Peptide Cyclols. Crystal Structure and Molecular Conformation of the Oxacyclol derived from L-2-Hydroxyisovaleryl-L-phenylalanyl-L-proline †

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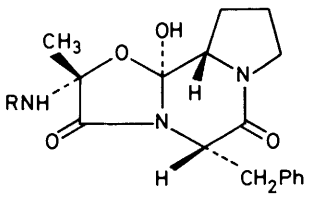
Cyclization of L-2-hydroxyisovaleryl-L-phenylalanyl-L-proline *p*-nitrophenyl ester gives the corresponding tricyclic oxacyclol. The *X*-ray crystallographic analysis of the oxa-cyclol is reported; crystals are monoclinic, space group $P2_1$, a = 6.794, b = 14.379, c = 9.260 Å, β = 92.75°, Z = 2. The final R and R_w values are 0.039 and 0.054, respectively, for 1 890 independent reflections. The conformation of the rings, the torsion angles, and several conformational details found in the solid state for the oxa-cyclol are discussed and compared with those found for natural ergot alkaloids and related synthetic compounds. A comparison between the conformation of the oxa-cyclol in the crystal with that found in solution by means of ^{1}H n.m.r. spectroscopy, is also reported.

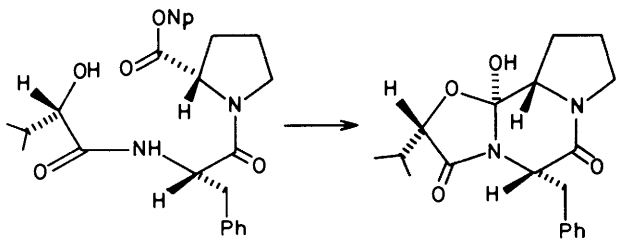
ALTHOUGH the occurrence of cyclols as key intermediates in intramolecular reactions involving peptides and oligocyclopeptides has often been reported,[1] peptide cyclols stable enough to be isolated are rarely encountered. The tricyclic system (1) found in the peptide



(1)

a; R = lysergyl
b; R = dihydrolysergyl

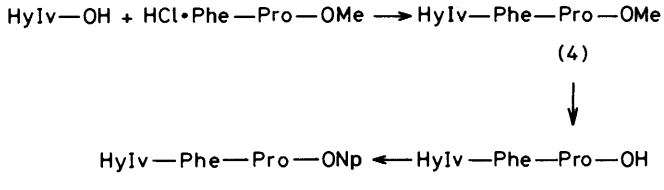
portion of the ergot alkaloids and in related synthetic compounds,[2] represents an outstanding example of a structure possessing steric and electronic features suitable for the formation of quite stable hydroxylated tetrahedral intermediates (cyclols). However, due to



(2) (3)

their intrinsic chemical lability, only a few chemical reactions can be carried out on cyclols. *X*-Ray crystallographic analysis together with spectroscopic studies are of particular aid in defining conformational features contributing to the stability of cyclols and in assessing, on a molecular basis, the potent pharmacological effects observed for peptide ergot alkaloids.[3,4]

In this paper we report the synthesis and molecular structure of the oxa-cyclol (3) and correlate its conformational features with those of known peptide cyclols. Oxacyclol (3) was obtained from the corresponding linear *C*-activated hydroxypeptide (2).[5] Cyclization was accomplished by treating (2) in mild aqueous alkaline medium according to the procedure already adopted for the preparation of azacyclols.[2a] The formation of the linear precursor (2) is shown in the Scheme.



SCHEME

EXPERIMENTAL

General Conditions.—All m.p.s are uncorrected. I.r. spectra were recorded with a Perkin-Elmer 521 spectrophotometer. ^{1}H N.m.r. spectra for compounds (2), (4), and (5) were recorded on a Varian EM-390 spectrometer and for compound (3) on a Brüker WP-200 instrument (Me_4Si as internal standard). ^{13}C N.m.r. spectra were run at 50.28 MHz on a Brüker WP-200 instrument. Mass spectra were determined with a Hewlett–Packard 5980 A spectrometer operating at 70 eV. Optical rotations were taken at 20 °C with a Schmidt–Haensch 16065 polarimeter.

Synthesis.—*L-α-Hydroxyisovaleryl-L-phenylalanyl-L-proline methyl ester* (4). To a stirred ice-cold solution of L-phenylalanyl-L-proline methyl ester hydrochloride (9.5 g) in methanol (30 ml), L-α-hydroxyisovaleric acid (3.5 g) and dicyclohexylcarbodi-imide (6.2 g) in methanol (30 ml) were added. After addition of *N*-methylmorpholine (3.0 g) the mixture was stirred 1.0 h at 0 °C and 48 h at 5 °C. The solid form was removed by filtration and the solution evaporated under vacuum. The residue taken up in chloroform was washed with 1N-HCl, saturated aqueous $NaHCO_3$, and water; drying and evaporation gave an oil

† For a preliminary account of part of this work, see G Lucente, F. Pinnen, G. Zanotti, S. Cerrini, W. Fedeli, and F. Mazza, *Cryst. Struct. Commun.*, 1981, **10**, 103.

(12.0 g). Column chromatography [silica gel; benzene–ethyl acetate (6 : 4) as eluant] afforded *compound* (4) (6.0 g) as an oil, $[\alpha]_D$ −75° (*c* 2.00 in absolute EtOH); $\nu_{max.}$ ($CHCl_3$) 3 395, 1 732, 1 630, and 1 495 cm^{-1}; δ($CDCl_3$) 0.7 (3 H, d, *J* 7.5 Hz, CH_3), 0.95 (3 H, d, *J* 7.5 Hz, CH_3), 1.8—2.3 (5 H, m, β-H_2 Pro, γ-H_2 Pro and β-H HyIv), 3.0—3.3 (4 H, m, β-H_2 Phe and δ-H_2 Pro), 3.68 (3 H, s, OCH_3), 3.90 (1 H, m, α-H HyIv), 4.45 (1 H, m, α-H Pro), 5.0 (1 H, m, α-H Phe), and 7.60 (1 H, d, *J* 9.5 Hz, NH Phe) (Found: C, 63.7; H, 7.55; N, 7.4. $C_{20}H_{28}N_2O_5$ requires C, 63.8; H, 7.5; N, 7.4%).

L-α-*Hydroxyisovaleryl*-L-*phenylalanyl*-L-*proline* (5). To a solution of the methyl ester (4) (1.8 g) in methanol (6 ml), 2N-NaOH (4.8 ml) was added. After 6 h at room temperature the solution was evaporated under vacuum and the residue taken up in water. The aqueous alkaline solution was washed with ethyl acetate, acidified to pH 3.5 with 6N-HCl, and extracted with chloroform. The organic layer was washed with water and the residue obtained after drying and evaporation was crystallised (ethyl acetate) to give *compound* (5) (1.0 g), m.p. 159—160 °C, $[\alpha]_D$ −70° (*c* 2.00 in absolute EtOH); $\nu_{max.}$ (KBr) 3 430—3 280, 1 700, and 1 630 cm^{-1}; δ([$^2H_6$]DMSO) 0.68 (3 H, d, *J* 7.0 Hz, CH_3), 0.75 (3 H, d, *J* 7.0 Hz, CH_3), 3.65 (1 H, m, α-H HyIv), 4.3 (1 H, m, α-H Pro), 4.85 (1 H, m, α-H Phe), and 7.60 (1 H, d, *J* 10 Hz, NH Phe) (Found: C, 62.9; H, 7.25; N, 7.7. $C_{19}H_{26}N_2O_5$ requires C, 63.0; H, 7,2; N, 7.7%).

L-α-*Hydroxyisovaleryl*-L-*phenylalanyl*-L-*proline* p-*nitrophenyl ester* (2). To a solution of compound (5) (5.7 g) and *p*-nitrophenol (3.25 g) in ethyl acetate (120 ml) and tetrahydrofuran (30 ml), dicyclohexylcarbodi-imide (3.2 g) was added at 0 °C under stirring. After 3 h at 0 °C and 12 h at 5 °C, the mixture was filtered and the solution evaporated under vacuum. The residue taken up in ethyl acetate was washed with saturated aqueous Na_2CO_3 and water. After drying and evaporation the crude active ester (6.6 g) was chromatographed (silica gel, ethyl acetate as eluant), to give the *title compound* (2) (5 g) as an oil, pure by t.l.c. analysis, $[\alpha]_D$ −86° (*c* 1.00 in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 3 400, 1 765, and 1 660—1 630 cm^{-1}; δ($CDCl_3$) 0.70 (3 H, d, *J* 7.5 Hz, CH_3), 0.95 (3 H, d, *J* 7.5 Hz, CH_3), 3.95 (1 H, m, α-H HyIv), 4.65 (1 H, m, α-H Pro), 5.05 (1 H, m, α-H Phe), 7.25 (7 H, m, aromatic), 7.5 (1 H, d, *J* 9.0 Hz, NH Phe), and 8.30 (2 H, m, aromatic); *m/e* 344 (M^+ − 139, 19%), 139 (100), 91 (25), and 70 (80).

5-*Benzyl*-10b-*hydroxy*-2-*isopropylperhydro-oxazolo*[3,2-a]-*pyrrolo*[2,1-c]*pyrazine*-3,6-*dione* (3). To a solution of active ester (2) (1.0 g) in dioxan (50 ml), aqueous 0.1M-$NaHCO_3$ (25 ml), and aqueous 0.1M-Na_2CO_3 (25 ml) were added. After 5 h at room temperature the solution was evaporated under vacuum. The residue was partitioned between water and chloroform and the organic layer was washed with saturated Na_2CO_3 solution and water. After drying and removal of the chloroform, the residue (0.7 g) was purified by p.l.c. [chloroform–ether (1 : 1) as eluant] and crystallised (ethyl acetate) to give *compound* (5) (110 mg), m.p. 195—196 °C; $[\alpha]_D$ +22° (*c* 1.00 in $CHCl_3$); $\nu_{max.}$ (KBr) 3 400—3 100, 1 720, and 1 610 cm^{-1}; *m/e* 344 (M^+, 28%), 253 (19), 201 (40), 91 (33), and 70 (100) (Found: C, 66.3; H, 7.1; N, 8.2. $C_{19}H_{24}N_2O_4$ requires C, 66.3; H, 7.0; N, 8.1%). ^{13}C chemical shifts in $CDCl_3$ for compound (3) are given in Table 5; the ^{13}C spectrum in [$^2H_6$]DMSO does not sensibly differ, except for the signal for C(16) which is shifted downfield by *ca.* 4 p.p.m.

TABLE 1

Final fractional co-ordinates, with estimated standard deviations in parentheses, for the non-hydrogen atoms of oxacyclol (3)

	x/a	*y/b*	*z/c*
O(1)	0.292 2(3)	0.857 8(2)	0.048 4(2)
C(2)	0.267 0(4)	0.893 7(2)	−0.097 1(3)
C(3)	0.101 9(4)	0.834 7(2)	−0.166 8(3)
N(4)	0.058 4(3)	0.769 2(2)	−0.068 8(2)
C(5)	−0.109 3(3)	0.706 9(2)	−0.085 1(3)
C(6)	−0.240 2(3)	0.710 6(2)	0.044 3(3)
N(7)	−0.182 8(3)	0.763 0(2)	0.156 7(2)
C(8)	−0.293 6(4)	0.765 9(3)	0.291 2(3)
C(9)	−0.171 8(5)	0.831 7(3)	0.389 5(3)
C(10)	0.035 7(4)	0.828 3(3)	0.332 1(3)
C(11)	−0.006 8(3)	0.823 9(2)	0.169 3(3)
C(12)	0.152 1(3)	0.787 4(2)	0.073 5(3)
C(13)	0.462 1(4)	0.888 6(2)	−0.173 2(3)
C(14)	0.438 5(6)	0.922 0(4)	−0.327 7(5)
C(15)	0.617 1(4)	0.945 2(3)	−0.088 0(4)
C(16)	−0.047 0(4)	0.605 0(2)	−0.116 3(3)
C(17)	0.060 8(4)	0.599 4(2)	−0.254 3(3)
C(18)	0.262 0(4)	0.615 4(3)	−0.255 9(4)
C(19)	0.357 9(6)	0.617 9(3)	−0.385 4(5)
C(20)	0.254 6(6)	0.6009 *	−0.514 6(4)
C(21)	0.058 5(6)	0.582 3(3)	−0.514 7(4)
C(22)	−0.039 2(5)	0.581 8(3)	−0.385 3(4)
O(2)	0.021 8(3)	0.845 2(2)	−0.285 6(2)
O(3)	−0.392 6(3)	0.663 6(2)	0.041 1(2)
O(4)	0.240 0(2)	0.710 7(2)	0.136 8(2)

* This co-ordinate was kept fixed during refinement.

Crystallographic Analysis.—Suitable single crystals of the oxacyclol (3) were obtained from ethyl acetate by slow evaporation. Approximate unit cell parameters were determined from oscillation and Weisenberg photographs. Intensity data were collected on to an automatic four-circle Syntex $P2_1$ diffractometer equipped with a graphite

TABLE 2

Bond lengths (Å) and angles (°) with e.s.d.s in parentheses of oxacyclol (3)

O(1)–C(2)	1.445(3)	C(8)–C(9)	1.529(5)
O(1)–C(12)	1.416(3)	C(9)–C(10)	1.531(4)
C(2)–C(3)	1.524(4)	C(10)–C(11)	1.523(4)
C(2)–C(13)	1.533(4)	C(11)–C(12)	1.522(3)
C(3)–N(4)	1.350(4)	C(12)–O(4)	1.373(4)
C(3)–O(2)	1.214(3)	C(13)–C(14)	1.510(5)
N(4)–C(5)	1.451(3)	C(13)–C(15)	1.521(4)
N(4)–C(12)	1.459(3)	C(16)–C(17)	1.506(4)
C(5)–C(6)	1.526(3)	C(17)–C(18)	1.387(4)
C(5)–C(16)	1.556(4)	C(17)–C(22)	1.385(4)
C(6)–N(7)	1.329(3)	C(18)–C(19)	1.393(6)
C(6)–O(3)	1.236(3)	C(19)–C(20)	1.379(6)
N(7)–C(8)	1.487(4)	C(20)–C(21)	1.359(6)
N(7)–C(11)	1.482(3)	C(21)–C(22)	1.398(5)
C(2)–O(1)–C(12)	111.0(2)	C(6)–N(7)–C(11)	127.0(2)
O(1)–C(2)–C(3)	104.4(2)	C(8)–N(7)–C(11)	110.9(2)
O(1)–C(2)–C(13)	110.2(2)	N(7)–C(8)–C(9)	103.6(2)
C(3)–C(2)–C(13)	114.4(2)	C(8)–C(9)–C(10)	104.7(3)
C(2)–C(3)–N(4)	106.5(2)	C(9)–C(10)–C(11)	102.2(2)
C(2)–C(3)–O(2)	127.2(3)	N(7)–C(11)–C(10)	102.5(2)
N(4)–C(3)–O(2)	126.3(3)	N(7)–C(11)–C(12)	110.1(2)
C(3)–N(4)–C(5)	123.8(2)	C(10)–C(11)–C(12)	119.0(2)
C(3)–N(4)–C(12)	112.4(2)	O(1)–C(12)–N(4)	104.3(2)
C(5)–N(4)–C(12)	120.7(2)	O(1)–C(12)–C(11)	110.5(2)
N(4)–C(5)–C(6)	112.4(2)	O(1)–C(12)–O(4)	111.2(2)
N(4)–C(5)–C(16)	112.4(2)	N(4)–C(12)–C(11)	107.3(2)
C(6)–C(5)–C(16)	110.6(2)	N(4)–C(12)–O(4)	113.8(2)
C(5)–C(6)–N(7)	118.3(2)	C(11)–C(12)–O(4)	109.5(2)
C(5)–C(6)–O(3)	118.8(2)	C(2)–C(13)–C(14)	111.5(3)
N(7)–C(6)–O(3)	122.9(2)	C(2)–C(13)–C(15)	109.2(3)
C(6)–N(7)–C(8)	122.1(2)	C(14)–C(13)–C(15)	111.1(3)
		C(5)–C(16)–C(17)	110.8(2)

monochromator using Mo-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 the reciprocal space.

Crystal Data.—Oxacyclol $C_{19}H_{24}N_2O_4$, $M = 344.4$. Monoclinic, $a = 6.794(1)$, $b = 14.379(3)$, $c = 9.260(1)$ Å, $\beta = 92.75$ (1)°, $U = 903.6$ (3) Å^3, $Z = 2$, $D_c = 1.26$ g cm^{-3}, $D_m = 1.26$ g cm^{-3}. Mo-K_α radiation, $\lambda = 0.7107$ Å; μ(Mo-K_α) = 0.96 cm^{-1}. Space group $P2_1$ from systematic absences and chiral properties of the compound. Intensities were collected up to a maximum 2θ value of 55.0° by the ω-scan tecnique using a scan speed within the interval 0.5—29.3° min^{-1} over a range of 0.8°. Background counts were taken for a time equal to that of the scan. Out of a total of *ca.* 1 993 independent recorded reflections, the intensities of 1 892 were considered observed [$I > 2\sigma(I)$]. The intensities of three standard reflections monitored out of every 100 remained essentially constant throughout data collection. Lorentz and polarization factors were applied, taking into account the monochromator crystal. No absorption or extinction corrections were applied.

Structure Solution and Refinement.—The structure was solved by direct methods with the MULTAN program employing 300 reflections with $|E| > 1.40$. An E map computed with phases of the set with the highest figures of merit revealed all the non-hydrogen atoms, which were refined isotropically and anisotropically, successively. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$ where $w = (a + |F_o| + c|F_o|^2)^{-1}$ with a and c of the order of $2F_{o(min.)}$ and $2/F_{o(max.)}$, respectively. A difference synthesis showed all the hydrogen atoms in stereochemically feasible positions; no residual significant peak was present. The hydrogen atom positional parameters together with the individual isotropic thermal values assumed from the carrier atoms, were included and kept fixed in the refinement. The 1 0 0 and 0 0 1 reflections were excluded from the last cycles of refinement because they were judged to be severely influenced by the extinction effect. When the refinement was stopped the sum of the square of the ratios between the parameter shifts and the e.s.d.s was 0.5. 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. The final R and R_w values were 0.039 and 0.054, respectively. All the calculations were carried out on the HP 21MX minicomputer of the CNR Research Area and on

TABLE 3

Torsion angles (°) * of compounds (3), (6), (1b), and (8). Estimated standard deviations of compounds (3) are in parentheses

Compound	(3)	(6)	(1b)	(8)
Ring A				
O(1)–C(2)–C(3)–N(4)	−4.7(3)	−8.9	4.4	−11.4
C(2)–C(3)–N(4)–C(12)	10.8(3)	6.2	−14.1	1.4
C(3)–N(4)–C(12)–O(1)	−12.7(3)	−0.4	18.1	9.6
N(4)–C(12)–O(1)–C(2)	9.2(3)	−5.6	−14.5	−17.4
C(12)–O(1)–C(2)–C(3)	−3.2(3)	8.5	6.8	17.7
Ring B				
N(4)–C(5)–C(6)–N(7)	−4.2(3)	13.3	3.6	−39.9
C(5)–C(6)–N(7)–C(11)	3.4(4)	−1.5	−5.6	−1.4
C(6)–N(7)–C(11)–C(12)	−27.0(4)	−32.8	−23.2	33.9
N(7)–C(11)–C(12)–N(4)	48.5(3)	52.9	51.7	−20.6
C(11)–C(12)–N(4)–C(5)	−56.5(3)	−48.1	−60.3	−22.2
C(12)–N(4)–C(5)–C(6)	33.4(3)	14.4	30.9	53.4
Ring C				
N(7)–C(8)–C(9)–C(10)	−23.3(3)	−25.9	−8.4	28.0
C(8)–C(9)–C(10)–C(11)	38.4(3)	39.9	23.5	−38.0
C(9)–C(10)–C(11)–N(7)	−37.9(3)	−37.9	−28.8	32.4
C(10)–C(11)–N(7)–C(8)	24.7(3)	21.4	25.0	−15.5
C(11)–N(7)–C(8)–C(9)	−0.9(3)	3.2	−10.6	−7.8
Peptide groups				
C(5)–N(4)–C(3)–C(2)	171.2(2)			
C(5)–N(4)–C(3)–O(2)	−7.4(4)			
C(12)–N(4)–C(3)–O(2)	−167.8(3)			
C(8)–N(7)–C(6)–O(3)	2.9(4)			
C(8)–N(7)–C(6)–C(5)	−175.8(3)			
C(11)–N(7)–C(6)–O(3)	−177.9(3)			
Isopropyl group				
O(1)–C(2)–C(13)–C(14)	177.7(3)			
O(1)–C(2)–C(13)–C(15)	−59.2(3)			
C(3)–C(2)–C(13)–C(14)	60.5(4)			
C(3)–C(2)–C(13)–C(15)	−176.4(3)			
Phenyl group				
N(4)–C(5)–C(16)–C(17)	−60.5(3)			
C(6)–C(5)–C(16)–C(17)	173.0(2)			
C(5)–C(16)–C(17)–C(18)	85.5(3)			
C(5)–C(16)–C(17)–C(22)	−91.8(3)			

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

the UNIVAC 1110 computer of the University of Rome. Observed and calculated structure factors, anisotropic thermal parameters for the non-hydrogen atoms, fractional co-ordinates of the hydrogen atoms, and bond angles not reported in Table 2, are listed in Supplementary Publication No. SUP 23351 (13 pp.).*

RESULTS AND DISCUSSION

Stereochemical and conformational details are displayed in Figure 1 where a general view of the molecule, together with the numbering scheme adopted, is shown.

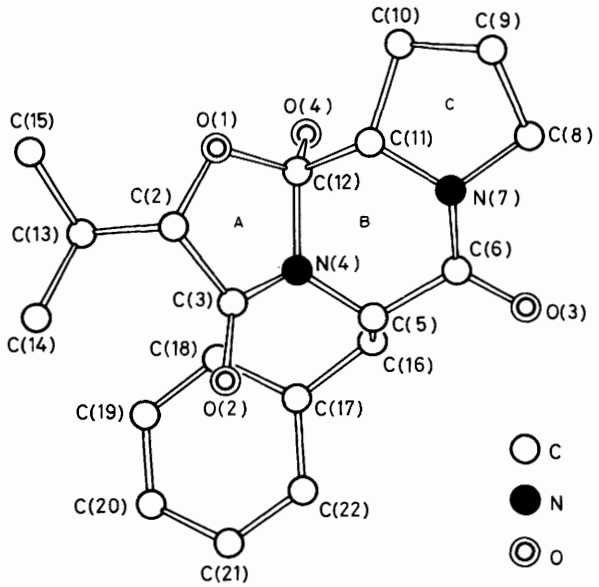
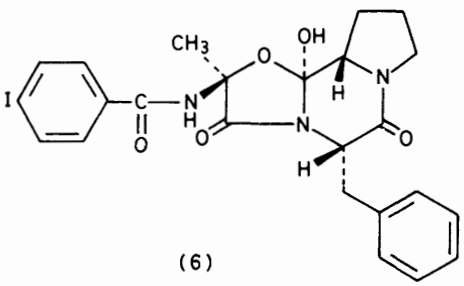


FIGURE 1 The crystal conformation of oxacyclol (3) with the numbering scheme

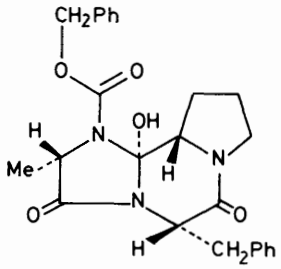
From a knowledge of the absolute configuration in the starting linear tripeptide (2), the configuration of the new asymmetric centre at C(12) was assigned as *S*, resulting into an *anti*-11-H–12-OH arrangement. The stereochemistry at the other three chiral centres is such that the isopropyl group, the benzylic side chain, and the cyclol hydroxy are on one side, whereas the three α-hydrogens at C(2), C(5), and C(11) lie on the other side of the tricyclic system. Analogous stereochemistry is found in the *aci*-isomers of natural ergot alkaloids [6] and in peptide azacyclols; [2a] the stereochemistry of both classes of compounds was unambiguously established by *X*-ray analysis of the *aci-p*-iodobenzoylamino-oxacyclol [7] (6) and the azacyclol [8] (7).

The *anti*-orientation of the hydrogen at C(11) and the hydroxy-group C(12) is a common feature found in natural alkaloids and in synthetic peptide oxa-, aza-, and thia-cyclols. Cyclization reactions leading to cyclols have been found to follow a stereospecific course in which 11,12-*syn* isomers are not formed.[9]

Very recently the *X*-ray crystal structure analysis of a photochemically generated *O*-methyl derivative of the

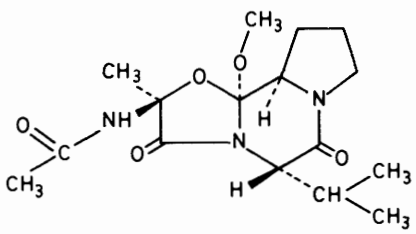


(6)



(7)

oxa-cyclol (8) containing an unusual 11,12-*syn* arrangement, has been reported.[10] Compound (8) lacks the free hydroxy-group which is responsible for the chemical lability and tautomerism characteristic of cyclols; nevertheless a comparison of the conformational features shown by (8) with those found in 11,12-*anti*-isomers is of particular interest in order to gain deeper knowledge of the factors determining the relative stability of the two classes of compounds.



(8)

In the tricyclic system of oxacyclol (3) the junction between the A and B rings is of quasi-*cis*-type: the torsion angles of the junction are −12.7 and −56.5° in the two rings, respectively.[11] A similar situation is present in the oxacyclol (6) with slightly different values for the torsion angles (−0.4 and −48.1°, respectively). This same junction is of a quasi-*trans*-type for the peptide portion of ergot alkaloid (1b) studied by Hebert,[12] with values of 18.1 (ring A) and −60.3° (ring B), as well as for compound (8), with torsion angles of 9.6 and −22.2°, respectively. The junction between the B and C rings of oxacyclol (3) is of a quasi-*trans*-type: the torsion angles are −27.0 and 24.7°, respectively, in the two rings. A similar situation is present in the oxacyclol (6) with torsion angles respectively of −32.8 and 21.4°, as well as in dihydroergotamine (1b), with angles of −23.2 and

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25.0°. The 11,12-*syn*-compound (8), on the other hand, has inversion of the signs of the torsion angles with values of 33.9 and −15.5°, respectively.

The oxazolidin-4-one ring A of oxacyclol (3) adopts an approximate C(2)–N(4)–C(12) half-chair conformation with small internal torsion angles. This ring assumes an envelope conformation in compound (6), a half-chair conformation in compound (1b) [with inversion of all the signs of the torsion angles by comparison with compound (3)], and a C_s envelope conformation for O(1) in structure (8).

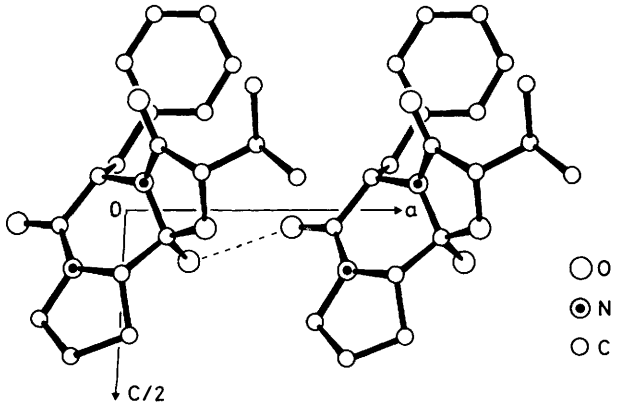

FIGURE 2 Molecular packing of oxacyclol (3). The dashed line indicates the intermolecular hydrogen bonding

Ring B of oxacyclol (3) assumes a half-boat conformation with approximate C_s symmetry through C(6) and C(12); the pyrrolidine ring C adopts, in oxacyclol (3), a C_s envelope conformation at C(10) with this atom displaced out of the mean plane of the other four ring atoms by 0.603 Å on the same side of the hydroxy-group. A very similar conformation is found for ring C in compound (6), whereas compounds (1b) and (8) adopt C_2 half-chair conformations for C(10)–C(11) and C(9)–C(10), respectively.

An interesting structural feature of oxacyclol (3) is the significant pyramidal character of the amide nitrogen atom N(4): the sum of the bond angles around this atom is 356.9° and it lies 0.143 Å out of the plane of its three substituents. An analogous structural situation is present in the other structures examined; the deviation of N(4) from the plane of its three substituents is 0.101 Å in compound (6), 0.116 Å in compound (1b), and 0.191 Å in compound (8).

The benzylic side chain of oxacyclol (3) adopts in the crystal an extended form toward the nitrogen conformation; χ_1 and χ_2 values are −60.5 and 85.5°, respectively. This conformation differs from that found in structure (6) where the benzylic side chain is in a folded conformation reinforced by an intramolecular hydrogen bond between the cyclol hydroxy and the benzene ring.[7] A still different conformation is found in structure (1b) where the χ_1 torsion angle assumes a value of −123.4°.

An intermolecular hydrogen bond of 2.772(3) Å is present between the carbonyl O(3) atom of the reference molecule and the hydroxy O(4) atom of another molecule translated by a $-a$ unit as shown in Figure 2. The distance between O(3) and the hydrogen at O(4) is 1.993(2) Å; the angle between the C(6)–O(3) bond and the O(4) atom engaged in the hydrogen bond is 128.7(2)°, while the angle that the same bond forms with the hydrogen atom HO(4) is 126.2(2)°; finally the torsion angle C(6)–O(3) . . . HO(4)–O(4) is −136.7(7)°.

The ^{1}H n.m.r. spectra of compound (3) were taken for $CDCl_3$ and [$^2H_6$]DMSO solutions; solvents like acetone and acetonitrile show intermediate behaviour. Chemical shifts, coupling constants, and assignments are reported in Table 4. From these data some information on local

TABLE 4

^{1}H N.m.r. chemical shifts (p.p.m. from Me_4Si) and coupling constants (Hz). The numbering of the hydrogen atoms is that of Figure 1

	[$^2H_6$]DMSO	$CDCl_3$
H(5)	4.42	4.83
Ha(16)	3.33	3.58
Hb(16)	2.76	3.25
Ha(8)	3.3—3.4	3.5—3.6
Hb(8)	3.3—3.4	3.5—3.6
Ha(9)	1.85—2.0	1.9—2.1
Hb(9)	1.85—2.0	1.9—2.1
Ha(10)	1.85—2.0	1.9—2.1
Hb(10)	1.85—2.0	1.9—2.1
H(11)	3.72	3.55
HO(4)	~7.3	1.75
H(2)	4.08	4.15
H(13)	1.86	2.05
Ha,b,c(14)	0.87	0.99
Ha,b,c(15)	0.78	0.86
H(18),H(22)	7.32	7.26
H(19),H(21)	7.19	7.26
H(20)	7.19	7.26
$J_{H(5)-Ha(16)}$	3.42	5.5
$J_{H(5)-Hb(16)}$	10.97	6.0
$J_{Ha(16)-Hb(16)}$	−13.67	−13.7
$J_{H(2)-H(13)}$	3.91	3.66
$J_{H(13)-Ha,b,c(14)}$	7.08	7.0
$J_{H(13)-Ha,b,c(15)}$	6.84	7.0
$J_{H(11)-HO(4)}$	n.o.*	2.5
$J_{Ha(10)-H(11)}$	~6.8	n.o.*
$J_{Hb(10)-H(11)}$	~7.0	n.o.*

* n.o. = Not obtained.

TABLE 5

^{13}C N.m.r. chemical shifts (p.p.m. from Me_4Si) of oxacyclol (3)

C(2)	83.284 (d)
C(3)	169.957 * (s)
C(5)	55.995 (d)
C(6)	164.494 * (s)
C(8)	46.454 (t)
C(9)	26.546 (t)
C(10)	30.260 (t)
C(11)	63.764 (d)
C(12)	104 624 (s)
C(13)	22.249 (d)
C(14)	18.267 (q)
C(15)	16.349 (q)
C(16)	36.524 (t)
C(17)	137.327 (s)
C(18), C(22)	130.359 (d)
C(19), C(21)	128.563 (d)
C(20)	127.276 (d)

* Carbonyls assigned through their long range coupling constants.

conformations in oxacyclol (3) can be derived. The low value found for the H(2), H(13) coupling constant (3.91 in [$^2H_6$]DMSO and 3.66 Hz in $CDCl_3$) indicates a gauche (or gauche*) conformation of these two protons. The *trans*-conformation found in the solid state for the isopropyl group is thus not retained in solution. Coupling constants between H(5) and the two protons at C(16) are very similar in $CDCl_3$ solution (5.5 and 6.0 Hz) and are close to those expected for a freely rotating benzyl group; accordingly the aromatic protons have very similar chemical shifts. In [$^2H_6$]DMSO however $J_{H(5)-H_a(16)}$ is 3.42 Hz while $J_{H(5)-H_b(16)}$ is 10.97 Hz; these values strongly favour one of the two extended conformations for the benzylic side chain. An extended conformation toward nitrogen, analogous to that found in the solid state for azacyclols,[2d,8] should be disfavoured due to steric interaction with the isopropyl group in the gauche conformation. The conformation extended toward oxygen does not present, on the other hand, any steric hindrance.

Finally, it is worth noting the high value (2.5 Hz in $CDCl_3$; see Table 4) found for the H(11),OH coupling constant. The only known four-bond couplings with such high values are those involved in a W conformation. The HO(4)–O(4)–C(12)–C(11)–H(11) system must be then arranged in a W conformation. This arrangement rules out, at least for $CDCl_3$, an interaction *via* the hydrogen bond of the hydroxylic proton with the aromatic ring, a situation found in the solid state for the oxacyclol (6).[7] The orientation of the hydroxylic hydrogen found in $CDCl_3$ for oxacyclol (3) is maintained in the solid state as shown by the torsion angles HO(4)–O(4)–C(12)–O(1) and HO(4)–O(4)–C(12)–N(4) found in the crystal, which are −35.7(3) and 81.8(3)°, respectively.

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