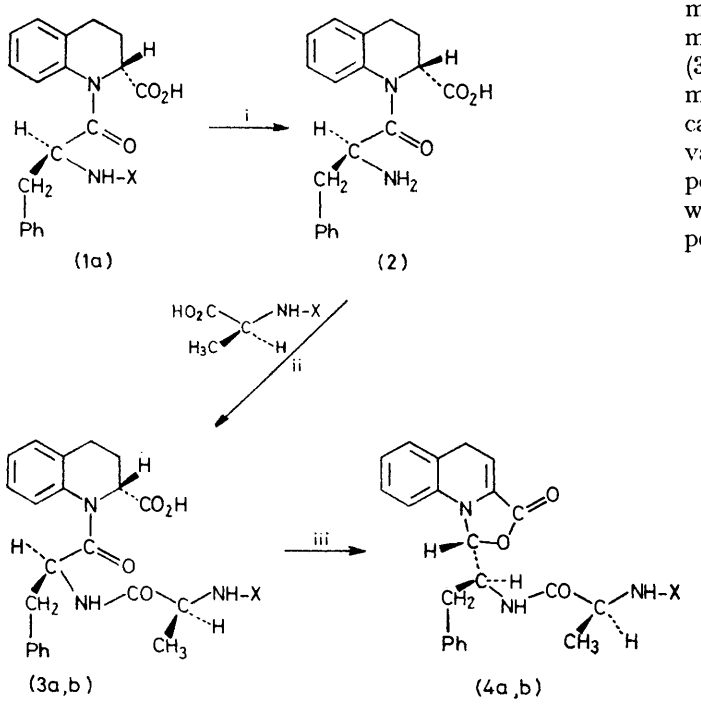
Treatment of *N*-benzyloxycarbonyl-(*S*)-alanyl-(*S*)-phenylalanyl-(*R*)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (1a) with acetic anhydride–sodium acetate gives a cyclization product (4a) containing the 1*H*,3*H*,5*H*-oxazolo[3,4-*a*]quinoline system. The structure of the bromo-derivative (4b) was examined by crystallographic and spectroscopic methods. Crystals are monoclinic, space group $P2_1$, a = 9.835, b = 26.018, c = 10.856 Å, β = 93.78°, Z = 4. The structure has been refined to R 0.08 for 3 615 reflections. The two molecules found in the asymmetric unit assume slight different conformations. Some spectroscopic data for the new peptide are described in relation to the conformations found in the crystals. The mechanism of the cyclization is discussed and related to the Dakin–West reaction.

WE have previously reported [1] some peptides containing 1,2,3,4-tetrahydroquinoline-2-carboxylic acid, and the absolute configuration of this cyclic imino-acid was defined. We report here the cyclization of the tripeptide *N*-benzyloxycarbonyl-(*S*)-alanyl-(*S*)-phenylalanyl-(*R*)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (3a). Formation of a tetracyclic aza-cyclol or of the tautomeric *N*-benzyloxycarbonyl(alanyl)dioxopiperazine [2] may be expected for a reaction pathway analogous to that observed in the case of the corresponding proline-containing linear tripeptides.



SCHEME 1 Reagents: i, $H_2/Pd(Al_2O_3)$; ii, $ClCO_2Et$; iii, Ac_2O–AcONa. In compounds numbered a, X = $PhCH_2·O·CO$; b, X = p-$BrC_6H_4·CH_2·CO$

Two cyclization methods were considered: [2] treatment of the *p*-nitrophenyl ester of the tripeptide (3a) in mild alkaline aqueous medium and reaction of the acid (3a) with sodium acetate–acetic anhydride. Neither method afforded the expected compounds: in the first case the hydrolysis of the activated ester was the prevailing reaction. In the second case a neutral compound, isomeric with the expected cyclization products was isolated. We now report the structure and properties of this new peptidic derivative.

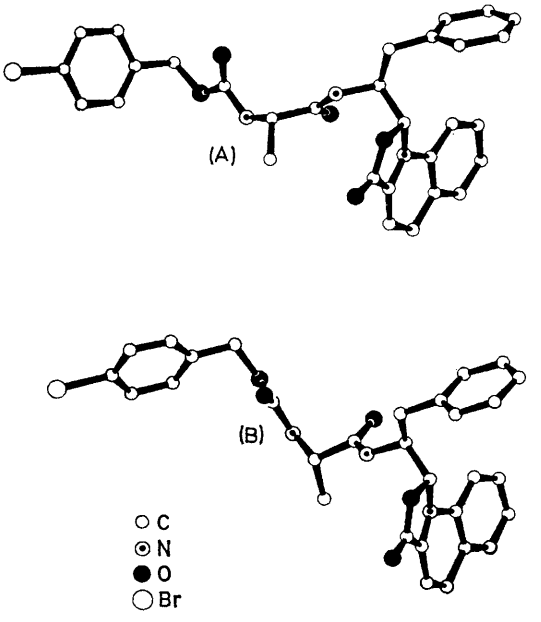


FIGURE 1 General view of the two conformers of (4b); the two molecules are not relatively oriented

Tripeptide (3a) has been synthesized according to Scheme 1, from the dipeptide *N*-benzyloxycarbonyl-

(*S*)-phenylalanyl-(*R*)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (1a).[1]

Treatment of (3a) with acetic anhydride and sodium acetate at 100° for 1 h gave the cyclization product (4a) in *ca.* 50% yield. The presence of the unexpected tricyclic system in (4) was established by crystallographic and spectroscopic methods.

ledge of the absolute configuration of the alanine residue in the starting tripeptide, together with the *X*-ray data, allows unequivocal configurational assignments to the other two asymmetric centres in (4). The crystallographic numbering scheme shown in Figure 2 is adopted throughout the work. Atomic co-ordinates are reported in Table 1. Intramolecular bond distances and angles

TABLE 1

Final fractional atomic co-ordinates with standard deviations in parentheses

	Molecule (A)			Molecule (B)		
Atom	*x/a*	*y/b*	*z/c*	*x/a*	*y/b*	*z/c*
N(1)	6 355(8)	2 130(3)	3 778(7)	1 349(8)	3 439(3)	−92(7)
C(2)	5 401(9)	2 159(4)	4 671(8)	2 749(10)	3 496(4)	−345(9)
C(3)	5 369(11)	1 790(4)	5 579(10)	3 272(12)	3 272(5)	−1 367(11)
C(4)	4 391(11)	1 807(5)	6 476(10)	4 653(14)	3 334(6)	−1 579(13)
C(5)	3 468(14)	2 208(6)	6 430(12)	5 458(16)	3 646(7)	−837(14)
C(6)	3 538(13)	2 588(5)	5 538(11)	4 927(14)	3 871(5)	170(12)
C(7)	4 511(10)	2 578(4)	4 657(9)	3 573(10)	3 818(4)	418(9)
C(8)	4 547(12)	3 000(5)	3 713(10)	3 046(12)	4 081(6)	1 552(11)
C(9)	5 742(12)	2 949(5)	2 894(10)	1 516(11)	4 072(5)	1 546(10)
C(10)	6 547(9)	2 540(4)	3 015(9)	839(10)	3 757(4)	740(9)
C(11)	7 833(10)	2 454(4)	2 465(9)	−656(10)	3 733(4)	528(9)
O(11)	8 398(9)	2 680(4)	1 707(8)	−1 554(8)	3 928(3)	1 089(7)
O(12)	8 416(7)	2 027(3)	2 997(6)	−947(7)	3 443(3)	−483(6)
C(13)	7 525(9)	1 795(4)	3 841(8)	295(9)	3 274(4)	−1 020(8)
C(14)	7 203(9)	1 236(4)	3 384(8)	216(10)	2 694(4)	−1 258(9)
C(15)	8 356(11)	869(4)	3 791(10)	−1 119(11)	2 556(4)	−2 085(10)
C(16)	8 554(10)	830(4)	5 173(9)	−1 122(11)	2 822(4)	−3 296(10)
C(17)	7 538(12)	570(5)	5 825(11)	−235(13)	2 674(5)	−4 174(11)
C(18)	7 690(17)	581(7)	7 165(15)	−191(15)	2 952(6)	−5 314(13)
C(19)	8 747(17)	818(7)	7 763(15)	−1 028(17)	3 356(7)	−5 557(16)
C(20)	9 693(17)	1 075(7)	7 183(15)	−1 971(16)	3 487(6)	−4 712(14)
C(21)	9 624(12)	1 076(5)	5 791(11)	−2 007(13)	3 222(6)	−3 548(12)
N(22)	6 942(7)	1 221(3)	2 044(7)	286(8)	2 413(3)	−105(8)
C(23)	5 696(9)	1 273(4)	1 462(9)	1 217(9)	2 040(4)	130(8)
O(23)	4 641(7)	1 312(3)	2 022(7)	2 035(7)	1 904(3)	−631(6)
C(24)	5 691(11)	1 293(5)	69(10)	1 212(9)	1 827(4)	1 429(8)
C(25)	6 073(18)	1 845(7)	−325(16)	2 126(14)	2 166(6)	2 268(12)
N(26)	4 379(8)	1 140(3)	−516(7)	1 682(8)	1 297(3)	1 484(7)
C(27)	4 175(10)	670(4)	−953(9)	842(9)	921(4)	1 093(8)
O(27)	4 995(9)	313(4)	−896(8)	−372(7)	956(3)	846(6)
O(28)	2 901(8)	626(3)	−1 529(7)	1 537(8)	474(3)	1 062(7)
C(29)	2 578(14)	140(6)	−2 093(12)	719(13)	23(6)	709(12)
C(30)	3 158(13)	121(5)	−3 393(11)	−11(11)	−189(4)	1 765(10)
C(31)	3 732(14)	−335(6)	−3 750(13)	−1 332(13)	−350(5)	1 625(12)
C(32)	4 246(15)	−369(6)	−4 949(13)	−2 002(13)	−575(5)	2 591(12)
C(33)	4 102(12)	53(5)	−5 715(11)	−1 357(12)	−601(5)	3 693(10)
C(34)	3 589(14)	511(6)	−5 358(13)	−16(15)	−426(6)	3 965(13)
C(35)	3 099(13)	540(5)	−4 169(12)	656(14)	−215(6)	2 938(13)
Br	4 671(2)	0 *	−7 366(2)	−2 212(2)	−890(1)	5 056(2)

* This co-ordinate was kept fixed during refinement.

The *X*-ray analysis, performed on the bromo-derivative (4b), shows that two molecules are present in the asymmetric unit, with slight conformational differences.

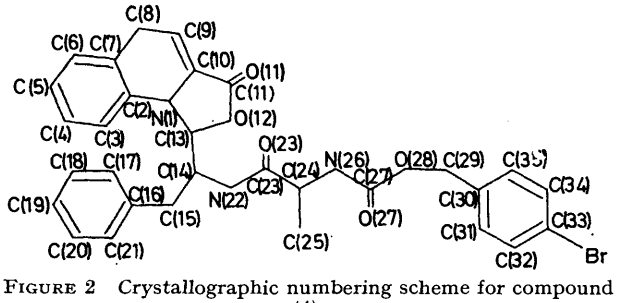


FIGURE 2 Crystallographic numbering scheme for compound (4)

The two conformers are labelled molecules (A) and (B) (Figure 1). In the text values for molecule (A) are given with those for molecule (B) in parentheses. A know-

for the two conformers (A) and (B) are compared in Table 2, and Table 3 lists relevant least-squares planes and atomic displacements from them.

In both molecules (A) and (B) the C(8) and N(1) atoms of the dihydropyridine ring deviate significantly on the same side from the plane of the four sp^2 carbon atoms (see Table 3). The oxazolidinone ring assumes a distorted planar conformation. The largest deviation of the five ring atoms from the best plane is 0.03 Å (0.07 Å) (see Table 3).

Table 4 reports the internal torsion angles for the heterocyclic rings. The nitrogen atom of the tricyclic system and its substituents form a pyramid with a height of 0.16 Å (0.22 Å); the sum of bond angles around the nitrogen atom is 356.0° (352.6°).

Information regarding the planarity of the CO–NH groups can be obtained from the torsion angles: C(14)–N(22)–C(23)–O(23) −3.6 (−2.5), C(14)–N(22)–

TABLE 2

Bond lengths (Å) and interbond angles (°) with standard deviations in parentheses

	Molecule (A)	Molecule (B)
(*a*) Bond lengths		
N(1)–C(2)	1.40(1)	1.43(1)
N(1)–C(10)	1.37(1)	1.35(1)
N(1)–C(13)	1.44(1)	1.46(1)
C(2)–C(3)	1.38(1)	1.38(2)
C(2)–C(7)	1.40(1)	1.40(1)
C(3)–C(4)	1.41(2)	1.40(2)
C(4)–C(5)	1.38(2)	1.36(2)
C(5)–C(6)	1.39(2)	1.37(2)
C(6)–C(7)	1.40(2)	1.38(2)
C(7)–C(8)	1.50(2)	1.53(2)
C(8)–C(9)	1.53(2)	1.50(2)
C(9)–C(10)	1.33(2)	1.34(2)
C(10)–C(11)	1.45(1)	1.48(1)
C(11)–O(11)	1.18(1)	1.22(1)
C(11)–O(12)	1.36(1)	1.35(1)
O(12)–C(13)	1.44(1)	1.46(1)
C(13)–C(14)	1.56(1)	1.53(1)
C(14)–C(15)	1.52(1)	1.58(1)
C(15)–C(16)	1.50(1)	1.49(2)
C(16)–C(17)	1.43(2)	1.39(2)
C(16)–C(21)	1.37(2)	1.37(2)
C(17)–C(18)	1.45(2)	1.44(2)
C(18)–C(19)	1.34(2)	1.35(2)
C(19)–C(20)	1.34(2)	1.39(2)
C(20)–C(21)	1.51(2)	1.44(2)
N(22)–C(14)	1.46(1)	1.45(1)
N(22)–C(23)	1.35(1)	1.35(1)
C(23)–O(23)	1.24(1)	1.24(1)
C(23)–C(24)	1.51(1)	1.52(1)
C(24)–C(25)	1.55(2)	1.52(2)
C(24)–N(26)	1.46(1)	1.45(1)
N(26)–C(27)	1.32(1)	1.33(1)
C(27)–O(27)	1.23(1)	1.21(1)
C(27)–O(28)	1.37(1)	1.35(1)
O(28)–C(29)	1.43(2)	1.46(2)
C(29)–C(30)	1.56(2)	1.50(2)
C(30)–C(31)	1.38(2)	1.37(2)
C(30)–C(35)	1.38(2)	1.39(2)
C(31)–C(32)	1.43(2)	1.40(2)
C(32)–C(33)	1.38(2)	1.32(2)
C(33)–Br	1.92(1)	1.90(1)
C(33)–C(34)	1.36(2)	1.41(2)
C(34)–C(35)	1.41(2)	1.44(2)
(*b*) Interbond angles		
C(2)–N(1)–C(10)	120.2(8)	118.0(8)
C(2)–N(1)–C(13)	124.8(8)	123.2(8)
C(10)–N(1)–C(13)	111.0(8)	111.4(8)
N(1)–C(2)–C(3)	120.5(9)	121.6(9)
N(1)–C(2)–C(7)	119.0(9)	118.5(9)
C(3)–C(2)–C(7)	120.5(9)	119.8(9)
C(2)–C(3)–C(4)	121.3(10)	119.9(11)
C(3)–C(4)–C(5)	118.3(11)	120.3(13)
C(4)–C(5)–C(6)	120.0(12)	119.3(14)
C(5)–C(6)–C(7)	122.0(12)	122.2(12)
C(2)–C(7)–C(6)	117.7(10)	118.2(10)
C(2)–C(7)–C(8)	122.3(9)	122.1(9)
C(6)–C(7)–C(8)	120.0(10)	119.6(10)
C(7)–C(8)–C(9)	112.8(10)	112.4(9)
C(8)–C(9)–C(10)	119.3(10)	117.7(10)
N(1)–C(10)–C(9)	125.3(9)	128.5(9)
N(1)–C(10)–C(11)	106.6(8)	106.3(8)
C(9)–C(10)–C(11)	127.9(10)	125.1(10)
C(10)–C(11)–O(11)	132.3(10)	130.8(9)
C(10)–C(11)–O(12)	107.8(8)	107.9(8)
O(11)–C(11)–O(12)	119.9(9)	121.3(9)
C(11)–O(12)–C(13)	110.8(7)	110.9(7)
N(1)–C(13)–O(12)	103.5(7)	102.2(7)
N(1)–C(13)–C(14)	113.8(7)	115.6(8)
O(12)–C(13)–C(14)	107.9(7)	109.3(8)
C(13)–C(14)–C(15)	111.0(7)	110.5(8)
C(13)–C(14)–N(22)	111.0(7)	110.7(8)
C(15)–C(14)–N(22)	110.5(7)	111.4(8)
C(14)–C(15)–C(16)	112.1(8)	110.5(9)
C(15)–C(16)–C(17)	118.4(9)	120.9(10)
C(15)–C(16)–C(21)	120.2(10)	119.6(10)
C(17)–C(16)–C(21)	121.2(10)	119.5(11)
C(16)–C(17)–C(18)	117.2(11)	120.5(12)
C(17)–C(18)–C(19)	121.3(15)	120.5(14)
C(18)–C(19)–C(20)	123.0(16)	119.1(15)
C(19)–C(20)–C(21)	119.1(14)	121.2(14)
C(16)–C(21)–C(20)	118.2(12)	119.0(12)
C(14)–N(22)–C(23)	124.0(8)	121.4(8)
N(22)–C(23)–O(23)	122.8(8)	122.8(9)
N(22)–C(23)–C(24)	114.5(8)	113.3(8)
O(23)–C(23)–C(24)	122.6(8)	123.8(8)
C(23)–C(24)–C(25)	108.8(10)	107.8(9)
C(23)–C(24)–N(26)	111.8(9)	111.4(8)
C(25)–C(24)–N(26)	110.9(10)	110.6(8)
C(24)–N(26)–C(27)	121.2(9)	119.6(7)
N(26)–C(27)–O(27)	126.7(9)	126.7(9)
N(26)–C(27)–O(28)	110.8(9)	109.6(8)
O(27)–C(27)–O(28)	122.5(10)	123.6(9)
C(27)–O(28)–C(29)	116.2(9)	115.3(8)
O(28)–C(29)–C(30)	109.4(11)	112.2(10)
C(29)–C(30)–C(31)	117.6(12)	121.9(10)
C(29)–C(30)–C(35)	121.8(12)	119.8(11)
C(31)–C(30)–C(35)	120.6(12)	118.2(11)
C(30)–C(31)–C(32)	119.1(13)	122.4(11)
C(31)–C(32)–C(33)	118.1(14)	118.5(12)
C(32)–C(33)–Br	118.8(10)	121.0(10)
C(32)–C(33)–C(34)	123.4(12)	124.2(12)
C(34)–C(33)–Br	117.8(10)	114.8(9)
C(33)–C(34)–C(35)	117.6(13)	115.5(12)
C(30)–C(35)–C(34)	121.0(13)	120.9(12)

C(23)–C(24) 174.8 (174.6), C(24)–N(26)–C(27)–O(27) 2.4 (−11.6), and C(24)–N(26)–C(27)–O(28) 176.0 (171.3)°. The HN(26)–C(27)O group of molecule (B) thus shows a significant deviation from planarity.

TABLE 3

Equations of least-squares planes in the form $Ax + By + Cz + D = 0$ where x, y, and z are fractional coordinates. Deviations (Å) of atoms from the plane are given in square brackets; values for molecule (A) precede those for molecule (B)

Plane (*a*): C(2), C(7), C(9), C(10)

(A) $5.6563x + 12.6573y + 6.7130z - 8.9321 = 0$
(B) $1.2421x - 19.7596y + 6.8226z + 6.8086 = 0$

[C(2) 0.009, −0.006; C(7) −0.009, 0.006; C(9) 0.009, −0.006; C(10) −0.010, 0.007; N(1) 0.106, −0.119; C(8) 0.071, −0.182; C(11) −0.259, 0.290; C(13) −0.174, 0.319]

Plane (*b*): N(1), C(10), C(11), O(12), C(13)

(A) $3.8346x + 14.0209y + 7.8097z - 8.3959 = 0$
(B) $-0.9248x - 21.3202y + 6.1919z + 7.5809 = 0$

[N(1) 0.023, −0.068; C(10) −0.030, 0.049; C(11) 0.027 −0.009; O(12) −0.014, −0.030; C(13) −0.006, 0.057; O(11) 0.085, −0.024; C(14) 1.258, −1.038]

The conformation of the peptidic side-chain is extended in both molecules as can be deduced from the corresponding large values of the torsion angles. The smallest values correspond to the ϕ of the alanine residue −99.0° (78.0°). The conformational differences, significant but not large, can be ascribed to the ϕ and ψ torsion angles of the phenylalanine residue and to the ϕ value of the alanine residue.

The moderate variations found in the torsion angles of the two conformers may in part be caused by the intermolecular hydrogen bonds. All the NH groups of both

TABLE 4

Torsion angles (°) * with estimated standard deviations in parentheses

	Molecule (A)	Molecule (B)
Dihydropyridine ring		
N(1)–C(2)–C(7)–C(8)	−0.1(14)	3.8(15)
C(2)–C(7)–C(8)–C(9)	−6.6(14)	−15.4(16)
C(7)–C(8)–C(9)–C(10)	4.7(15)	13.4(16)
C(8)–C(9)–C(10)–N(1)	4.3(16)	0.0(16)
C(9)–C(10)–N(1)–C(2)	−11.9(14)	−13.0(16)
C(10)–N(1)–C(2)–C(7)	9.3(13)	10.3(13)
Oxazolidinone ring		
N(1)–C(10)–C(11)–O(12)	−5.5(10)	−5.7(11)
C(10)–C(11)–O(12)–C(13)	3.9(10)	−1.9(11)
C(11)–O(12)–C(13)–N(1)	−0.8(9)	8.0(10)
O(12)–C(13)–N(1)–C(10)	−2.8(9)	−11.9(10)
C(13)–N(1)–C(10)–C(11)	5.1(10)	11.1(11)
Chain		
N(1)–C(13)–C(14)C–(15)	−164.6(8)	169.6(8)
N(1)–C(13)–C(14)–N(22)	72.0(9)	45.6(11)
O(12)–C(13)–C(14)–C(15)	81.2(9)	55.0(10)
O(12)–C(13)–C(14)–N(22)	−42.2(9)	−68.9(9)
C(13)–C(14)–C(15)–C(16)	62.5(10)	60.3(11)
N(22)–C(14)–C(15)–C(16)	−173.8(8)	−176.1(9)
C(14)–C(15)–C(16)–C(17)	70.6(12)	71.0(13)
C(14)–C(15)–C(16)–C(21)	−104.0(12)	−108.5(12)
C(13)–C(14)–N(22)–C(23)	−91.2(10)	−125.8(9)
C(15)–C(14)–N(22)–C(23)	145.2(9)	110.8(10)
C(14)–N(22)–C(23)–O(23)	−3.6(15)	−2.5(14)
C(14)–N(22)–C(23)–C(24)	174.8(8)	174.6(8)
N(22)–C(23)–C(24)–C(25)	−80.5(12)	−86.2(10)
N(22)–C(23)–C(24)–N(26)	156.7(9)	152.2(8)
O(23)–C(23)–C(24)–C(25)	97.9(13)	90.8(12)
O(23)–C(23)–C(24)–N(26)	−24.9(14)	−30.8(12)
C(23)–C(24)–N(26)–C(27)	−99.0(11)	−78.0(10)
C(25)–C(24)–N(26)–C(27)	139.4(11)	162.0(9)
C(24)–N(26)–C(27)–O(27)	2.4(16)	−11.6(14)
C(24)–N(26)–C(27)–O(28)	−176.0(8)	171.3(8)
N(26)–C(27)–O(28)–C(29)	177.2(9)	177.0(8)
O(27)–C(27)–O(28)–C(29)	−1.3(15)	−0.2(13)
C(27)–O(28)–C(29)–C(30)	−82.7(12)	−80.9(12)
O(28)–C(29)–C(30)–C(31)	140.2(12)	137.7(12)
O(28)–C(29)–C(30)–C(35)	−40.2(16)	−41.0(16)

* Computed according to W. Klyne and V. Prelog, *Experientia*, 1960, **16**, 521.

molecules are involved in hydrogen bonding with the carbonyl groups of different molecules along the *a* direction: the scheme of interaction, as well as the geometry, are reported in Table 5. Relevant intra- and inter-molecular van der Waals contacts are listed in Table 6. Figure 3 shows the crystal packing viewed approximately along the *c* axis.

A characteristic feature of the ^{1}H n.m.r. spectra of (4a) and (4b) * in $CDCl_3$ is the shielding of the proton at C(3). The low δ value (6.2 p.p.m.) found for this aromatic proton, can be, in part, due to the magnetic shielding effect of the phenylalanine aromatic ring. Crystallographic analysis shows that this hydrogen, assumed to be located 1.09 Å from C(3) in the plane of the ring, falls in the shielding region of the phenylalanine aromatic, with half-angle of the cone of 28.3° (40.5°) and at a distance from the centre of the ring of 3.11 (4.35) Å. It seems therefore that in $CDCl_3$ solution an orientation of the phenylalanine portion similar to that found in the crystals, is adopted. In the ^{1}H n.m.r. spectrum, however, no coupling between vicinal protons at C(13) and C(14) could be observed. Since the HC(13)–C(14)H dihedral angle is 74.9 (48.4°), the preferred conformation in $CDCl_3$ solution is probably closer to that adopted by conformer (A). The vinylic proton appears as triplet at δ 5.56 p.p.m. superimposed on the signal of the oxazolidinonic proton, which appears as a singlet.

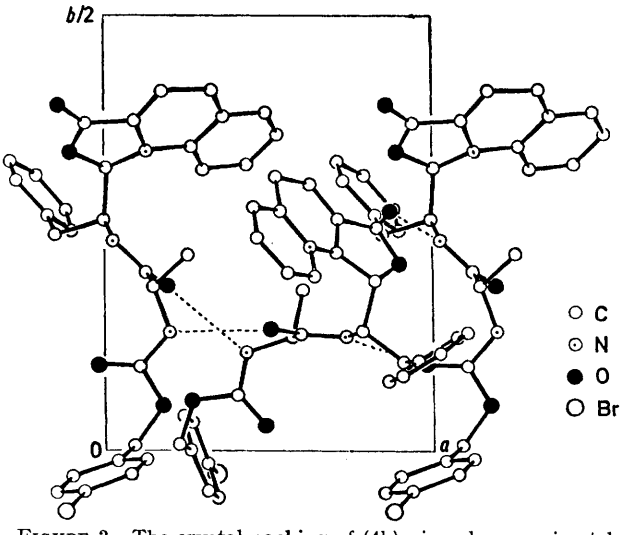


FIGURE 3 The crystal packing of (4b) viewed approximately along the *c* axis

TABLE 5

Geometry of hydrogen bonds

	Distances (Å)		Angles (°)			
	O · · · N	O · · · H	O · · · H–N	C–O · · · H	C–O · · · N	C–O · · · H–N
C(11A)–O(11A) · · · N(22B^{II})	2.88	1.88	177.9	134.6	135.3	−176.3
C(23A)–O(23A) · · · N(26B)	2.93	1.99	155.5	142.2	138.8	−70.0
N(22) · · · O(27B)–C(27B^{II})	3.10	2.12	164.9	144.9	141.3	−43.5
N(26) · · · O(23B)–C(23B)	3.04	2.04	176.5	134.2	133.0	3.9

Roman numeral superscripts refer to the equivalent positions described in the footnote to Table 6.

In the ^{13}C n.m.r. spectrum of (4a) sixteen resonance lines can be observed, besides an unresolved group of signals in the region of the aromatic carbon atoms (127—130 p.p.m.). The assignments listed in Table 7 were made by an inspection of the proton-decoupled and off-resonance decoupled ^{13}C n.m.r. spectra, on the basis of the comparison of literature δ values for related compounds. The characteristic chemical shift of the C(13) carbon is in agreement with that reported for –OCH(R)N systems.[3] The highfield position of the C(9), C(3), and C(7) signals, must be due to the nitrogen-atom shielding β-effect on the olefinic and aromatic carbons.

* Identical patterns were found in the ^{1}H n.m.r. spectra of compounds (4a) and (4b). The only differences concern the signals of the aromatic protons of the protecting groups.

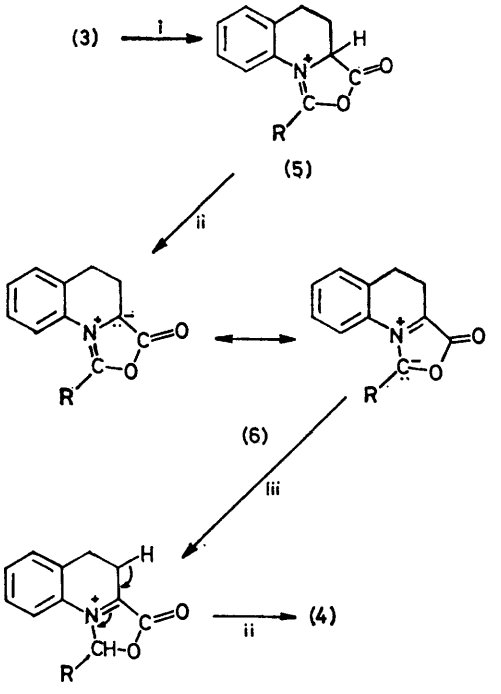
Recent literature data [4] do not allow unequivocal assignment to the doublet at 123.7 p.p.m. Singlets arising from C(2) and C(10), expected to be located downfield of the typical aromatic resonances, could not be observed in the adopted conditions, probably because of overlapping and/or long relaxation time.

TABLE 6

Relevant short interatomic contacts (Å) between non-bonded atoms

C(3A) · · · C(13A)	2.93	C(27A) · · · C(30A)	3.12
C(7A) · · · C(25B)	3.55	O(27A) · · · C(29A)	2.67
C(8A) · · · C(25B)	3.51	O(28A) · · · C(35A)	2.89
C(11A) · · · C(18B^{I})	3.26	Br(A) · · · C(32B^{III})	3.60
C(11A) · · · C(19B^{I})	3.33	N(1B) · · · N(22B)	2.87
O(11A) · · · C(11B^{II})	3.19	C(3B) · · · C(13B)	2.98
O(12A) · · · C(15A)	3.13	C(3B) · · · C(14B)	3.37
O(12A) · · · N(22A)	2.71	O(12B) · · · C(15B)	2.89
C(13A) · · · C(16A)	3.04	C(13B) · · · C(16B)	3.00
C(13A) · · · C(23A)	3.34	C(14B) · · · C(17B)	3.17
C(14A) · · · C(17A)	3.16	C(14B) · · · O(23B)	2.78
C(14A) · · · O(23A)	2.84	N(22B) · · · C(25B)	3.12
N(22A) · · · C(25A)	3.11	C(23B) · · · C(27B)	3.12
C(23A) · · · C(27A)	3.32	O(23B) · · · C(25B)	3.22
O(23A) · · · C(25A)	3.30	O(23B) · · · N(26B)	2.83
O(23A) · · · C(25B)	3.35	C(24B) · · · O(27B)	2.80
O(23A) · · · N(26A)	2.79	C(27B) · · · C(30B)	3.11
C(24A) · · · O(27A)	2.82	O(27B) · · · C(29B)	2.66
C(25A) · · · C(27A)	3.62	O(28B) · · · C(35B)	2.89

Roman numeral superscripts refer to the following equivalent positions relative to x,y,z: I $1+x, y, 1+z$; II $1+x, y, z$; III $1+x, y, z-1$.



SCHEME 2 Reagents: i, Ac_2O–AcONa; ii, $-H^+$; iii, $+H^+$

In the i.r. spectrum the strong absorption at 1 780 cm^{-1} accounts for the presence of a conjugated carbonyl group in a strained lactone ring.

The unexpected result of cyclization of (3) may be rationalized by the assumption that the reaction proceeds through the oxazolonium cation (5) and the mesoionic intermediate (6) according to Scheme 2.

TABLE 7

^{13}C N.m.r. chemical shifts and multiplicities for (4a)

δ/p.p.m.	Atom	δ/p.p.m.	Atom
19.1 (q)	C(25)	110.8 (d)	C(3)
28.1 (t)	C(8)	119.3 (s)	C(7)
36.9 (t)	C(15)	123.7 (d)	C(5) or C(6)
50.8 (d), 51.3 (d)	C(14), C(24)	136.7 (s), 138.0 (s)	C(16), C(30)
67.1 (t)	C(29)	156.0 (s)	C(27)
88.7 (d)	C(13)	163.6 (s)	C(11)
101.5 (d)	C(9)	173.3 (s)	C(23)

Cations analogous to (5) have been previously postulated (see *e.g.* the mechanism of formation of benzaldehyde from Reissert compounds).[5] Mesoionic oxazoles, on the other hand, have been shown by several workers to be intermediates during the conversion of an α-acylamino-acid to the corresponding α-acylamino-ketone (Dakin–West reaction). It should be pointed out that the overall 1,4-hydrogen transfer, which transforms the dipolar structure (6) into the final product (4) is in this case the preferred pathway. The alternative electrophilic substitution at C(10) in (6) by acetic anhydride, followed by nucleophilic ring-opening, to give the Dakin–West-type ketone, is not observed.[6] The planarity of the system induced by the fused aromatic ring should favour the 1,4-shift through a stereoelectronic control.

The study of this cyclization is currently being extended to other peptides and amides containing 1,2,3,4-tetrahydroquinoline-2-carboxylic acid.

EXPERIMENTAL

M.p.s were determined with a Büchi oil-bath apparatus. Optical rotations were taken at 20 °C with a Schmidt–Haensch polarimeter (1 dm cell). I.r. spectra were recorded with a Perkin-Elmer 521 spectrophotometer. ^1H N.m.r. spectra were measured with Varian EM 390 and Bruker HX 90 spectrometers (Me_4Si as internal standard). ^{13}C N.m.r. spectra were recorded on a Bruker WH 90/DS spectrometer operating at 22.63 MHz, for solutions in $CDCl_3$; chemical shifts are given in p.p.m. (δ) from Me_4Si as internal standard.

(S)-*Phenylalanyl*-(R)-1,2,3,4-*tetrahydroquinoline*-2-*carboxylic Acid* (2).—A solution of *N*-benzyloxycarbonyl-(*S*)-phenylalanyl-(*R*)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (1) (4.3 g) in methanol (300 ml) containing acetic acid (2.2 ml), was subjected to catalytic hydrogenolysis, using 5% Pd on alumina as catalyst (1.0 g) for 3 h under standard conditions. Catalyst was removed by filtration through Celite and the solution concentrated under reduced pressure. Addition of ethyl ether and cooling afforded a white precipitate of (S)-*phenylalanyl*-(R)-1,2,3,4-*tetrahydroquinoline*-2-*carboxylic acid* (2) (2.02 g), m.p. 136—138 °C; $[\alpha]_D$ +320° (*c* 1.0 in AcOH). This was characterized as a hydrochloride salt, m.p. 190—191 °C; $[\alpha]_D$ +290° (*c* 1.0 in MeOH); $\nu_{max.}$(KBr) 3 420br, 3 110, 1 720, 1 650, and 698 cm^{-1}; δ[$(CD_3)_2SO$] 1.3 (2 H, m, CH_2–CH_2–CH), 2.26 (2 H, m, CH_2–CH_2–CH), 2.97 (2 H, AB part of ABX system, CH–CH_2–Ph, J_{gem} 13.0 Hz, J_{vic} 5.0 and 9.6 Hz), 4.63 (2 H, m, CH–CH_2–Ph superimposed on CH–CO_2H), 7.72—6.68 (10 H, m, aromatic and CO_2H), and 9.4 (3 H, br

signal removed in D_2O, NH_3^+) (Found: C, 63.2; H, 5.9; Cl, 9.7; N, 7.8. $C_{19}H_{21}ClN_2O_3$ requires C, 63.25; H, 5.9; Cl, 9.85; N, 7.75%).

N-*Benzyloxycarbonyl*-(S)-*alanyl*-(S)-*phenylalanyl*-(R)-1,2,3,4-*tetrahydroquinoline*-2-*carboxylic Acid* (3a).—To a solution of *N*-benzyloxycarbonyl-(*S*)-alanine (0.9 g) in tetrahydrofuran (40 ml) cooled to −5 °C triethylamine (0.6 ml) and ethyl chlorocarbonate (0.4 ml) were added. After stirring for 0.5 h at −5 °C, the dipeptide (2) (1.3 g) and triethylamine (1.2 ml) were added. The mixture was stirred for 5 min at −5 °C and then for 45 min whilst it was permitted to warm to room temperature. Solvent was removed under reduced pressure at room temperature and the residue partitioned between 3% $NaHCO_3$ and AcOEt. The aqueous phase was acidified with 2N-hydrochloric acid and then extracted with ether. The ethereal layers were washed (water) to neutrality, dried, and evaporated. The oily residue (1.44 g), $[\alpha]_D$ +131° (*c* 1.0 in $CHCl_3$), nearly homogeneous on t.l.c., was esterified with ether–diazomethane and chromatographed on silica (p.l.c.) [benzene–ethyl acetate (1 : 3) as eluant]. The oily pure tripeptide ester, $[\alpha]_D$ +140° (*c* 1.0 in $CHCl_3$), was hydrolyzed as described previously for analogous dipeptide esters [1] to yield pure N-*benzyloxycarbonyl*-(S)-*alanyl*-(S)-*phenylalanyl*-(R)-1,2,3,4-*tetrahydroquinoline*-2-*carboxylic acid* (3a) as an oil, $[\alpha]_D$ +141° (*c* 1.0 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 400, 3 300, 1 715, and 1 665—1 625 cm^{-1}; δ($CDCl_3$) 1.6—1.1 [5 H, CH_3 (at 1.33, d, *J* 6.6 Hz) superimposed on CH_2–CH_2–CH, m], 2.3 (2 H, br m, CH_2–CH_2–CH), 2.88 (2 H, apparent d, *J* 7.2 Hz, Ph–CH_2–CH), 4.77—4.15 [2 H, m, CH–CO_2H and CH–CH_3 (the signal for CH–CH_3 is simplified to a quartet at 4.36, *J* 6.6 Hz, by exchange with D_2O)], 5.08 (2 H, s, Ph–CH_2–O), 5.71 (1 H, m, simplified to a triplet, *J* 7.2, by exchange with D_2O, Ph–CH_2–CH), 6.0 (1 H, d, removed in D_2O, NH–CO_2), 7.45—6.68 (14 H, m, aromatic), 7.69 (1 H, br s, removed in D_2O, CO_2H), and 8.13 (1 H, br d, removed in D_2O, NH–CO–CH).

The *p*-nitrophenyl ester of (3a) was synthesized by use of *p*-nitrophenyl sulphite in dry pyridine; m.p. 115—117 °C, $[\alpha]_D$ +126° (*c* 1.0 in $CHCl_3$) (Found: C, 66.3; H, 5.35; N, 8.55. $C_{36}H_{34}N_4O_8$ requires C, 66.45; H, 5.3; N, 8.6%).

Cyclization of Tripeptide (3a) *with Acetic Anhydride and Sodium Acetate*.—A mixture of the tripeptide (3a) (2.4 g), acetic anhydride (23 ml), and sodium acetate (8.6 g) was heated at 100° for 1 h and then evaporated under vacuum to dryness. Chloroform was added and the organic solution washed (aqueous $NaHCO_3$ and H_2O), dried (Na_2SO_4), and evaporated under reduced pressure. T.l.c. of the residue (2.3 g) gave a main product which was purified by column chromatography on silica gel (70 g). Elution with dichloromethane–ether (9 : 1) afforded the 1H,3H,5H-*oxazolo*[3,4-a]*quinolin*-3-*one derivative* (4a) (1.1 g), m.p. 186—189 °C (decomp.) (from ethyl acetate–ether); $[\alpha]_D$ −21° (*c* 1.0 in $CHCl_3$); $\nu_{max.}$(KBr) 3 375, 3 275, 1 780, 1 720, 1 685, 1 630, 1 225, and 698 cm^{-1}; δ($CDCl_3$) 1.25 (3 H, d, *J* 6.6 Hz, CH_3), 2.97 (2 H, d, *J* 8.2 Hz, Ph–CH_2–CH), 3.57 (2 H, apparent d, *J* 4.5 Hz, CH_2–CH=C), 4.28 (1 H, m, simplified to a quartet, *J* 6.6 Hz by exchange with D_2O, CH_3–CH), 4.9 (1 H, m, simplified to a triplet, *J* 8.2 Hz, by exchange with D_2O, Ph–CH_2–CH), 5.1 (2 H, s, $PhCH_2O$), 5.43 (1 H, d, *J* 8.0 Hz, removed in D_2O, NH–CO_2), 5.56 [2 H, m, vinylic (t, *J* 4.5 Hz) superimposed on N–CH–O signal], 6.2 (1 H, apparent d, aromatic), 6.8 (1 H, br d, removed in D_2O, NH–CO–CH), and 7.43—6.87 (13 H, m, aromatic). Irradiation of the multiplet at δ 4.28 caused the doublets at δ 1.25 and 5.43 to collapse to singlets; the same was observed for the doublets at δ 2.97 and 6.8 after irradiation of the multiplet at δ 4.9. Irradiation of the multiplet at δ 5.56 changed the apparent doublet at δ 3.57 to a broad signal. Irradiation of the doublet at δ 3.57 caused the multiplet at δ 5.56 to collapse to a broad singlet (Found: C, 70.4; H, 5.75; N, 8.2. $C_{30}H_{29}N_3O_5$ requires C, 70.45; H, 5.7; N, 8.2%).

N-p-*Bromobenzyloxycarbonyl*-(S)-*alanine*.—To an aqueous solution of (*S*)-alanine in 1N-NaOH, *p*-bromobenzyloxycarbonyl chloride was added at 0 °C with stirring. Standard work-up afforded the acylamino-acid (80%), m.p. 125—126 °C; $[\alpha]_D$ −24° (*c* 2.0 in AcOH) (Found: C, 43.7; H, 4.1; Br, 26.55; N, 4.6. $C_{11}H_{12}BrNO_4$ requires C, 43.75; H, 4.0; Br, 26.45; N, 4.65%).

N-p-*Bromobenzyloxycarbonyl*-(S)-*alanyl*-(S)-*phenylalanyl*-(R)-1,2,3,4-*tetrahydroquinoline*-2-*carboxylic Acid* (3b).—By following the procedure described for (3a) the *brominated tripeptide* (3b) was synthesized starting from the dipeptide (2) and *p*-bromobenzyloxycarbonyl-(*S*)-alanine; m.p. 181—183 °C (from ether); $[\alpha]_D$ +150° (*c* 1.0 in $CHCl_3$) (Found: C, 59.2; H, 5.05; Br, 13.0; N, 6.8. $C_{30}H_{30}BrN_3O_6$ requires C, 59.2; H, 4.95; Br, 13.15; N, 6.9%).

Cyclization of (3b) *with Acetic Anhydride and Sodium Acetate*.—*Compound* (4b) was obtained from (3b) according to the procedure described for (4a); m.p. 170—172 °C (from ethyl acetate–ether); $[\alpha]_D$ −17° (*c* 1.0 in $CHCl_3$) (Found: C, 60.9; H, 4.85; Br, 13.45; N, 7.1. $C_{30}H_{28}BrN_3O_5$ requires C, 61.0; H, 4.8; Br, 13.55; N, 7.1%).

Crystallographic Analysis of (4b).—Suitable single crystals of the compound (4b) were obtained from ethanol. Approximate unit-cell dimensions and space group were determined from oscillation and Weissenberg photographs of a crystal of dimensions *ca.* 0.2 × 0.4 × 0.8 mm, which was then transferred onto an automatic four-circle Syntex $P2_1$ diffractometer equipped with a graphite monochromator and using Cu-K_α radiation. Refined unit-cell parameters were obtained by a least-squares fit of the θ angles of 15 high-order reflections widely separated in reciprocal space.

Crystal data. $C_{30}H_{28}N_3O_5Br$, M = 590.5. Monoclinic, a = 9.835(1), b = 26.018(3), c = 10.856(1) Å, β = 93.78(1)°, U = 2 772.1 Å^3, Z = 4, D_c = 1.41 g cm^{-3}. Cu-K_α radiation, λ = 1.541 8 Å; μ(Cu-K_α) = 25.9 cm^{-1}. Space group $P2_1$ from systematic absences.

Intensities were collected in the range $2.0 \leqslant 2\theta \leqslant 115.0°$ by means of the ω-scan technique, using a scan speed within the interval 1.5 ÷ 29.3 min^{-1} over a range of 1.00°. Background counts were taken for a time equal to that of the scan. Out of a total of *ca.* 3 800 independent reflections the intensities of 3 615 reflections were considered observed [$I > 3\sigma(I)$]. The intensities of three standard reflections monitored every 100 reflections, remained essentially constant throughout data collection. In the estimation of σ(I) the uncertainty factor p was set equal to 0.000 2, as indicated by the variance of the standard reflections.[7] Lorentz and polarization factors were applied taking into account the monochromator crystal.[8] No absorption correction was applied. Calculations were carried out on an HP 21MX minicomputer of the CNR Research Area [9] and on a UNIVAC 1110 computer at the University of Rome.[10]

Structure solution and refinement. The structure was solved by the combined interpretation of the Patterson and Fourier maps and refined anisotropically for the bromine

atoms and isotropically for all other non-hydrogen atoms by block-diagonal least-squares methods (9 × 9 and 4 × 4 respectively), using all observed reflections. Atomic scattering factors were taken from ref. 11. Anomalous dispersion of the bromine atoms was taken into account in the structure-factor calculations. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$ where $w = (a + |F_o| + c|F_o|^2)^{-1}$ and a and c are of the order of $2F_{o(min.)}$ and $2/F_{o(max.)}$ respectively. The adequacy of the weighting scheme was checked by inspection of the mean of $w|\Delta F^2|$ as a function of the $|F_o|$ and sin θ/λ ranges: in both cases the function was nearly constant. Refinement was considered complete when the parameter shifts were $<0.1\sigma$. The final R and R' are 8.0 and 10.9% for all observed reflections. Observed and calculated structure factors and thermal parameters are listed in Supplementary Publication No. SUP 22355 (20 pp.).*

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* See Notice to Authors No. 7 in *J.C.S. Perkin I*, 1978, Index issue.

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