Structural Studies of Azacyclols derived from Linear Tripeptides

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N-Benzyloxycarbonyl-L-alanyl-L-phenylalanyl-L-proline *p*-nitrophenyl ester (4) and its *N*-*p*-bromobenzyloxycarbonyl analogue (2) each cyclize in alkaline aqueous medium to give a tricyclic system containing a free hydroxy-group derived from intramolecular addition of NH to amide carbonyl. Both the five-membered rings of the tricyclic system assume an envelope conformation. In the six-membered ring only the carbon atom bearing the cyclolic hydroxy-group is out of the plane of the other ring atoms. The benzylic side-chain of the phenylalanine residue adopts an extended conformation in both azacyclols. The crystal and molecular structures and spectral data for the tricyclic compounds (3) and (5) are reported.

HYDROXYLATED tetrahedral intermediates derived from intramolecular addition of NH, OH, or SH groups to an amide carbonyl, are usually known as aza-, oxa-, and thia-cyclols respectively. These compounds, of particular interest in the field of peptides [1] and cyclopeptides,[2,3] are stable only in exceptional cases. The peptide annular rearrangements,[8] and amino-acid insertion, only a few stable peptidic azacyclols are known.[9,10]

The reasons why in certain cases azacyclol forms are sufficiently stable to be isolated and are preferred over the isomeric cyclopeptide and *N*-(α-amidoacyl)dioxopiperazine forms are just becoming apparent.[2,3,10] The

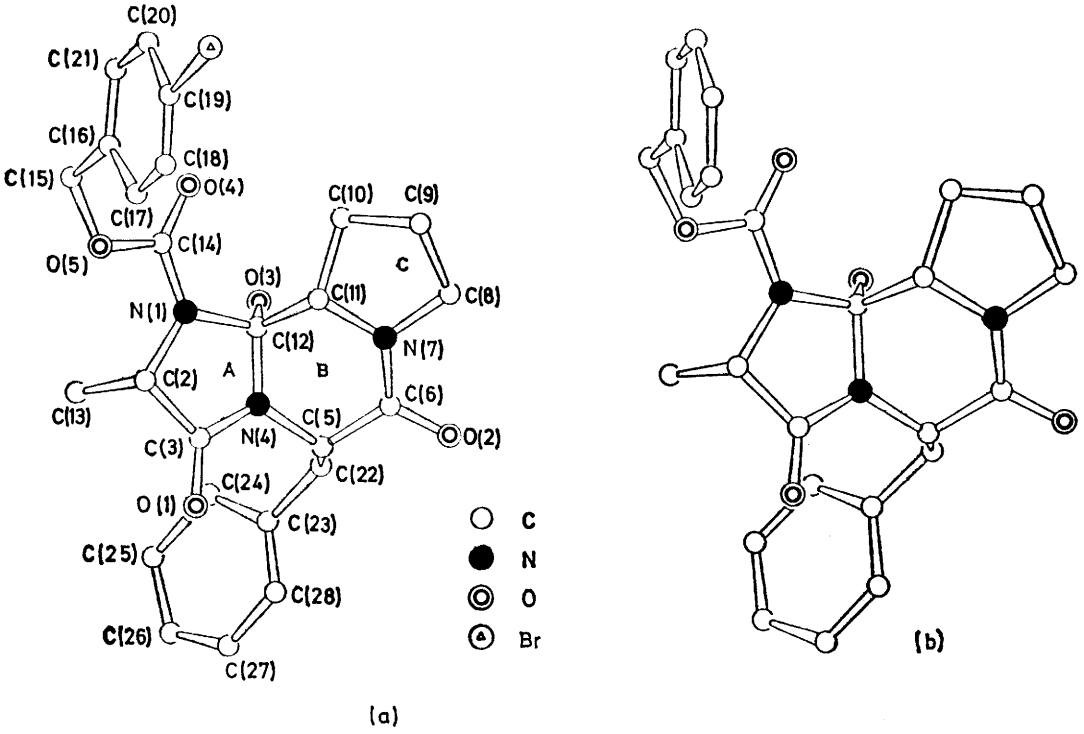


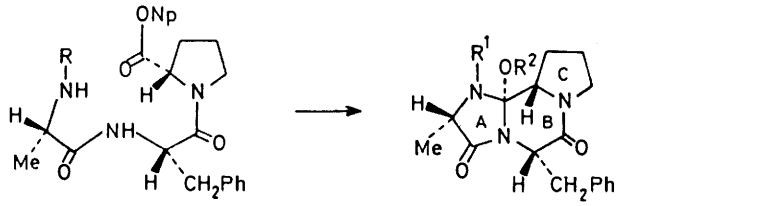
FIGURE 1 The molecular structure of (a) compound (3) and (b) compound (5) viewed along the same direction; the atom numbering system used in the crystallographic analysis is shown

portion of the Ergot alkaloids constitutes an outstanding example of stable oxacyclols [4] and since the total synthesis of ergotamine by the Sandoz group,[5] and the researches of Shemyakin and co-workers, [6] several oxacyclols have been studied and synthesized.

Though azacyclols derived from amide–amide interaction have been suggested as structural units in proteins [1] and as key intermediates in several reactions involving irregular fission of cyclopeptides,[7] transpresence in compounds such as azacyclols (3) and (5) of an acyl group on each of the nitrogen atoms of the tripeptidic system, is probably an important perequisite for the stability: [3] attempts to obtain cyclotripeptides from *N*-(α-aminoacyl)dioxopiperazines by aminoacyl insertion leads in fact to acylamidines or to ketenaminals (anhydrocyclols) through elimination of water from the intermediate azacyclols.[2]

Preliminary results concerning the synthesis of the

peptidic azacyclols (3) and (5) and the *X*-ray crystallographic analysis of the brominated azacyclol (3) have been published previously.[9] In order to gain deeper knowledge of the factors contributing to stabilize this class of compounds, we report here final results concerning the two azacyclols (3) and (5) as well as a crystallographic analysis of cyclol (5). The structure of (5) was determined because of the poor intensity data for (3) due to decay of the crystals in the *X*-ray beam and to the low-intensity scattering of the crystals. The numbering scheme used throughout the work is reported in Figure 1a. Cyclols (3) and (5) were both obtained by cyclization of the corresponding *N*-protected linear tripeptide *p*-nitrophenyl esters by treatment at room temperature with dioxan containing aqueous carbonate buffer.



(2); R = *p*-BrC$_6$H$_4$·CH$_2$·O·CO
(4); R = PhCH$_2$·O·CO
Np = C$_6$H$_4$·NO$_2$-*p*

(3); R^1 = *p*-BrC$_6$H$_4$·CH$_2$·O·CO, R^2 = H
(5); R^1 = PhCH$_2$·O·CO, R^2 = H
(6); R^1 = PhCH$_2$·O·CO, R^2 = Me

SCHEME

TABLE 1

Final fractional atom co-ordinates (× 10^4) and thermal parameters, with estimated standard deviations in parentheses, for compound (3)

	x/a	*y/b*	*z/c*	*B*
Br	−416(1)	−1 368(3)	−1 291(8)	*
N(1)	2 696(5)	398(8)	1 101(21)	3.0(2)
C(2)	3 044(6)	−234(10)	2 138(25)	3.1(3)
C(3)	3 190(6)	202(9)	4 125(26)	2.9(3)
N(4)	3 035(5)	1 033(8)	3 946(21)	2.9(2)
C(5)	3 108(7)	1 641(9)	5 710(27)	3.1(3)
C(6)	2 579(7)	2 163(10)	6 037(28)	3.3(3)
N(7)	2 173(5)	2 103(8)	4 638(22)	3.5(3)
C(8)	1 646(8)	2 603(12)	4 845(33)	4.5(4)
C(9)	1 269(8)	2 298(12)	3 092(34)	4.9(4)
C(10)	1 687(8)	1 888(12)	1 508(33)	4.8(4)
C(11)	2 106(7)	1 457(10)	2 974(25)	3.2(3)
C(12)	2 706(6)	1 226(9)	2 196(24)	2.7(3)
C(13)	3 599(8)	−473(12)	896(35)	5.1(4)
C(14)	2 399(6)	262(9)	−685(24)	2.8(3)
C(15)	2 107(7)	−788(10)	−2 997(29)	3.7(3)
C(16)	1 469(7)	−895(11)	−2 531(29)	3.6(3)
C(17)	1 302(9)	−1 185(13)	−558(35)	5.1(4)
C(18)	745(10)	−1 329(14)	−238(38)	6.2(5)
C(19)	386(9)	−1 171(13)	−1 669(36)	5.3(4)
C(20)	501(9)	−844(13)	−3 582(38)	5.7(5)
C(21)	1 088(8)	−693(12)	−4 052(35)	5.0(4)
C(22)	3 633(7)	2 211(11)	5 405(28)	3.7(3)
C(23)	4 192(7)	1 792(11)	5 630(30)	3.8(3)
C(24)	4 485(10)	1 656(15)	3 800(42)	6.9(6)
C(25)	5 075(14)	1 212(21)	4 088(53)	9.6(8)
C(26)	5 214(11)	1 007(17)	6 218(48)	7.5(6)
C(27)	4 894(11)	1 172(17)	7 723(42)	7.4(6)
C(28)	4 367(9)	1 532(13)	7 483(34)	5.2(4)
O(1)	3 441(5)	−109(7)	5 705(19)	4.1(2)
O(2)	2 577(5)	2 689(7)	7 492(17)	3.5(2)
O(3)	2 964(4)	1 860(7)	1 060(18)	3.5(2)
O(4)	2 160(4)	789(7)	−1 730(18)	3.4(2)
O(5)	2 419(5)	−564(7)	−1 191(19)	3.7(2)

* Br had anisotropic temperature factors in the form: exp[−($b_{11}h^2$ + $b_{12}hk$ + $b_{13}hl$ + $b_{22}k^2$ + $b_{23}kl$ + $b_{33}l^2$)], with b_{11} 0.0019(1), b_{12} −0.0013(2), b_{13} 0.0067(6), b_{22} 0.0130(2), b_{23} 0.0146(14), and b_{33} 0.1150(23)

Reaction of azacyclol (5) with methyl iodide–silver oxide gave the *O*-methyl derivative (6). This compound could be also obtained by treating (5) with diazomethane, but in this case the reaction was very slow. Unlike the azacyclols, the *O*-methyl derivative is not soluble in aqueous sodium hydroxide and is unaffected when treated at room temperature with methanolic hydrazine hydrate.

TABLE 2

Final fractional atom co-ordinates (× 10^4), with estimated standard deviations in parentheses, for the non-hydrogen atoms of compound (5)

	x/a	*y/b*	*z/c*
N(1)	4 021(8)	1 944 *	5 138(4)
C(2)	3 327(8)	1 286(4)	5 861(5)
C(3)	1 476(8)	1 712(4)	6 218(5)
N(4)	1 489(7)	2 528(4)	5 926(4)
C(5)	−76(8)	3 120(4)	6 155(5)
C(6)	−905(8)	3 709(4)	5 084(5)
N(7)	31(7)	3 692(4)	4 164(4)
C(8)	−668(12)	4 258(5)	3 121(6)
C(9)	801(12)	4 044(6)	2 307(6)
C(10)	2 777(11)	3 604(5)	3 166(6)
C(11)	1 666(9)	3 093(4)	3 980(5)
C(12)	3 038(8)	2 763(4)	5 224(5)
C(13)	5 124(10)	1 051(6)	7 026(6)
C(14)	5 485(9)	1 814(5)	4 471(5)
C(15)	7 492(10)	745(5)	3 813(6)
C(16)	6 274(11)	527(4)	2 513(5)
C(17)	4 228(12)	163(5)	2 254(6)
C(18)	3 148(16)	−71(6)	1 026(8)
C(19)	4 209(22)	49(7)	123(8)
C(20)	6 299(18)	412(7)	416(8)
C(21)	7 320(13)	639(6)	1 574(7)
C(22)	818(10)	3 628(5)	7 338(6)
C(23)	1 157(10)	3 101(5)	8 474(5)
C(24)	3 205(14)	2 946(8)	9 223(8)
C(25)	3 447(19)	2 441(8)	10 296(9)
C(26)	1 677(23)	2 130(8)	10 567(10)
C(27)	−385(21)	2 296(7)	9 841(10)
C(28)	−642(13)	2 778(6)	8 791(7)
O(1)	194(7)	1 390(4)	6 699(4)
O(2)	−2 363(7)	4 208(4)	5 120(4)
O(3)	4 482(6)	3 334(4)	5 922(4)
O(4)	6 250(7)	2 342(4)	3 954(4)
O(5)	5 994(7)	999(4)	4 517(4)

* This co-ordinate was kept fixed during refinement.

The atom co-ordinates together with the thermal para-

TABLE 3

Fractional atom co-ordinates ($\times 10^3$) of the hydrogen atoms located from the final difference-Fourier synthesis for compound (5)

	x/a	*y/b*	*z/c*
H(C2)	273	82	530
H(C5)	−123	280	617
H(C8)	−200	449	283
H(C9)	−14	357	170
H(C10)	297	316	273
H(C11)	96	265	344
H1(C13)	443	67	739
H2(C13)	638	88	691
H1(C15)	837	117	378
H2(C15)	840	40	416
H(C17)	334	7	297
H(C21)	875	87	177
H1(C22)	207	391	728
H2(C22)	−7	399	745
H(C24)	425	319	890

meters of the brominated azacyclol (3) are reported in Table 1, while Tables 2 and 3 list the atom co-ordinates of the azacyclol (5). The intramolecular bond distances and the angles common to the two cyclols are compared in Tables 4 and 5, whereas Table 6 lists relevant least-squares planes common to the two structures and the atom displacements from these planes. In the case of (3) the mean of the three partial double bonds N⁻⁻C=O is 1.35(3) Å, while that of the six N–C bonds is 1.47(4) Å. The corresponding means for the azacyclol (5) are 1.35(2) and 1.47(1) Å. The means for the two aromatic ring bonds are 1.38(8) for (3) and 1.39(3) Å for (5).

The sums of the bond angles around the three nitrogen atoms N(1), N(4), and N(7) are 360.0, 358.8, and 358.9° for (3) and 360.0, 359.7, and 359.7° for (5). The three

TABLE 4

Intramolecular bond distances (Å), with estimated standard deviations in parentheses, for compounds (3) and (5)

	(3)	(5)
Br–C(19)	1.95(2)	
N(1)–C(2)	1.46(2)	1.478(8)
N(1)–C(12)	1.48(2)	1.475(7)
N(1)–C(14)	1.35(2)	1.364(8)
C(2)–C(3)	1.48(2)	1.509(9)
C(2)–C(13)	1.59(3)	1.542(8)
C(3)–N(4)	1.37(2)	1.357(9)
C(3)–O(1)	1.27(2)	1.213(8)
N(4)–C(5)	1.49(2)	1.452(8)
N(4)–C(12)	1.39(2)	1.472(8)
C(5)–C(6)	1.52(2)	1.519(8)
C(5)–C(22)	1.55(2)	1.543(8)
C(6)–N(7)	1.32(2)	1.331(8)
C(6)–O(2)	1.24(2)	1.237(8)
N(7)–C(8)	1.49(2)	1.463(9)
N(7)–C(11)	1.48(2)	1.475(8)
C(8)–C(9)	1.51(3)	1.517(12)
C(9)–C(10)	1.56(3)	1.541(10)
C(10)–C(11)	1.53(3)	1.541(10)
C(11)–C(12)	1.56(2)	1.539(7)
C(12)–O(3)	1.38(2)	1.389(7)
C(14)–O(4)	1.21(2)	1.208(9)
C(14)–O(5)	1.35(2)	1.352(10)
C(15)–C(16)	1.56(2)	1.509(8)
C(15)–O(5)	1.41(2)	1.455(9)
C(16)–C(17)	1.39(3)	1.385(10)
C(16)–C(21)	1.36(3)	1.409(11)
C(17)–C(18)	1.36(3)	1.426(11)
C(18)–C(19)	1.27(3)	1.381(16)
C(19)–C(20)	1.35(3)	1.408(17)
C(20)–C(21)	1.45(3)	1.348(11)
C(22)–C(23)	1.49(2)	1.508(9)
C(23)–C(24)	1.37(3)	1.373(9)
C(23)–C(28)	1.31(3)	1.388(11)
C(24)–C(25)	1.58(4)	1.437(15)
C(25)–C(26)	1.43(5)	1.341(20)
C(26)–C(27)	1.25(4)	1.374(17)
C(27)–C(28)	1.39(3)	1.393(14)

TABLE 5

Intramolecular bond angles (°), with estimated standard deviations in parentheses, for compounds (3) and (5)

	(3)	(5)
C(2)–N(1)–C(12)	112.6(1.2)	114.3(5)
C(2)–N(1)–C(14)	124.6(1.2)	123.1(4)
C(12)–N(1)–C(14)	122.8(1.2)	122.6(4)
N(1)–C(2)–C(3)	101.6(1.2)	101.0(5)
N(1)–C(2)–C(13)	114.5(1.4)	112.8(5)
C(3)–C(2)–C(13)	109.9(1.3)	109.6(5)
C(2)–C(3)–N(4)	108.2(1.3)	108.7(5)
C(2)–C(3)–O(1)	127.2(1.4)	126.3(6)
N(4)–C(3)–O(1)	124.5(1.4)	125.1(6)
C(3)–N(4)–C(5)	121.8(1.3)	123.1(5)
C(3)–N(4)–C(12)	115.3(1.3)	115.5(5)
C(5)–N(4)–C(12)	121.7(1.2)	121.1(5)
N(4)–C(5)–C(6)	110.9(1.3)	112.2(5)
N(4)–C(5)–C(22)	112.1(1.3)	113.2(4)
C(6)–C(5)–C(22)	111.7(1.3)	109.2(5)
C(5)–C(6)–N(7)	118.5(1.5)	118.6(5)
C(5)–C(6)–O(2)	117.8(1.4)	118.9(6)
N(7)–C(6)–O(2)	123.2(1.5)	122.4(6)
C(6)–N(7)–C(8)	121.4(1.4)	121.0(6)
C(6)–N(7)–C(11)	127.7(1.3)	127.1(5)
C(8)–N(7)–C(11)	109.8(1.3)	111.6(5)
N(7)–C(8)–C(9)	105.5(1.5)	104.2(6)
C(8)–C(9)–C(10)	103.3(1.5)	104.6(6)
C(9)–C(10)–C(11)	102.2(1.6)	101.4(6)
N(7)–C(11)–C(10)	101.4(1.3)	100.8(5)
N(7)–C(11)–C(12)	106.9(1.2)	110.2(5)
C(10)–C(11)–C(12)	120.8(1.4)	119.6(5)
N(1)–C(12)–N(4)	101.0(1.2)	99.3(5)
N(1)–C(12)–C(11)	110.0(1.2)	113.4(5)
N(1)–C(12)–O(3)	113.8(1.2)	113.9(4)
N(4)–C(12)–C(11)	108.3(1.2)	106.6(4)
N(4)–C(12)–O(3)	109.0(1.2)	107.4(4)
C(11)–C(12)–O(3)	113.8(1.2)	114.6(5)
N(1)–C(14)–O(4)	126.6(1.4)	125.6(6)
N(1)–C(14)–O(5)	109.6(1.3)	108.7(5)
O(4)–C(14)–O(5)	123.8(1.4)	125.7(6)
C(16)–C(15)–O(5)	112.7(1.4)	111.1(5)
C(15)–C(16)–C(17)	119.0(1.6)	120.8(6)
C(15)–C(16)–C(21)	119.3(1.6)	118.9(6)
C(17)–C(16)–C(21)	121.7(1.7)	120.1(6)
C(16)–C(17)–C(18)	117.9(1.9)	119.8(8)
C(17)–C(18)–C(19)	121.0(2.2)	118.8(9)
C(18)–C(19)–C(20)	125.6(2.2)	120.1(8)
Br–C(19)–C(18)	122.6(1.8)	
Br–C(19)–C(20)	111.8(1.6)	
C(19)–C(20)–C(21)	116.4(2.0)	121.4(10)
C(16)–C(21)–C(20)	117.2(1.9)	119.8(8)
C(5)–C(22)–C(23)	116.6(1.4)	112.1(6)
C(22)–C(23)–C(24)	116.2(1.8)	121.6(7)
C(22)–C(23)–C(28)	120.5(1.7)	119.5(5)
C(24)–C(23)–C(28)	123.2(1.9)	118.9(7)
C(23)–C(24)–C(25)	115.1(2.2)	119.6(9)
C(24)–C(25)–C(26)	114.7(2.6)	120.0(9)
C(25)–C(26)–C(27)	122.2(2.7)	121.0(11)
C(26)–C(27)–C(28)	123.6(2.6)	119.6(12)
C(23)–C(28)–C(27)	121.0(2.1)	120.9(8)
C(14)–O(5)–C(15)	114.8(1.2)	115.9(6)

CO–N bonds and their substituents are almost planar as can be seen from Table 6.

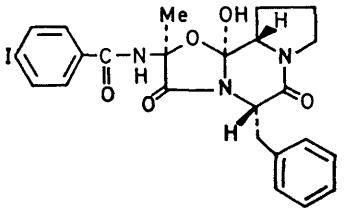
Stereochemical and conformational details can be obtained from Figure 1 which shows a general view of the molecules along the same direction. The absolute configurations, as deduced from a knowledge of the corresponding configurations in the starting linear tri-

peptides, are also shown. *X*-Ray analysis allowed unequivocal configurational assignment to the new formed asymmetric centre in C(12). As in the tricyclic oxacyclols related to the Ergot alkaloids,[11] ring closure to give azacyclols follows a stereospecific course, leading to an 11,12-*anti*-arrangement of H and OH substituents.

The imidazolidinonic ring A has an approximate $C_s(2)$ conformation in both azacyclols, with the C(2) atom displaced out of the plane of the others by −0.16 for (3) and by −0.17 Å for (5).

In both azacyclols the pyrrolidine ring C adopts the envelope conformation usually found in cyclic peptides containing proline. In fact Table 6 shows that ring C has a $C_s(10)$ conformation with the C(10) atom out of the plane of the others by −0.63 Å in both compounds.

The 2-oxopiperazinic ring B shows a 1,2-diplanar conformation with the smallest torsion angles centred on the carbonyl group. An approximate mirror plane cuts the six-atom ring through atoms C(6) and C(12). As can be seen from Table 6, five atoms of ring B lie almost in the same plane for both compounds. In fact C(12), which bears the cyclolic hydroxy-group, is displaced out of the plane of atoms C(5), C(6), O(2), N(7), C(8), and C(11) [plane (3)] by −0.57 in (3) and by −0.54 Å in (5), whereas N(4) is within this plane in both compounds. In the corresponding 2-oxopiperazinic ring of the *aci-p*-iodobenzoylamino-oxacyclol (7) studied by McPhail *et al.*[12] both atoms N(4) and C(12) are displaced by −0.29 and −0.58 Å out of this same plane. The internal torsion angles of the tricyclic system of the two azacyclols and of the oxacyclol (7)[12] are reported in Table 7. All compare well except for those around



(7)

C(5): the difference between them, which is −1.1° for the oxacyclol (7) (Table 7), confers isoclinal orientation on the phenylalanine C_α–C_β bond, whereas this difference in (3) (−42.2°) and (5) (−43.1°) confers more axial character on the same C_α–C_β bond.

The benzylic side-chain of the phenylalanine residue in the crystals of both azacyclols adopts an extended conformation towards the nitrogen. The N(4)–C(5)–C(22)–

TABLE 6

Details of planes in compounds (3) and (5). Equations of planes are in the form $Ax + By + Cz + D = 0$ where x, y, and z are fractional co-ordinates. Distances (Å × 10^3) of relevant atoms from the planes are in square brackets, values for compound (3) preceding those for compound (5)

Plane (1): N(1), C(2), C(12), C(14), O(4), O(5)

$19.2462x + 3.5393y - 3.4617z + 4.9525 = 0$

$3.5324x + 3.1147y + 7.1328z - 5.7009 = 0$

[N(1) 4, 10; C(2) −83, −56; C(12) 71, 41; C(14) 7, 10; O(4) −83, −56; O(5) 84, 51]

Plane (2): C(2), C(3), N(4), C(5), C(12), O(1)

$20.6790x + 4.2163y - 2.6591z + 5.5929 = 0$

$2.6385x + 3.4542y + 8.3829z - 6.1935 = 0$

[C(2), −34, −42; C(3) 8, 0; N(4) −69, −40; C(5) −9, −23; C(12) 64, 59; O(1) 41, 47]

Plane (3): C(5), C(6), N(7), C(8), C(11), O(2)

$9.5230x + 10.7882y - 3.8917z + 2.4720 = 0$

$3.8120x + 10.5315y + 3.2333z - 5.2171 = 0$

[N(4) 3, 71; C(5) −36, −30; C(6) 32, 12; N(7) −62, −30; C(8) −18, −22; C(11), 51, 39; C(12) −573, −539; O(2) 33, 31]

Plane (4): N(7), C(8), C(9), C(11)

$9.3834x + 10.3647y - 4.0957z + 2.2884 = 0$

$3.8067x + 10.1668y + 3.5770z - 5.2226 = 0$

[N(7) −31, −33; C(8) 30, 31; C(9) −19, −19; C(10) −634, −631; C(11) 20, 20]

Plane (5): N(1), C(3), N(4), C(12)

$20.0348x + 3.5040y - 3.1338z + 5.1833 = 0$

$3.0915x + 2.8308y + 7.8588z - 5.8295 = 0$

[N(1) −12, −2; C(2) −163, −169; C(3) 14, 2; N(4) −23, −4; C(12) 20, 3]

TABLE 7

Torsion angles (°), with estimated standard deviations in parentheses, for compounds (3), (5), and (7)

	(3)	(5)	(7)
Ring A *			
C(12)–N(1)–C(2)–C(3)	9.4(1.5)	10.7(5)	8.5
N(1)–C(2)–C(3)–N(4)	−11.5(1.5)	−10.4(5)	−8.9
C(2)–C(3)–N(4)–C(12)	10.5(1.7)	7.4(5)	6.2
C(3)–N(4)–C(12)–N(1)	−4.2(1.6)	−0.6(5)	−0.4
N(4)–C(12)–N(1)–C(2)	−3.9(1.5)	−6.8(5)	−5.6
Ring B			
C(12)–N(4)–C(5)–C(6)	33.5(1.9)	35.2(6)	14.4
N(4)–C(5)–C(6)–N(7)	−8.7(2.0)	−7.9(7)	13.3
C(5)–C(6)–N(7)–C(11)	13.9(2.4)	7.5(9)	−1.5
C(6)–N(7)–C(11)–C(12)	−35.0(2.1)	−28.9(8)	−32.8
N(7)–C(11)–C(12)–N(4)	51.1(1.5)	47.6(7)	52.9
C(11)–C(12)–N(4)–C(5)	−56.2(1.7)	−55.9(6)	−48.1
Ring C			
N(7)–C(8)–C(9)–C(10)	−20.5(1.9)	−20.7(7)	−25.9
C(8)–C(9)–C(10)–C(11)	38.5(1.8)	38.1(7)	39.9
C(9)–C(10)–C(11)–N(7)	−41.1(1.6)	−40.1(6)	−37.9
C(10)–C(11)–N(7)–C(8)	29.6(1.7)	29.4(6)	21.4
C(11)–N(7)–C(8)–C(9)	−5.5(1.9)	−5.8(7)	3.2
Benzyloxy-residue			
C(2)–N(1)–C(14)–O(4)	−170.5(1.5)	−173.1(5)	
C(2)–N(1)–C(14)–O(5)	7.6(2.0)	4.9(6)	
C(12)–N(1)–C(14)–O(4)	8.5(2.4)	5.3(7)	
C(12)–N(1)–C(14)–O(5)	−173.4(1.2)	−176.7(4)	
N(1)–C(14)–O(5)–C(15)	178.0(1.3)	151.7(6)	
O(4)–C(14)–O(5)–C(15)	−3.9(2.2)	−4.1(7)	
C(14)–O(5)–C(15)–C(16)	−80.6(1.6)	−88.4(7)	
O(5)–C(15)–C(16)–C(17)	−31.8(2.2)	−34.0(10)	
O(5)–C(15)–C(16)–C(21)	147.4(1.6)	151.0(7)	
Phenyl residue			
N(4)–C(5)–C(22)–C(23)	−70.4(1.9)	−68.3(7)	
C(6)–C(5)–C(22)–C(23)	164.6(1.5)	166.0(5)	
C(5)–C(22)–C(23)–C(24)	106.4(2.0)	113.1(8)	
C(5)–C(22)–C(23)–C(28)	−69.9(2.3)	−68.4(9)	
Peptidic groups			
C(12)–N(4)–C(3)–O(1)	−172.8(1.4)	−173.4(5)	
C(5)–N(4)–C(3)–O(1)	−5.2(2.2)	−0.5(8)	
C(5)–N(4)–C(3)–C(2)	178.0(1.3)	−179.6(4)	
C(8)–N(7)–C(6)–O(2)	−7.1(2.5)	−1.6(9)	
C(11)–N(7)–C(6)–O(2)	−173.9(1.5)	−175.5(6)	
C(8)–N(7)–C(6)–C(5)	−179.3(1.4)	−178.6(5)	

* For compound (7), substitute N(1) by O(1).

C(23) and C(5)–C(22)–C(23)–C(24) torsion angles (Table 7) for the azacyclols are in perfect agreement with the χ_1 and χ_2 dihedral angles quoted by Young and co-workers [13] for the second minimum of their conformational energy map for cyclo-(L-Pro-L-Phe). This minimum corresponds to the third one in the analysis of Ajò *et al.*[14] for

TABLE 8

Relevant short interatomic contacts (Å) between non-bonded atoms for compound (3)

Br · · · C(10^{I})	3.61	C(12)–C(22)	3.39
C(2)–O(5)	2.64	C(12)–O(4)	2.90
N(4)–C(13)	3.35	C(13)–C(14)	3.25
N(4)–C(23)	3.19	C(13)–O(1^{III})	3.37
C(5)–C(28)	3.21	C(13)–O(1)	3.13
C(5)–O(1)	2.88	C(13)–O(5)	3.11
C(5)–O(3)	2.99	C(14)–C(16)	3.10
C(5)–O(4^{II})	3.09	C(14)–O(3)	3.07
C(6)–O(4^{II})	2.78	C(15)–O(4)	2.63
C(8)–O(2)	2.79	C(17)–O(5)	2.86
C(10)–C(14)	3.38	C(22)–C(12)	3.39
C(10)–O(3)	3.05	C(22)–O(2)	2.94
C(10)–O(4)	2.92	C(23)–N(4)	3.19
C(11)–C(14)	3.08	C(26)–C(26^{IV})	3.35
C(12)–C(13)	3.53	O(2)–O(3^{II})	2.78

Roman numeral superscripts denote the following equivalent positions relative to the reference molecule at x, y, z:

I $\bar{x}, \bar{y}, z$ III $x, y, z - 1$
II $x, y, z + 1$ IV $\bar{x} + 1, \bar{y}, z$

the same substance. In the case of the oxacyclol (7),[12] the phenylalanine side-chain adopts a different conformation. This is, in fact, folded so as to face the hydroxy-group and establish a hydroxy–benzene intramolecular hydrogen bond.

It is interesting that the isoclinal orientation found for the C_α–C_β phenylalanine bond in the oxacyclol (7) is

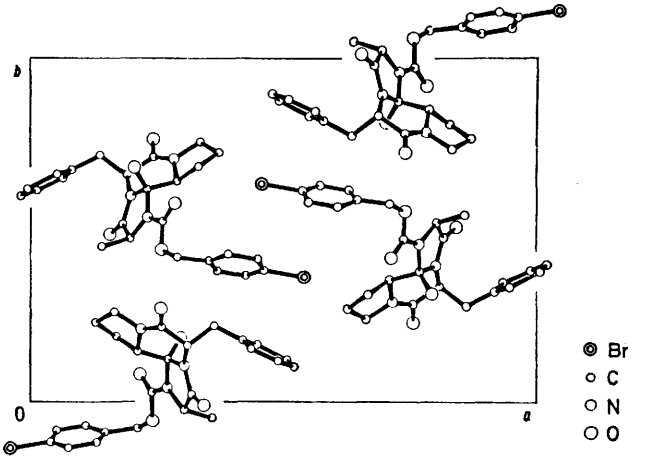


FIGURE 2 The molecular packing of the structure of (3) viewed down the *c* axis

related to a folded conformation of the benzylic side-chain, while the more axial orientation of the same bond, found in both azacyclols (3) and (5), corresponds to an extended conformation.

The ^{1}H n.m.r. spectra in deuteriochloroform for the azacyclols are in agreement with a preferred extended conformation for the phenylalanine side-chain. The two H_α–H_β coupling constants found for the C_βH protons are in fact significantly different (*ca.* 10 and 5 Hz, with the larger $J_{\alpha\beta}$ associated with the higher-field proton). These data, together with the chemical shifts of the C_βH protons are very similar to those found in the case of the *cis*-cyclodipeptides cyclo-(L-Pro-L-Phe) and cyclo-(L-Aze-L-Phe) [15] for which an unfolded conformation in chloroform, with the aromatic ring oriented toward the nitrogen, is preferred.[15,16]

An interesting feature concerning the conformation of

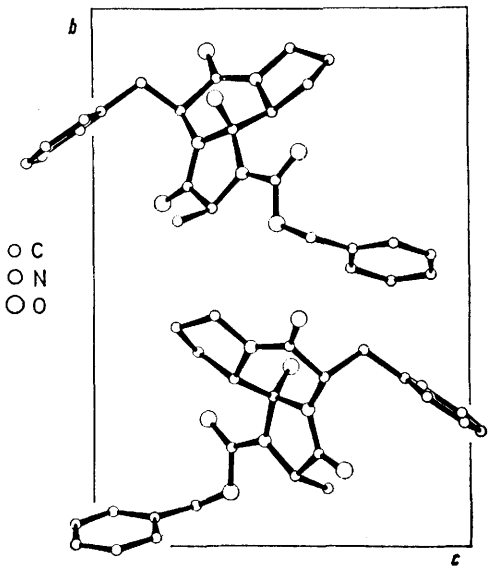


FIGURE 3 The molecular packing of the structure of (5) projected on the *bc* plane

the benzylic side-chain of the phenylalanine residue and of the benzyloxycarbonyl group is found in the crystals of the azacyclols. The two aromatic rings, in fact, face the adjacent carbonyl group, so that small dipole–induced dipole and dipole–dipole interactions may contri-

TABLE 9

Relevant short interatomic contacts (Å) between non-bonded atoms for compound (5)

C(2) · · · O(5)	2.61	C(12)–O(4)	2.88
N(4)–C(13)	3.32	C(12)–C(22)	3.39
N(4)–C(23)	3.09	C(13)–C(14)	3.21
C(5)–O(1)	2.86	C(13)–O(1)	3.11
C(5)–O(3)	3.00	C(13)–O(1^{II})	3.39
C(5)–C(28)	3.15	C(13)–O(5)	3.04
C(6)–O(4^{I})	2.92	C(14)–C(16)	3.17
C(10)–O(3)	3.05	O(2)–O(3^{I})	2.80
C(10)–O(4)	2.96	O(2)–C(22)	2.92
C(11)–C(14)	3.12	O(4)–C(15)	2.71
C(12)–C(13)	3.48	O(5)–C(17)	2.85

Roman numeral superscripts define the following equivalent positions relative to the reference molecule at x, y, z:

I $x - 1, y, z$ II $x + 1, y, z$

bute to maintain the observed conformation in the two different crystal systems.

Relevant intra- and inter-molecular van der Waals contacts are listed in Tables 8 and 9 for both azacyclols. In (3) the carbonylic oxygen O(2) forms a hydrogen bond of 2.78 Å with the hydroxy-oxygen O(3) of a molecule translated by a *c* unit. The angle C(6)–O(2) · · · O(3) is

106.8° and O(2) · · · O(3)–C(12) 128.5°. In (5) oxygen atom O(2) forms a hydrogen bond of 2.80 Å with oxygen O(3) of another molecule translated by $-a$. The angle C(6)–O(2) · · · O(3) is 107.0° and O(2) · · · O(3)–C(12) 124.9°. Figures 2 and 3 show the crystal packing of the two compounds.

EXPERIMENTAL

M.p.s were determined with a Büchi oil-bath apparatus; optical rotations were taken at 20 °C with a Schmidt-Haensch 16065 polarimeter (1 dm cell). I.r. spectra were recorded with a Perkin-Elmer 521 spectrophotometer. ^{1}H N.m.r. spectra were measured with a Varian HA 100 spectrometer (Me_4Si as internal standard). Mass spectra were determined with an AEI MS 12 spectrometer.

N-Benzyloxycarbonyl-L-alanyl-L-phenylalanyl-L-proline (1).—To a solution of *N*-benzyloxycarbonyl-L-alanyl-L-phenylalanyl hydrazide (6.15 g, 16 mmol) in glacial acetic acid (57 ml), methylene chloride (34 ml) was added. Sodium nitrite (2.21 g, 32 mmol) dissolved in the minimum of cold water, was then added with stirring to the hydrazide solution cooled at 0 °C. After 3 min the reaction mixture was poured into ice–water and extracted with methylene chloride; the organic layer was rapidly washed at 0 °C with water, saturated sodium hydrogen carbonate solution (× 3), and water, and then dried (Na_2SO_4) and evaporated under vacuum (bath temperature 30 °C). The oily residue was dissolved in tetrahydrofuran (0 °C) and added dropwise during 1 h to a stirred solution cooled at 0 °C of L-proline (3.1 g, 27 mmol) in aqueous 0.5N-sodium hydroxide. Stirring was continued at 0 °C for an additional hour during which time 0.5N-sodium hydroxide was added to maintain the reaction mixture alkaline. Tetrahydrofuran was evaporated under vacuum and the resulting aqueous solution washed with diethyl ether. Acidification followed by extraction with ethyl acetate gave the crude *N*-benzyloxycarbonyl tripeptide (1) (6.8 g). Crystallization from ethyl acetate removed the urea derivative as impurity (580 mg) leaving compound (1) in the mother-liquor. Compound (1) was crystallized for analysis from ethyl acetate, m.p. 174—176 °C; $[\alpha]_D$ −45° (*c* 1.0 in $CHCl_3$), $\nu_{max.}$($CHCl_3$) 3 400, 1 710, 1 650, and 1 590 cm^{-1} (Found: C, 64.15; H, 6.3; N, 9.05. $C_{25}H_{29}N_3O_6$ requires C, 64.23; H, 6.25; N, 8.99%).

N-Benzyloxycarbonyl-L-alanyl-L-phenylalanyl-L-proline p-*Nitrophenyl Ester* (4).—To a solution of the acid tripeptide (1) (5.16 g, 11 mmol) in dry pyridine (28 ml) was added di-*p*-nitrophenyl sulphite (3.9 g, 12.1 mmol). After 3.5 h at room temperature the mixture was evaporated under vacuum and the residue dissolved in ethyl acetate. The solution was washed with 1N-hydrochloric acid, saturated sodium carbonate solution (0 °C), and water, and then dried (Na_2SO_4) and evaporated under reduced pressure to give the active ester (4) (4.63 g), which was crystallized from ethyl acetate–diethyl ether, m.p. 109—111 °C; $[\alpha]_D$ −48° (*c* 0.5 in ethyl acetate); $\nu_{max.}$(KBr) 3 350, 1 775, 1 735, 1 660—1 630, and 1 530 cm^{-1} (Found: C, 63.2; H, 5.35; N, 9.5. $C_{31}H_{32}N_4O_8$ requires C, 63.25; H, 5.48; N, 9.52%).

N-p-Bromobenzyloxycarbonyl-L-alanyl-L-phenylalanyl-L-proline p-*Nitrophenyl Ester* (2).—*p*-Bromobenzyloxycarbonyl chloride (2.0 g, 8.04 mmol) in dioxan (9 ml) was added dropwise under stirring to a cooled (0 °C) solution of L-alanyl-L-phenylalanyl-L-proline (2.33 g, 7 mmol) in 1N-$NaHCO_3$ (30 ml). The mixture was stirred for 30 min at 0 °C and then for 2.5 h at room temperature whilst dioxan (9 ml) was added. After extraction with chloroform the aqueous phase was acidified with 6N-hydrochloric acid and extracted with ethyl acetate. Drying (Na_2SO_4) and evaporation gave the acid tripeptide (3.1 g) as an oil homogeneous on t.l.c. Treatment with di-*p*-nitrophenyl sulphite–pyridine according to the procedure already reported for the active ester (4), gave the active ester (2) (65%), m.p. 165—166 °C (from ethyl acetate); $[\alpha]_D$ −49° (*c* 1.0 in dioxan); $\nu_{max.}$(KBr) 3 300—3 270, 1 775, 1 720, 1 660—1 630, and 1 520 cm^{-1} (Found: C, 55.75; H, 4.75; Br, 11.85; N, 8.65. $C_{31}H_{31}BrN_4O_8$ requires C, 55.78; H, 4.68; Br, 11.97; N, 8.39%).

Cyclization of N-*Benzyloxycarbonyl-L-alanyl-L-phenylalanyl-L-proline* p-*Nitrophenyl Ester* (4).—To a solution of the active ester (4) (4.29 g, 7.3 mmol) in dioxan (200 ml) were added aqueous 0.1M sodium hydrogen carbonate (100 ml) and aqueous 0.1M-sodium carbonate (100 ml). After 1 h at room temperature the reaction mixture was evaporated under vacuum to dryness. The residue was partitioned between water and chloroform and the organic layer washed with saturated sodium carbonate solution and water. After drying (Na_2SO_4) and removal of the chloroform, the residue (2.4 g) was crystallized from ethyl acetate as the cyclol (5) (1.5 g), m.p. 183—185 °C; $[\alpha]_D$ −36° (*c* 1.0 in absolute ethanol); $\nu_{max.}$($CHCl_3$) 3 500—3 400, 1 720—1 690, 1 650—1 635, and 1 445 cm^{-1}; $\nu_{max.}$(KBr) 3 210br, 1 725—1 710, and 1 615 cm^{-1}; δ($CDCl_3$) 1.30 (3 H, d, *J* 6.5 Hz, CH_3), 1.5—2.3 (4 H, m, CH·C*H*$_2$·C*H*$_2$), 3.13 and 3.45 (2 H, AB part of ABX system, J_{vic} 10.0 and 4.8 Hz, J_{gem} 13.5 Hz, Ph–C*H*$_2$–CH), 3.6 (3 H, unresolved m, CH_2·N and C*H*·CH_2·CH_2), 3.95 (1 H, q, *J* 6.5 Hz, C*H*·CH_3), 4.57 (1 H, br s, exchangeable, OH), 4.84 (1 H, 4 lines, X part of ABX system, PhCH_2·C*H*), 5.16 (2 H, s, PhC*H*$_2$·O), and 7.15—7.5 (10 H, m, aromatic H); δ(perdeuteriodimethyl sulphoxide) 1.30 (3 H, d, *J* 6.5 Hz, CH_3), 1.4—2.3 (4 H, m, C*H*·CH_2·CH_2), 2.90 and 3.30 (2 H, AB part of ABX system, J_{vic} 10 and 6 Hz, J_{gem} 13 Hz, PhC*H*$_2$·CH), 3.80 (1 H, t, C*H*·CH_2·CH_2), 4.05 (1 H, q, *J* 6.5 Hz, C*H*·CH_3), 4.53 (1 H, 4 lines, X part of ABX system, PhCH_2·C*H*), 5.18 (2 H, s, PhCH_2·O), 7.10—7.55 (10 H, m, aromatic H), and 7.84 (1 H, s, exchangeable, OH); *m/e* 449 (M^+, 12%), 431 (2), 358 (5), 341 (3), 335 (2), 314 (3), 271 (3), 245 (7), 244 (6), 243 (6), 201 (9), 200 (8), 178 (6), 153 (5), 134 (15), 131 (10), 125 (5), 91 (100), and 70 (43) (Found: C, 67.0; H, 6.2; N, 9.25. $C_{25}H_{27}N_3O_5$ requires C, 66.80; H, 6.05; N, 9.35%).

Cyclization of N-p-*Bromobenzyloxycarbonyl-L-alanyl-L-phenylalanyl-L-proline* p-*Nitrophenyl Ester* (2).—The procedure adopted for the synthesis of cyclol (5) was followed from ester (2) (2.6 g). Crystallization from ethyl acetate of the residue (1.65 g) gave cyclol (3) (0.65 g), m.p. 167—168 °C; $[\alpha]_D$ −23° (*c* 1.5 in chloroform); $\nu_{max.}$($CHCl_3$) 3 500, 1 720—1 690, 1 650—1 640, and 1 445 cm^{-1}; $\nu_{max.}$(KBr) 3 210br, 1 720, and 1 615 cm^{-1}; δ($CDCl_3$) 1.28 (3 H, d, *J* 6.5 Hz, CH_3), 1.5—2.4 (4 H, m, CH·C*H*$_2$·C*H*$_2$), 3.15 and 3.45 (2 H, AB part of ABX system, J_{AX} 9.5 Hz, J_{BX} 5.0 Hz, J_{AB} 13.5 Hz, PhC*H*$_2$·CH), 3.55 (3 H, unresolved m, C*H*$_2$N and C*H*·CH_2·CH_2), 3.95 (1 H, q, *J* 6.5 Hz, C*H*·CH_3), 4.45 (1 H, br s, exchangeable, OH), 4.84 (1 H, 4 lines, X part of ABX system, PhCH_2·C*H*), 5.08 (2 H, s, CH_2O), and 7.1—7.6 (9 H, m, aromatic H) (Found: C, 56.9; H, 5.0; Br, 15.05; N, 7.8. $C_{25}H_{26}BrN_3O_5$ requires C, 56.83; H, 4.96; Br, 15.12; N, 7.95%).

Synthesis of Cyclol O-Methyl Ether (6).—Methyl iodide (6.0 g, 42.3 mmol) and silver oxide (320 mg) were added with stirring to a solution of cyclol (5) (200 mg, 0.45 mmol) in chloroform (0.5 ml) containing dry methanol (0.25 ml). After 7 h of stirring at room temperature the filtered mixture was evaporated to dryness under vacuum and the residue crystallized from benzene–hexane to give the *O*-methyl ether (6) (140 mg), m.p. 143—144 °C; $[\alpha]_D$ −23° (*c* 1.0 in chloroform); $\nu_{max.}$(CHCl$_3$) 1 715, 1 650—1 640, and 1 440 cm^{-1}; δ(CDCl$_3$) 1.38 (3 H, d, *J* 6.5 Hz, C–CH$_3$), 1.5—2.4 (4 H, complex m, CH$_2$·CH$_2$), 3.02 (3 H, s, O·CH$_3$), 3.05—2.80 (1 H, A part of ABX system, J_{vic} 7.5 Hz, J_{gem} 14 Hz, PhC*H*$_2$·CH), 3.75—3.35 [4 H, complex m, C*H*·CH$_2$·CH$_2$, PhC*H*$_2$·CH (B part of the ABX), CH$_2$·N], 4.10 (1 H, q, *J* 6.5 Hz, CH$_3$·C*H*), 4.90 (1 H, X part of the ABX, PhCH$_2$·C*H*), 5.15 (2 H, s, PhC*H*$_2$·O), and 7.1—7.5 (10 H, m, aromatic H); *m/e* 463 (M^+, 11%), 432 (2), 431 (2), 388 (3), 297 (5), 274 (3), 244 (15), 231 (7), 201 (12), 173 (27), 153 (9), 131 (8), 125 (15), 91 (100), 78 (23), and 70 (90) (Found: C, 67.3; H, 6.45; N, 9.2. $C_{26}H_{29}N_3O_5$ requires C, 67.37; H, 6.31; N, 9.07%).

Crystallographic Analysis.—Suitable single crystals of (3) and (5) were obtained from ethyl acetate. Approximate unit-cell parameters and the space group of each compound were determined from oscillation and Weissenberg photographs. Intensities for (3) were collected on an off-line Siemens diffractometer by use of Zr-filtered Mo-K_α radiation, whereas data for (5) were recorded by a Syntex $P2_1$ automatic four-circle diffractometer, equipped with graphite monochromator, by use of Mo-K_α radiation. Refined unit-cell parameters for both compounds were obtained by a least-squares fit of the θ angles of 15 high-order reflections widely separated in reciprocal space.

Crystal data for compound (3). $C_{25}H_{26}N_3O_5Br$, M = 528.4. Orthorhombic, a = 23.819(15), b = 15.826(10), c = 6.351(7) Å, U = 2 394.1 Å^3, Z = 4, D_c = 1.46 g cm^{-3}. Mo-K_α radiation, λ = 0.7107 Å; μ(Mo-K_α) = 18.5 cm^{-1}. Space group $P2_12_12$ from systematic absences.

Intensities were collected up to $2\theta_{max.}$ of 5.0° by the ω-scan technique with a constant scan-speed of 2.3 min^{-1} over a range of 0.5°. Only the 1 325 independent reflections having $I > 3\sigma(I)$ were considered observed. The low scattering power of the crystal together with the fact that it was damaged by *X*-rays prevented larger data collection. Three standard reflections, monitored every 50, showed significant decay in the *X*-ray beam: intensities were put on roughly the same scale by taking into account the regular decrease of the standard reflections. Lorentz and polarization factors were applied but not those for absorption or extinction.

Crystal data for compound (5). $C_{25}H_{27}N_3O_5$, M = 449.5. Monoclinic, a = 6.359(1), b = 16.138(4), c = 11.319(2) Å, β = 105.56(1)°, U = 1 119.0 Å^3, D_c = 1.33 g cm^{-3}, Z = 2, D_m = 1.32 g cm^{-3}. Mo-K_α radiation, λ = 0.710 7 Å, μ(Mo-K_α) = 1.01 cm^{-1}. Space group $P2_1$.

Intensities were collected in the range $2.0 \leqslant 2\theta \leqslant 55.0°$ by the ω-scan technique, using a scan speed within the interval 1.5—29.3 min^{-1} over a range of 1.00°. Of a total of *ca.* 2 570 independent reflections, 2 042 were considered observed as before. Three standard reflections monitored every 100 remained essentially constant. Lorentz and polarization factors were applied taking into account the monochromator crystal. No absorption or extinction corrections were applied.

Structure solutions and refinements. The structure of (3) was solved by combined interpretation of Patterson and Fourier maps and refined anisotropically for the bromine atom and isotropically for all other non-hydrogen atoms by block-diagonal least-squares methods (one block for all the co-ordinates and another block for the thermal parameters and the scale factor), using all observed reflections. The final Fourier difference [σ(ρ) 0.4 e Å^{-3}] revealed few peaks >1σ of the electron density, mainly around the bromine atom. Atomic scattering factors were taken from ref. 17. Anomalous dispersion of the bromine atom 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 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 sinθ/λ ranges: in both cases the function was nearly constant. Refinement was considered complete when the parameter shifts were <0.1σ. The final R and R' are 0.11 and 0.14 for all observed reflections. Calculations were carried out on a UNIVAC 1108 computer at the University of Rome.[18] Observed and calculated structure factors for both compounds (3) and (5), and thermal parameters for (5) are listed in Supplementary Publication No. SUP 22645 (31 pp.).*

The structure of (5) was solved by direct methods with the program MULTAN [19] employing the 220 reflections with $|E| > 1.61$. An *E* map, computed with the phases of the set with the highest figures-of-merit, revealed all the non-hydrogen atom positions, and these were refined isotropically and anisotropically by block-diagonal least-squares methods (one block for all the co-ordinates and another for the thermal parameters and the scale factor), using all observed reflections. A difference-Fourier synthesis [σ(ρ) 0.1 e Å^{-3}] showed evidence for 15 out of the 27 hydrogen atoms at their approximate expected positions. These were included in the last three cycles of refinement with an overall B of 5.0 Å^2, with their positional parameters fixed. Scattering factors were taken from ref. 20. The function minimized was as for compound (3). When the refinement was stopped the sum of the square of the ratios between the parameters shifts and the estimated standard deviations was 0.03. The adequacy of the weighting scheme was checked as before and in both cases the function was nearly constant. The final R and R' are 0.06 and 0.10 respectively for all the observed reflections. All calculations were carried out on an HP 21MX minicomputer of the CNR Research Area [21] and on a UNIVAC 1110 computer of the University of Rome.[18]

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* See Notice to Authors No. 7 in *J.C.S. Perkin I*, 1979, Index issue.

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