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Molecular Structure of Opiate Alkaloids. III.* Crystal Structure of Two 7-(1-Cyclohexylethyl)oripavine Analogues

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Abstract

An X-ray crystallographic analysis and a conformational study of two oripavine opiate narcotic analgesics are reported. These compounds are C7-substituted analogues of 16-methyl- and 16-ethyl-6,14-*endo*-ethenotetrahydrooripavines, respectively. Crystals of both molecules are orthorhombic, space group $P2_12_12_1$, $Z = 4$, $T = 293$ K: compound (I), 7-(1-cyclohexyl-1-hydroxyethyl)-16-methyl-6,14-*endo*-etheno-6,7,8,14-tetrahydro-3-oripavinyl methyl ether, $a = 11{\cdot}441$ (2), $b = 21{\cdot}479$ (2), $c = 10{\cdot}570$ (2) Å; compound (II), 7-(1-cyclohexyl-1-hydroxyethyl)-16-ethyl-6,14-*endo*-6,7,8,14-tetrahydro-3-oripavinyl methyl ether, $a = 11{\cdot}364$ (2), $b = 21{\cdot}643$ (4), $c = 10{\cdot}946$ (2) Å. Both structures were solved by direct methods and refined by full-matrix least-squares procedures to $R = 0{\cdot}06$ and 0·05 for 1572 and 2666 reflections with $I \geq 2\sigma(I)$, respectively. The molecular structures are almost identical; the 16-alkyl substitutions do not modify the structure of the multi-ring system and, in particular, do not alter the orientation of the N atom. Both molecules have an intramolecular hydrogen bond between the C19—OH and C6—O—CH_3 groups. This feature is correlated to the differences in pharmacological activity between diastereoisomers at C19 and is used to build a general molecular model in the search for the biologically active conformation of opiate narcotics.

Introduction

In the last decade, considerable effort was made to elaborate a three-dimensional description for the opioid receptor. Beckett & Casy (1954) proposed a model based on the assumption that the association of a drug on the receptor site involved three specific subsites: an anionic center to interact with the N atom, a hydrophobic site where the aromatic ring lies and a 'hole' to accommodate C15 and C16. In a recent article (Michel, Evrard, Norberg & Milchert, 1988) we reported the conformational properties of two 16-alkyl analogues of thebaine and oripavine: compounds (III) and (IV) (Fig. 1). More recently, the discovery of three major receptor types (μ, K, δ) renewed the interest in the development of a better model for the opioid receptor which would account for the distinction between the three receptor types. This question was addressed in a previous study (DiMaio, Bayly, Villeneuve & Michel, 1986) where we demonstrated that the opiate alkaloid PEO (VI) was a good semirigid template on which analogs of enkephaline peptides (VII) could be fitted. Unfortunately, our attempts to obtain suitable crystals of PEO where unsuccessful and we decided to investigate the series of ethenotetrahydrothebaine and -oripavine analogues (I)–(V). Although different from the PEO template, these molecules allowed us to build a reasonable molecular model for PEO and also address pertinent conformational questions in relation to the description of the opiate receptor. Particularly, the presence of the 6–14 etheno bridge in conjunction with an intramolecular hydrogen bond will be correlated with the stereoselectivity observed at C19 and the high agonist potency (as much as 1000 times higher than morphine). The model of PEO based on the crystal structure determination will be shown to fit very well with cyclic analogs of enkephaline (VII) and will constitute an excellent template for further molecular modeling studies of the opiate receptor and particularly to distinguish between μ and δ receptors.

* Part I: Michel, Proulx, Evrard, Norberg & Milchert (1988). Part II: Michel, Evrard, Norberg & Milchert (1988).

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Experimental

Lewis and co-workers (Lewis, Bentley & Cowan, 1971; Lewis, Mayor & Haddlesey, 1973) prepared various 6,14-*endo*-ethenotetrahydrothebaines, with a variety of 16 and 19 substituents, in order to modulate the opioid activity. The syntheses of compounds (I) and (II) were reported in the course of those studies. Crystals of (I) and (II) were obtained by slow evaporation from 1:1 aqueous/2-propanolic solutions. Transparent prismatic colourless crystals grew slowly at 278 K.

The cell parameters and space groups were obtained from the diffractometer measurements. The cell constants were refined using 25 reflections in the 2θ range 20–40°. One set of independent reflections was collected on a Nonius CAD-4 automatic diffractometer. Experimental conditions related to the data acquisition are given in Table 1.

Absorption corrections were not applied because of the small size of the crystals and low values of linear absorption coefficients for Mo $K\alpha$. A partial solution of compound (I) including 15 non-H atoms was obtained from the E map subsequent to the application of direct methods (*MULTAN*; Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). Karle recycling techniques were applied to identify all remaining non-H atoms. The solution obtained for compound (I) was used to compute a difference Fourier map for compound (II): all non-H atoms were located in this way. The *XTAL* crystallographic system of programs (Stewart, Hall, Alden, Olthof-Hazekamp & Doherty, 1983) was used for subsequent calculations. After initial refinement, all H atoms were assigned positions 1·0 Å from their attached atoms and were given the isotropic thermal parameters of their adjacent atoms. The positions of the HO4 atoms were determined using a Fourier difference map. Although not refined, the H-atom parameters were included in the subsequent calculations. A weighting scheme based on counting statistics was used in the least-squares refinements. The final refinement undertaken under the conditions listed in Table 1, yielded the atomic coordinates of the non-H atoms as given in Table 2.* Relatively high values for mean Δ/σ and residual densities are attributed to the low quality of the crystals and data sets. Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974).

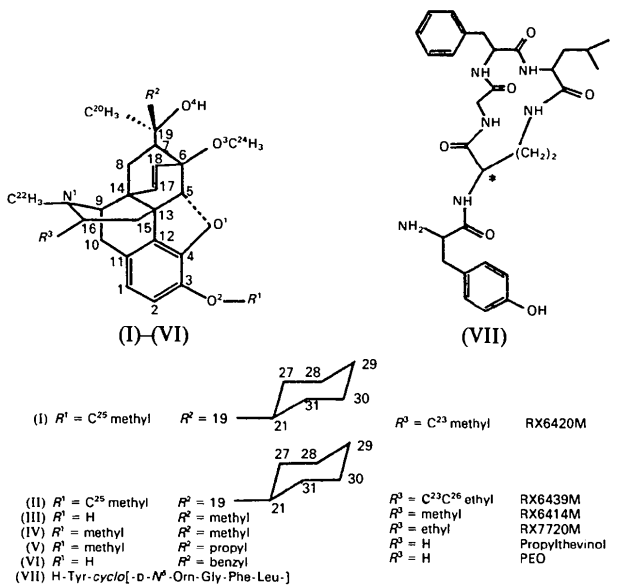

Fig. 1. Molecular formulae of compounds (I)–(VII). RX6420M, RX6439M, RX6414M and RX7720M are identification codes of the Reckitt & Colman Pharmaceutical Company, England. PEO is 7α-[(1*R*)-1-hydroxy-1-methyl-2-phenylethyl]-6,14-*endo*-etheno-6,7,8,14-tetrahydrooripavine.

Table 1. *Crystallographic data*

Temperature 293 K, Enraf–Nonius CAD-4 diffractometer, Mo $K\alpha$ radiation (λ = 0·71069 Å), graphite monochromator, take-off angle 3°, aperture 4·0 × 4·0 mm at a distance of 173 mm from the crystal, scan range extended by 25% on both sides for background measurement $\sigma^2(I) = C + 2B + [0{\cdot}04(C - B)]^2$ (C = scan count, B = normalized background count), function minimized: $\sum w(|F_o| - |F_c|)^2$ where $w = 1/\sigma^2(F)$, $R = \sum||F_o| - |F_c||/\sum|F_o|$, $wR = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$, $S = [\sum w|F_o| - |F_c|)^2/(m - n)]^{1/2}$. Values given for R, wR and S are based on those reflections with $I \geq 2\sigma(I)$.

	Compound (I)	Compound (II)
Formula	$C_{30}H_{41}NO_4$	$C_{31}H_{43}NO_4$
M_r	479·63	493·69
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a (Å)	11·441 (2)	11·364 (2)
b (Å)	21·479 (2)	21·643 (4)
c (Å)	10·570 (2)	10·946 (2)
V (Å^3)	2597·48	2692·18
Z	4	4
D_x (g cm^{-3})	1·23	1·22
$F(000)$	1040	1072
μ(Mo $K\alpha$) (cm^{-1})	0·700	0·703
Crystal dimensions (mm)	0·12 × 0·12 × 0·2	0·2 × 0·18 × 0·09
Scan type	ω–2θ	ω–2θ
Scan range (° in ω)	0·6 + 0·3 tanθ	0·6 + 0·3 tanθ
Scan speed (° min^{-1})	1–8	1–8
Data collected	$+h$, $+k$, $+l$	$+h$, $+k$, $+l$
2θ max. (°)	46	46
Crystal decay	Negligible	Negligible
Unique reflections	2892	3079
Reflections with $I \geq 2\sigma(I)$	1572	2666
Number of variables	317	326
R	0·063	0·046
wR	0·065	0·047
S	3·4	1·7
Mean Δ/σ (final cycle)	0·15	0·37
Max. Δ/σ (final cycle)	0·71	0·84
Residual density (e Å^{-3})	−0·16, 0·15	−0·10, 0·10

Results and discussion

Crystal structures

The molecular geometries of (I) and (II) are given in terms of bond lengths and bond angles in Tables 3 and 4, respectively. There is no significant difference

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52617 (52 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Fractional coordinates and equivalent B values* ($\times 10^4$) *for non-H atoms of compounds* (I) *and* (II)

$B_{eq} = (8\pi^2/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}(Å^2)
Compound (I)				
C1	2873 (7)	919 (3)	3042 (8)	3·88
C2	3891 (7)	622 (3)	2665 (7)	3·47
C3	3875 (7)	36 (3)	2101 (7)	3·20
C4	2776 (7)	−205 (3)	1816 (7)	2·86
C5	1297 (6)	−904 (3)	1478 (7)	2·98
C6	903 (6)	−1346 (3)	2541 (7)	2·61
C7	−473 (6)	−1366 (3)	2325 (7)	2·35
C8	−1011 (6)	−736 (3)	2748 (7)	2·72
C9	−438 (6)	426 (3)	3068 (7)	3·03
C10	620 (7)	873 (3)	3342 (7)	3·53
C11	1774 (6)	658 (3)	2746 (7)	2·85
C12	1791 (6)	124 (3)	2047 (7)	2·48
C13	748 (6)	−261 (3)	1737 (7)	2·63
C14	−22 (7)	−250 (3)	2895 (7)	2·67
C15	35 (7)	−36 (3)	545 (7)	3·19
C16	−613 (7)	591 (4)	714 (7)	4·00
C17	717 (7)	−499 (3)	3988 (7)	2·97
C18	1171 (7)	−1065 (3)	3806 (7)	2·89
C19	−1125 (6)	−1945 (3)	2842 (7)	2·68
C20	−938 (7)	−2013 (4)	4293 (7)	3·84
C21	−2470 (6)	−1908 (3)	2536 (7)	2·89
C22	−1835 (7)	1158 (4)	2200 (9)	5·71
C23	117 (8)	1155 (4)	335 (8)	4·97
C24	2545 (7)	−2062 (4)	2557 (10)	5·56
C25	5961 (7)	−42 (4)	1935 (9)	5·50
C27	−3131 (6)	−2469 (3)	3084 (8)	3·84
C28	−4408 (6)	−2496 (4)	2651 (8)	4·71
C29	−4519 (7)	−2469 (4)	1205 (8)	4·56
C30	−3943 (7)	−1892 (4)	693 (8)	4·66
C31	−2657 (7)	−1864 (4)	1061 (7)	3·79
N1	−1165 (5)	597 (3)	1989 (6)	3·77
O1	2574 (4)	−812 (2)	1411 (5)	3·23
O2	4844 (4)	−323 (2)	1810 (5)	4·57
O3	1338 (4)	−1964 (2)	2377 (5)	3·38
O4	−732 (4)	−2503 (2)	2237 (5)	3·54
Compound (II)				
C1	2788 (5)	0771 (2)	3279 (4)	4·36
C2	3814 (5)	0510 (2)	2823 (4)	4·62
C3	3788 (4)	−0041 (2)	2153 (4)	4·03
C4	2674 (4)	−0280 (2)	1914 (4)	3·60
C5	1180 (4)	−0974 (2)	1558 (4)	3·43
C6	0835 (4)	−1451 (2)	2538 (4)	3·35
C7	−0551 (4)	−1483 (2)	2384 (4)	3·09
C8	−1102 (4)	−0881 (2)	2928 (4)	3·67
C9	−0522 (4)	0275 (2)	3377 (4)	3·83
C10	0543 (5)	0706 (2)	3648 (4)	4·33
C11	1676 (4)	0531 (2)	3027 (4)	3·84
C12	1685 (4)	0028 (2)	2229 (4)	3·50
C13	0606 (4)	−0350 (2)	1901 (4)	3·25
C14	−0106 (4)	−0397 (2)	3108 (4)	3·33
C15	−0132 (4)	0090 (2)	0859 (4)	3·65
C16	−0790 (5)	0517 (2)	1143 (4)	4·06
C17	0684 (5)	−0668 (2)	4075 (4)	3·74
C18	1156 (4)	−1216 (2)	3797 (4)	3·81
C19	−1183 (4)	−2080 (2)	2843 (4)	3·38
C20	−0962 (5)	−2190 (2)	4193 (4)	4·72
C21	−2539 (4)	−2054 (2)	2534 (4)	3·84
C22	−2026 (5)	1013 (2)	2708 (6)	6·21
C23	−0066 (5)	1100 (2)	0850 (5)	4·71
C24	2522 (4)	−2148 (2)	2386 (6)	6·85
C25	5886 (5)	−0107 (3)	1964 (5)	6·38
C26	0212 (6)	1163 (3)	−0493 (5)	7·04
C27	−3148 (4)	−2645 (2)	2993 (5)	4·78
C28	−4432 (4)	−2695 (2)	2556 (5)	5·41
C29	−4555 (5)	−2617 (2)	1211 (5)	5·64
C30	−4058 (5)	−1997 (2)	0810 (5)	5·66
C31	−2747 (5)	−1959 (2)	1158 (4)	4·63
N1	−1299 (3)	0475 (2)	2374 (4)	4·21
O1	2465 (3)	−0867 (1)	1459 (3)	3·81
O2	4741 (3)	−0371 (2)	1747 (3)	5·00
O3	1296 (3)	−2056 (1)	2276 (3)	4·02
O4	−0764 (3)	−2608 (1)	2146 (3)	4·30

in the geometry of the two molecules as can be observed in Fig. 2, where molecules (I) and (II) are superimposed by their aromatic rings.

Table 3. *Intramolecular distances* (Å) *for compounds* (I) *and* (II)

Estimated standard deviations are indicated in parentheses.

	(I)	(II)		(I)	(II)
C2—C1	1·408 (10)	1·387 (7)	C14—C13	1·567 (11)	1·554 (7)
C11—C1	1·404 (10)	1·394 (7)	C15—C13	1·515 (12)	1·524 (7)
C3—C2	1·402 (10)	1·400 (7)	C17—C14	1·487 (12)	1·505 (7)
C4—C3	1·404 (10)	1·393 (7)	C16—C15	1·552 (12)	1·546 (7)
O2—C3	1·393 (10)	1·374 (7)	C23—C16	1·543 (13)	1·542 (7)
C12—C4	1·354 (11)	1·353 (7)	N1—C16	1·427 (12)	1·463 (6)
O1—C4	1·376 (9)	1·386 (5)	C18—C17	1·346 (12)	1·338 (7)
C6—C5	1·543 (11)	1·541 (6)	C20—C19	1·489 (12)	1·514 (6)
C13—C5	1·528 (11)	1·546 (6)	C21—C19	1·580 (12)	1·576 (7)
O1—C5	1·488 (8)	1·481 (6)	O4—C19	1·467 (9)	1·458 (5)
C7—C6	1·585 (11)	1·587 (6)	C27—C21	1·557 (12)	1·540 (7)
C18—C6	1·467 (12)	1·512 (7)	C31—C21	1·535 (12)	1·539 (7)
O3—C6	1·445 (9)	1·439 (5)	N1—C22	1·455 (11)	1·474 (7)
C8—C7	1·569 (10)	1·565 (6)	C26—C23		1·509 (8)
C19—C7	1·576 (11)	1·564 (6)	O3—C24	1·417 (10)	1·413 (6)
C14—C8	1·541 (12)	1·556 (7)	O2—C25	1·438 (11)	1·441 (7)
C10—C9	1·557 (12)	1·559 (7)	C28—C27	1·539 (12)	1·540 (7)
C14—C9	1·556 (11)	1·557 (6)	C29—C28	1·523 (14)	1·494 (8)
N1—C9	1·522 (11)	1·479 (6)	C30—C29	1·509 (13)	1·519 (8)
C11—C10	1·544 (12)	1·505 (7)	C31—C30	1·530 (13)	1·540 (8)
C12—C11	1·393 (11)	1·395 (6)			
C13—C12	1·501 (11)	1·515 (7)			

A bulkier substituent at C16 in molecule (II) does not introduce significant modification of the fused ring and particularly of the N15 orientation. This observation corroborates previous reports (Michel, Evrard, Norberg & Milchert, 1988; Van Den Hende & Nelson, 1967). It can be seen from Fig. 2 that in both compounds an intramolecular hydrogen bond exists between O4 and O3 with distances of 2·642 (7) Å (I) and 2·636 (4) Å (II). This is an experimental confirmation of the prediction made by Loew

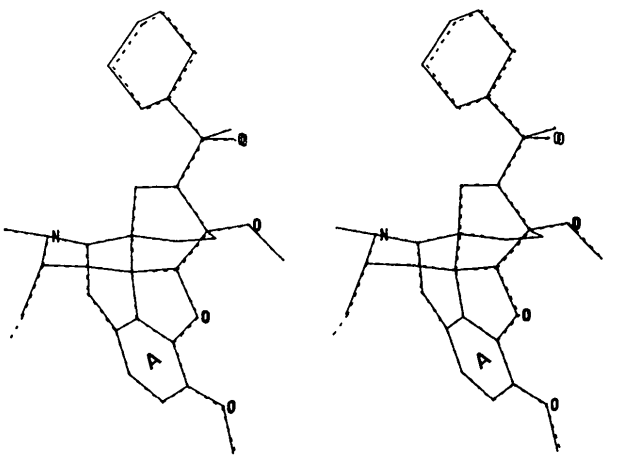

Fig. 2. Stereoviews of compounds (I) and (II) superimposed by their aromatic ring *A*.

Table 4. *Intramolecular valence angles* (°) *for compounds* (I) *and* (II)

Estimated standard deviations are indicated in parentheses.

	(I)	(II)		(I)	(II)
C11—C1—C2	119·1 (7)	122·5 (4)	C14—C9—C10	111·4 (7)	111·0 (4)
			N1—C9—C10	114·9 (7)	115·5 (4)
C3—C2—C1	122·2 (8)	121·2 (5)	N1—C9—C14	106·8 (6)	108·3 (4)
C2—C3—C4	116·6 (8)	115·8 (4)	C11—C10—C9	114·2 (7)	115·3 (4)
C2—C3—O2	126·4 (8)	126·7 (5)			
C4—C3—O2	117·0 (7)	117·5 (4)	C10—C11—C1	123·1 (7)	126·2 (4)
			C12—C11—C1	117·0 (8)	114·2 (4)
C12—C4—C3	120·5 (7)	121·5 (4)	C12—C11—C10	119·3 (7)	119·0 (4)
O1—C4—C3	124·4 (7)	124·4 (4)			
O1—C4—C12	114·7 (7)	113·7 (4)	C11—C12—C4	122·9 (7)	123·4 (4)
			C13—C12—C4	108·8 (7)	110·1 (4)
C13—C5—C6	108·6 (7)	107·9 (4)	C13—C12—C11	125·2 (7)	124·5 (4)
O1—C5—C6	113·5 (6)	114·0 (4)			
O1—C5—C13	106·7 (6)	107·3 (3)	C12—C13—C5	102·5 (7)	100·9 (4)
			C14—C13—C5	111·3 (6)	111·7 (4)
C7—C6—C5	100·5 (6)	101·9 (4)	C15—C13—C5	112·7 (7)	111·8 (4)
C18—C6—C5	110·9 (7)	110·4 (4)	C14—C13—C12	105·0 (6)	104·7 (4)
O3—C6—C5	110·9 (6)	112·1 (4)	C15—C13—C12	114·3 (7)	115·1 (4)
C18—C6—C7	111·4 (7)	110·6 (4)	C15—C13—C14	110·5 (7)	111·9 (4)
O3—C6—C7	106·9 (6)	107·5 (3)			
O3—C6—C18	115·1 (7)	113·7 (4)	C9—C14—C8	114·9 (7)	115·5 (4)
			C13—C14—C8	108·7 (6)	108·5 (4)
C8—C7—C6	108·4 (6)	108·7 (3)	C17—C14—C8	105·1 (6)	105·1 (3)
C19—C7—C6	115·9 (6)	117·3 (3)	C13—C14—C9	106·6 (6)	105·0 (3)
C19—C7—C8	111·6 (6)	112·2 (4)	C17—C14—C9	114·0 (7)	114·2 (4)
			C17—C14—C13	107·3 (7)	108·3 (4)
C14—C8—C7	108·3 (6)	108·4 (4)			
C16—C15—C13	116·4 (7)	115·4 (4)	C30—C31—C21	113·0 (7)	112·6 (4)
C23—C16—C15	112·5 (8)	113·1 (4)	C16—N1—C9	118·6 (7)	117·9 (4)
N1—C16—C15	109·4 (7)	109·0 (4)	C22—N1—C9	111·4 (7)	112·3 (4)
N1—C16—C23	118·2 (7)	117·0 (4)	C22—N1—C16	112·8 (7)	113·7 (4)
C18—C17—C14	115·6 (7)	115·0 (4)	C5—O1—C4	106·1 (6)	106·6 (3)
C17—C18—C6	114·1 (7)	114·2 (4)	C25—O2—C3	116·7 (7)	117·0 (4)
C20—C19—C7	112·7 (7)	111·8 (4)	C24—O3—C6	117·3 (6)	118·1 (3)
C21—C19—C7	109·7 (6)	110·8 (3)			
O4—C19—C7	108·5 (6)	109·1 (3)	C26—C23—C16		112·9 (4)
C21—C19—C20	112·1 (7)	112·2 (4)	C28—C27—C21	111·8 (7)	112·6 (4)
O4—C19—C20	109·9 (7)	109·5 (4)			
O4—C19—C21	103·5 (6)	103·4 (3)	C29—C28—C27	112·5 (7)	112·8 (4)
C27—C21—C19	109·8 (6)	109·9 (4)	C30—C29—C28	111·0 (8)	110·6 (4)
C31—C21—C19	111·6 (7)	111·5 (4)			
C31—C21—C27	111·8 (7)	111·2 (4)	C31—C30—C29	110·9 (8)	109·4 (4)

& Berkowitz (1979) using semiempirical quantum mechanical methods. The resulting six-membered ring (C3—H—O4—C19—C7—C6) introduces constraints on the molecular geometry. Particularly, it reduces the number of possible orientations for the R^2 group and it contributes to increase the differentiation between *R* and *S* isomers at C19. This observation is to be correlated with the higher opioid activities of *R* isomers (Lewis, Bentley & Cowan, 1971).

No abnormally short intramolecular contacts were noted in the crystal packings.

Molecular modeling

Using the crystal structures of compounds (I) and (II) as starting fragments we have generated the molecular structure of the potent opiate alkaloid PEO (VI) by substitution of the R^2 moiety. The energy-minimized structure is shown in Fig. 3(*a*), in superposition with compound (I). In order to generate all the possible conformers for PEO, a conformational search was performed with the restriction of the hydrogen bond between O3 and O4.

The resulting conformations of PEO were then submitted to molecular fitting with plausible structures of the cyclic peptide (VII). The tyramine group of (VII) was fitted to the related part of PEO, involving the aromatic ring and the N atom. The center of the phenylalanyl ring of Phe[4] in molecule (VII) was fitted to the phenyl group of the R^2 moiety of PEO. Fig. 3(*b*) shows one of the generated conformations of PEO in superposition with the peptide (VII). This exercise demonstrates that it is worth correlating the high potency and specificity of opiates containing a 6–14-etheno bridge and R^2 substitution with specific conformations presenting similarities with opioid peptides (VII).

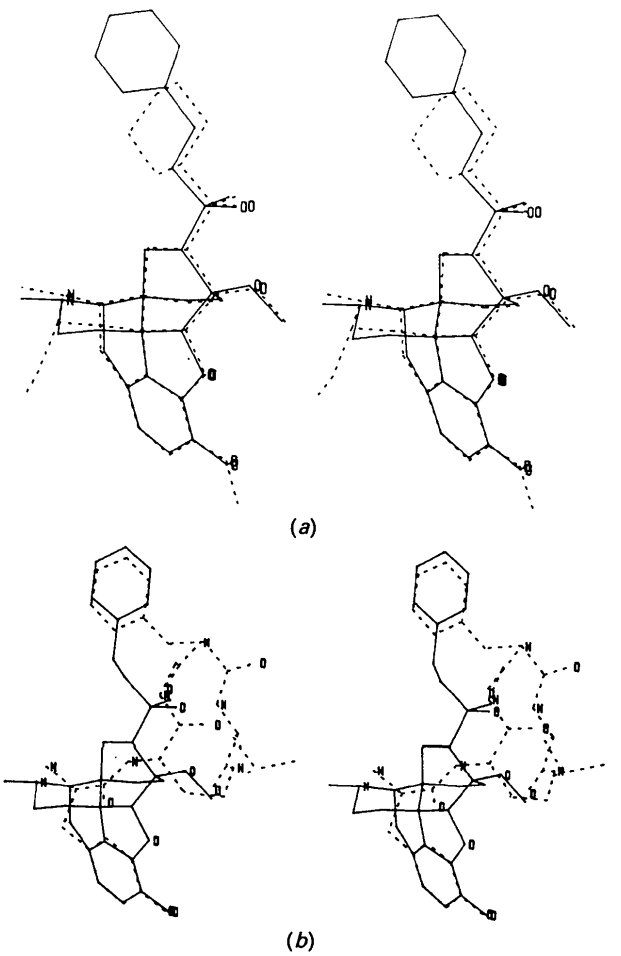

Fig. 3. Stereoviews of pairs of molecules superimposed by their aromatic rings *A*. (*a*) Full lines, compound (II); dashed lines, phenyloripavine (PEO). (*b*) Full lines, phenyloripavine (PEO); dashed line, cyclic peptide ORN.

Molecular structure design, search and energy calculations were performed using the *SYBYL* molecular modeling system (Tripos Associates Inc., 1983).

Concluding remarks

On the basis of the present study we are able to make the following inferences in relation to the description of the opiate receptor. The modulation of the activity by the C16 substituent should be interpreted by steric hindrance, incompatible with the receptor geometry, and not by a misalignment of the nitrogen N′ atom or a distortion of the fused ring system. Secondly, we can assume that the increased opiate activity related to the presence of the 6–14 etheno bridge along with the R^2 substituent must be correlated to the presence of the aforementioned hydrogen bond, which also accounts for the C19 stereoselectivity. Finally, the presence of this intramolecular hydrogen bond confers on the opioid alkaloids the conformational properties for adopting common conformations with cyclic opioid peptides. This argument constitutes a key feature in further molecular modeling studies to determine the receptor-bound conformation of opioid alkaloids and peptides. This major finding will lead to pertinent studies of the distinction between opioid receptor types that modulate physiological processes.

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Refinement of a Partially Oxygenated T State Human Haemoglobin at 1·5 Å Resolution

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Abstract

The degree of ligation of T state human haemoglobin crystals is reduced by inositol hexaphosphate (IHP). The structure of a partially ligated haemoglobin has been refined using fast Fourier restrained-least-squares techniques. Manual interventions were required to escape from local minima and introduce a large number of solvent molecules. Individual isotropic temperature factors were refined for all atoms and the final average atomic temperature factor is 32·3 Å^2. The final R factor is 19·6% for all data between 10 and 1·5 Å. The final model consists of 4560 protein atoms and 313 solvent molecules. The occupancies of the ligand atoms and the anisotropic behaviour of the iron atoms have been refined, demonstrating that the α haem groups are only partially ligated and that there is no ligation of the β haems. Density for the IHP indicates that it is not

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