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Structure of a κ-Opioid Receptor Misfit: (1*S*,5*R*,8*R*,9*R*)-2′-Hydroxy-5,9-dimethyl-8,2-epoxyethano-6,7-benzomorphan Hydrochloride*†

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Abstract. $C_{16}H_{22}NO_2^+.Cl^-$, $M_r = 295{\cdot}808$, monoclinic, $P2_1$, $a = 11{\cdot}967$ (1), $b = 12{\cdot}529$ (1), $c = 9{\cdot}9369$ (9) Å, $\beta = 93{\cdot}00$ (1)°, $V = 1487{\cdot}8$ (2) Å^3, $Z = 4$, $D_m = 1{\cdot}32$ (2), $D_x = 1{\cdot}321$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, μ(Cu $K\alpha$) = 2·289 mm^{-1}, $F(000) = 632$, $T = 291$ K, final $R = 0{\cdot}040$ for 2448 observed reflections. The two molecules present in the asymmetric unit are linked by an extensive network of hydrogen bonds, including several of the less common (C–)H···O and (C–)H···Cl types. This interpretation is substantiated by a Mulliken population analysis resulting from *CNDO*/2 calculations. The major effect of the presence of the epoxyethano bridge is a marked flattening about the N atom of the piperidinium ring. Whether this is sufficient to explain the inactivity of the compound at the opioid κ receptor is not clear.

Introduction. The title compound, although having an equatorial oxygen substituent at the same position as ketazocine [(1*S*,5*R*,9*R*)-2-cyclopropylmethyl-2′-hydroxy-5,9-dimethyl-8-oxo-6,7-benzomorphan] (Verlinde & De Ranter, 1983) has its keto oxygen, is devoid of the κ-opioid properties of this prototypical molecule. Apart from being about 150 times less active than ketazocine in the writhing test in mice (Merz, 1983), it fails completely to inhibit the contractions of the electrically stimulated rabbit vas deferens (Verlinde & De Ranter, 1988), a preparation containing exclusively opioid receptors of the κ type (Oka, Negishi, Suda, Matsumiya, Inazu & Ueki, 1980). A 2′-methoxy analogue lacking the 9-methyl group was reported to be inactive (Shiotani & Kometani, 1980). Other modifications of the structure of ketazocine, such as the replacement of the carbonyl by an equatorial hydroxy or methoxy group with retention of the *N*-cyclopropylmethyl [Michne & Albertson (1972) and Merz (1983), respectively] led also to inactive compounds.

In 1984 a model was proposed to explain κ-opioid activity in the 6,7-benzomorphan series, establishing a distinct role for this crucial O atom (De Ranter, Verlinde, Blaton & Peeters, 1984). This model explains how ketazocine, with its O atom on the benzomorphan nucleus, and reputed κ-opioid agonists such as bremazocine and Mr2034 where the O atom is incorporated in the *N*-side chain, can interact with the same receptor. Hydrogen bonding to a common group in the receptor is postulated. The main purpose of the present study is to find clues in the crystal structure that might explain the inactivity of the title compound in view of that model.

Experimental. Colourless prismatic crystals obtained at room temperature from an equimolar ethyl acetate–methanol solution. Density measured by flotation in *n*-heptane/CCl_4, ~0·5 × 0·3 × 0·25 mm, Hilger & Watts computer-controlled four-circle diffractometer, Ni-filtered Cu $K\alpha$ radiation, $\omega/2\theta$ scan technique

* *Chemical Abstracts* name: (1*R*,2*S*,6*R*,11*R*)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-1,3-epoxyethano-2,6-methano-3-benzazocin-8-ol hydrochloride.

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($2\theta_{max} = 130°$, $0 \le h \le 15$, $\overline{15} \le k \le 0$, $\overline{12} \le l \le 12$), cell dimensions by least-squares refinement of the θ values of 21 reflections with $44 < 2\theta < 50°$, space group $P2_1$ from systematic absences $0k0$ for k odd (optically active compound). Three standard reflections ($0\bar{6}0$, $60\bar{1}$, $1\bar{2}5$) monitored after every 50 reflections showed a uniform 0·13% decrease in intensity per hour, for which corrections were applied, 2617 independent reflections measured, 2453 observed reflections [$I > 3\sigma(I)$], Lorentz–polarization corrections, absorption corrections by the method of North, Phillips & Mathews (1968) with values between 0·995 and 0·794, scattering factors from Cromer & Mann (1968), and Stewart, Davidson & Simpson (1965) (for H), anomalous-dispersion correction for Cl (*International Tables for X-ray Crystallography*, 1974).

The positions of both chloride ions in the asymmetric unit obtained from a sharpened Patterson synthesis served as input for *DIRDIF* (Beurskens, Bosman, Doesburg, Gould, van den Hark, Prick, Noordik, Beurskens & Parthasarathi, 1981). The resulting E map showed all non-H atoms present in the asymmetric unit. Refinement with *XRAY*76 (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976) by block-diagonal least squares on F, first with isotropic temperature factors and then anisotropically; full-matrix least squares finally executed; five reflections badly affected by extinction were eliminated; H-atom positions from ΔF synthesis included in refinement with fixed isotropic temperature factors of their parent atoms; final $R = 0{\cdot}040$, $wR = 0{\cdot}055$ and $S = 0{\cdot}13$ for 492 parameters, $w = (7{\cdot}0 + |F_o| + 0{\cdot}06|F_o|^2)^{-1}$; $(\Delta/\sigma)_{ave} = 0{\cdot}15$, $(\Delta/\sigma)_{max} = 0{\cdot}32$ for non-H atoms and 2·00 for the H atoms [$(\Delta/\sigma) > 1{\cdot}00$ for H(1′*A*), H(4*BB*), H(10*CB*) and H(13*BB*) which were poorly located in the ΔF map], $-0{\cdot}44$ e Å$^{-3} \le$ final $\Delta\rho$ excursions $\le 0{\cdot}21$ e Å^{-3}. Molecular parameters derived from the crystal structure were calculated with the aid of the program *PARST* (Nardelli, 1983) except for the rigid-bond test (local program).

Discussion. The atomic numbering scheme is given in Fig. 1 and parameters are listed in Table 1.* The two molecules present in the asymmetric unit are labelled *A* and *B* respectively. Bond lengths and bond angles are listed in Table 2. An *ORTEP* (Johnson, 1965) stereopair of the *A* molecule is shown in Fig. 2. Through use of a weighted least-squares fit procedure with the program *BMFIT* (Nyburg, 1974) on the non-H atoms a close similarity between the molecules *A* and *B* is observed (r.m.s. deviation = 0·04 Å). However, the two molecules are subject to different environments in the crystal packing, as can be seen in Fig. 3 and from the list of close contacts in Table 3. Hydrogen bonds involving the chloride ion link the phenol function of one molecule with the N of a neighbouring molecule. In this way the *A* molecules form endless chains along **c** through translation, while the *B* molecules spiral along the twofold screw axis **b**. Apart from these classical hydrogen bonds several (C–)H···O and (C–)H···Cl contacts are present. Some of these can reasonably be described as hydrogen bonds as they satisfy the description established by Taylor & Kennard (1982), *i.e.* the donor (C–)H group has a decreased electron density resulting from the inductive effect of a neighbouring electronegative atom.

In order to substantiate this description further, net atomic charges resulting from a Mulliken population analysis of the wavefunction in the *CNDO*/2 approximation (Pople & Segal, 1966) have been calculated. H-atom positions obtained through an *MMP*2 force-field optimization (Allinger & Flanagan, 1983) were

Table 1. *Atomic coordinates* ($\times 10^4$) *and equivalent isotropic thermal parameters with e.s.d.'s in parentheses*

$$B_{eq} = \tfrac{4}{3}\sum_i\sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j$$

	x	y	z	B_{eq}(Å^2)
Cl(*A*)	4378 (1)	5001*	235 (1)	4·28 (3)
C(1′*A*)	3296 (3)	6495 (3)	6825 (4)	2·43 (9)
C(2′*A*)	3452 (3)	7331 (4)	7744 (4)	2·77 (9)
O(2′*A*)	3522 (3)	7151 (4)	9098 (3)	3·78 (8)
C(3′*A*)	3530 (3)	8367 (4)	7304 (4)	2·90 (10)
C(4′*A*)	3430 (3)	8575 (4)	5936 (4)	2·74 (10)
C(1*A*)	3147 (3)	7096 (4)	2577 (4)	2·43 (9)
N(2*A*)	4359 (2)	6821 (3)	2366 (3)	2·18 (7)
C(3*A*)	4991 (3)	6293 (4)	3537 (4)	2·65 (9)
C(4*A*)	4303 (3)	5409 (4)	4121 (4)	2·73 (10)
C(5*A*)	3118 (3)	5769 (4)	4442 (4)	2·48 (10)
C(6*A*)	3217 (3)	6692 (3)	5439 (4)	2·20 (8)
C(7*A*)	3274 (3)	7753 (3)	4991 (4)	2·20 (9)
C(8*A*)	3059 (3)	8043 (3)	3521 (4)	2·56 (9)
C(9*A*)	2531 (3)	6132 (4)	3103 (4)	2·68 (9)
C(10*A*)	1284 (3)	6393 (5)	3215 (5)	3·63 (12)
C(11*A*)	2493 (4)	4800 (4)	4997 (5)	3·67 (12)
C(12*A*)	4954 (4)	7805 (4)	1885 (4)	2·91 (10)
C(13*A*)	4841 (4)	8679 (4)	2900 (4)	3·31 (11)
O(14*A*)	3700 (3)	8938 (3)	3084 (3)	3·22 (7)
Cl(*B*)	7939 (1)	7300 (1)	12298 (1)	4·31 (3)
C(1′*B*)	10004 (3)	4452 (4)	7129 (4)	2·93 (10)
C(2′*B*)	9795 (3)	4099 (4)	5806 (4)	2·97 (10)
O(2′*B*)	10299 (3)	3190 (3)	5357 (3)	3·53 (8)
C(3′*B*)	9083 (3)	4658 (4)	4938 (4)	3·12 (10)
C(4′*B*)	8598 (3)	5586 (4)	5374 (4)	3·12 (10)
C(1*B*)	8470 (3)	7285 (4)	8553 (4)	2·84 (9)
N(2*B*)	7579 (3)	6733 (3)	9320 (4)	2·73 (8)
C(3*B*)	7713 (4)	5541 (4)	9471 (5)	3·67 (12)
C(4*B*)	8900 (5)	5259 (5)	9906 (4)	3·93 (14)
C(5*B*)	9769 (4)	5767 (4)	9012 (4)	3·53 (13)
C(6*B*)	9518 (3)	5393 (4)	7560 (4)	2·75 (9)
C(7*B*)	8794 (3)	5966 (4)	6679 (4)	2·65 (10)
C(8*B*)	8337 (3)	7055 (4)	7054 (4)	2·84 (10)
C(9*B*)	9641 (4)	6985 (4)	9104 (5)	3·46 (11)
C(10*B*)	10523 (4)	7618 (5)	8370 (6)	4·87 (15)
C(11*B*)	10944 (5)	5421 (7)	9546 (6)	5·47 (17)
C(12*B*)	6444 (4)	7019 (5)	8721 (5)	3·65 (12)
C(13*B*)	6382 (4)	6740 (5)	7232 (5)	3·58 (11)
O(14*B*)	7218 (3)	7271 (3)	6525 (3)	3·52 (7)

* Parameter kept fixed for origin definition.

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, bond lengths and angles involving H atoms, least-squares-planes data and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51626 (23 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Bond lengths* (Å) *and bond angles* (°)

C(1′*A*)–C(2′*A*)	1·396 (6)	C(1′*B*)–C(2′*B*)	1·397 (6)
C(1′*A*)–C(6*A*)	1·398 (5)	C(1′*B*)–C(6*B*)	1·392 (6)
C(2′*A*)–O(2′*A*)	1·362 (4)	C(2′*B*)–O(2′*B*)	1·374 (6)
C(2′*A*)–C(3′*A*)	1·375 (7)	C(2′*B*)–C(3′*B*)	1·372 (6)
C(3′*A*)–C(4′*A*)	1·383 (6)	C(3′*B*)–C(4′*B*)	1·379 (7)
C(4′*A*)–C(7*A*)	1·400 (6)	C(4′*B*)–C(7*B*)	1·389 (6)
C(1*A*)–N(2*A*)	1·516 (5)	C(1*B*)–N(2*B*)	1·510 (6)
C(1*A*)–C(8*A*)	1·520 (6)	C(1*B*)–C(8*B*)	1·518 (6)
C(1*A*)–C(9*A*)	1·521 (6)	C(1*B*)–C(9*B*)	1·524 (6)
N(2*A*)–C(3*A*)	1·508 (5)	N(2*B*)–C(3*B*)	1·508 (7)
N(2*A*)–C(12*A*)	1·513 (6)	N(2*B*)–C(12*B*)	1·498 (6)
C(3*A*)–C(4*A*)	1·514 (6)	C(3*B*)–C(4*B*)	1·504 (7)
C(4*A*)–C(5*A*)	1·537 (6)	C(4*B*)–C(5*B*)	1·540 (7)
C(5*A*)–C(6*A*)	1·522 (6)	C(5*B*)–C(6*B*)	1·532 (6)
C(5*A*)–C(9*A*)	1·541 (5)	C(5*B*)–C(9*B*)	1·537 (7)
C(5*A*)–C(11*A*)	1·543 (6)	C(5*B*)–C(11*B*)	1·539 (8)
C(6*A*)–C(7*A*)	1·404 (6)	C(6*B*)–C(7*B*)	1·398 (6)
C(7*A*)–C(8*A*)	1·514 (5)	C(7*B*)–C(8*B*)	1·524 (6)
C(8*A*)–O(14*A*)	1·439 (5)	C(8*B*)–O(14*B*)	1·438 (5)
C(9*A*)–C(10*A*)	1·538 (6)	C(9*B*)–C(10*B*)	1·535 (8)
C(12*A*)–C(13*A*)	1·499 (7)	C(12*B*)–C(13*B*)	1·518 (7)
C(13*A*)–O(14*A*)	1·425 (6)	C(13*B*)–O(14*B*)	1·419 (6)
C(2′*A*)–C(1′*A*)–C(6*A*)	120·8 (4)	C(2′*B*)–C(1′*B*)–C(6*B*)	120·0 (4)
C(1′*A*)–C(2′*A*)–O(2′*A*)	121·4 (4)	C(1′*B*)–C(2′*B*)–O(2′*B*)	120·6 (4)
C(1′*A*)–C(2′*A*)–C(3′*A*)	120·6 (4)	C(1′*B*)–C(2′*B*)–C(3′*B*)	120·3 (4)
O(2′*A*)–C(2′*A*)–C(3′*A*)	118·0 (4)	O(2′*B*)–C(2′*B*)–C(3′*B*)	119·2 (4)
C(2′*A*)–C(3′*A*)–C(4′*A*)	119·1 (4)	C(2′*B*)–C(3′*B*)–C(4′*B*)	119·4 (4)
C(3′*A*)–C(4′*A*)–C(7*A*)	121·5 (4)	C(3′*B*)–C(4′*B*)–C(7*B*)	121·9 (4)
N(2*A*)–C(1*A*)–C(8*A*)	111·1 (3)	N(2*B*)–C(1*B*)–C(8*B*)	111·6 (3)
N(2*A*)–C(1*A*)–C(9*A*)	110·6 (3)	N(2*B*)–C(1*B*)–C(9*B*)	111·4 (3)
C(8*A*)–C(1*A*)–C(9*A*)	110·9 (3)	C(8*B*)–C(1*B*)–C(9*B*)	110·7 (3)
C(1*A*)–N(2*A*)–C(3*A*)	116·0 (3)	C(1*B*)–N(2*B*)–C(3*B*)	115·4 (3)
C(1*A*)–N(2*A*)–C(12*A*)	109·2 (3)	C(1*B*)–N(2*B*)–C(12*B*)	109·8 (3)
C(3*A*)–N(2*A*)–C(12*A*)	112·1 (3)	C(3*B*)–N(2*B*)–C(12*B*)	111·5 (3)
N(2*A*)–C(3*A*)–C(4*A*)	110·9 (3)	N(2*B*)–C(3*B*)–C(4*B*)	110·8 (4)
C(3*A*)–C(4*A*)–C(5*A*)	113·0 (4)	C(3*B*)–C(4*B*)–C(5*B*)	113·1 (4)
C(4*A*)–C(5*A*)–C(6*A*)	108·5 (3)	C(4*B*)–C(5*B*)–C(6*B*)	108·2 (4)
C(4*A*)–C(5*A*)–C(9*A*)	106·9 (3)	C(4*B*)–C(5*B*)–C(9*B*)	107·7 (4)
C(4*A*)–C(5*A*)–C(11*A*)	108·2 (3)	C(4*B*)–C(5*B*)–C(11*B*)	108·5 (4)
C(6*A*)–C(5*A*)–C(9*A*)	110·7 (3)	C(6*B*)–C(5*B*)–C(9*B*)	110·2 (4)
C(6*A*)–C(5*A*)–C(11*A*)	112·8 (3)	C(6*B*)–C(5*B*)–C(11*B*)	111·6 (4)
C(9*A*)–C(5*A*)–C(11*A*)	109·4 (3)	C(9*B*)–C(5*B*)–C(11*B*)	110·6 (4)
C(1′*A*)–C(6*A*)–C(5*A*)	120·4 (4)	C(1′*B*)–C(6*B*)–C(5*B*)	119·0 (4)
C(1′*A*)–C(6*A*)–C(7*A*)	118·5 (3)	C(1′*B*)–C(6*B*)–C(7*B*)	119·8 (4)
C(5*A*)–C(6*A*)–C(7*A*)	121·1 (3)	C(5*B*)–C(6*B*)–C(7*B*)	121·2 (4)
C(4′*A*)–C(7*A*)–C(6*A*)	119·4 (3)	C(4′*B*)–C(7*B*)–C(6*B*)	118·5 (4)
C(4′*A*)–C(7*A*)–C(8*A*)	118·7 (4)	C(4′*B*)–C(7*B*)–C(8*B*)	119·4 (4)
C(6*A*)–C(7*A*)–C(8*A*)	121·6 (4)	C(6*B*)–C(7*B*)–C(8*B*)	121·7 (4)
C(1*A*)–C(8*A*)–C(7*A*)	113·2 (3)	C(1*B*)–C(8*B*)–C(7*B*)	112·9 (3)
C(1*A*)–C(8*A*)–O(14*A*)	111·6 (3)	C(1*B*)–C(8*B*)–O(14*B*)	111·8 (3)
C(7*A*)–C(8*A*)–O(14*A*)	114·3 (3)	C(7*B*)–C(8*B*)–O(14*B*)	114·7 (3)
C(1*A*)–C(9*A*)–C(5*A*)	108·9 (3)	C(1*B*)–C(9*B*)–C(5*B*)	108·4 (4)
C(1*A*)–C(9*A*)–C(10*A*)	110·2 (4)	C(1*B*)–C(9*B*)–C(10*B*)	110·1 (4)
C(5*A*)–C(9*A*)–C(10*A*)	113·6 (3)	C(5*B*)–C(9*B*)–C(10*B*)	114·3 (4)
N(2*A*)–C(12*A*)–C(13*A*)	108·8 (3)	N(2*B*)–C(12*B*)–C(13*B*)	109·2 (4)
C(12*A*)–C(13*A*)–O(14*A*)	112·0 (4)	C(12*B*)–C(13*B*)–O(14*B*)	112·0 (4)
C(8*A*)–O(14*A*)–C(13*A*)	113·0 (3)	C(8*B*)–O(14*B*)–C(13*B*)	113·5 (3)

Table 3. *Close contacts* (*distances in* Å, *angles in* °)

A	*B*	*C*	*AB*	*BC*	*AC*	*ABC*
O(2′*A*)	H(2′*A*)	Cl(*A*^{i})	0·81 (6)	2·27 (6)	3·075 (4)	169 (5)
C(1*A*)	H(1*A*)	O(2′*A*^{ii})	1·02 (4)	2·62 (4)	3·510 (4)	146 (3)
N(2*A*)	H(2*A*)	Cl(*A*)	0·87 (5)	2·26 (5)	3·113 (3)	168 (4)
C(10*A*)	H(10*AA*)	O(2′*B*^{i})	0·98 (5)	2·52 (5)	3·309 (6)	138 (4)
C(11*A*)	H(11*BA*)	O(14*B*^{vi})	1·06 (5)	2·63 (6)	3·536 (6)	144 (4)
C(12*A*)	H(12*AA*)	Cl(*B*^{ii})	0·92 (5)	2·75 (5)	3·629 (5)	161 (4)
C(12*A*)	H(12*BA*)	O(2′*A*^{ii})	0·95 (5)	2·56 (5)	3·284 (5)	133 (4)
O(2′*B*)	H(2′*B*)	Cl(*B*^{iv})	0·88 (5)	2·39 (5)	3·257 (3)	170 (5)
C(1′*B*)	H(1′*B*)	Cl(*B*^{iv})	1·02 (5)	2·82 (5)	3·676 (5)	142 (3)
N(2*B*)	H(2*B*)	Cl(*B*)	0·74 (5)	2·31 (5)	3·051 (4)	174 (5)
C(3*B*)	H(3*BB*)	O(14*A*^{vi})	1·00 (5)	2·65 (5)	3·591 (6)	156 (4)
C(8*B*)	H(8*B*)	O(2′*B*^{iii})	1·00 (5)	2·42 (5)	3·292 (5)	145 (4)
C(12*B*)	H(12*AB*)	Cl(*A*^{i})	1·11 (5)	2·81 (5)	3·892 (5)	165 (4)
C(13*B*)	H(13*AB*)	O(14*A*^{vi})	1·03 (5)	2·50 (5)	3·526 (7)	171 (4)

Symmetry operators: (i) $x, y, z+1$; (ii) $x, y, z-1$; (iii) $-x, +2, y+\frac{1}{2}, -z+1$; (iv) $-x+2, y+\frac{1}{2}, -z+2$; (v) $-x+1, y+\frac{1}{2}, -z+1$; (vi) $-x+1, y-\frac{1}{2}, -z+1$.

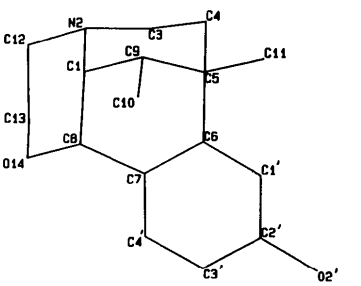

Fig. 1. Atomic numbering scheme.

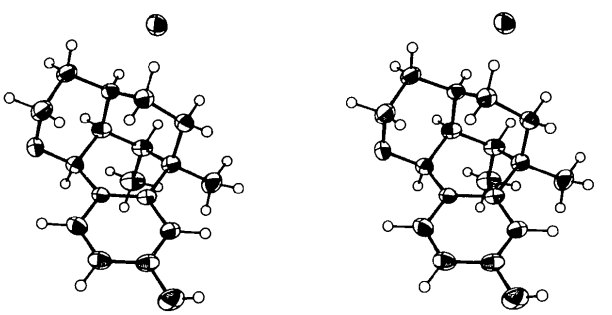

Fig. 2. Stereoscopic view of molecule *A* with 50% probability anisotropic displacement ellipsoids for the non-H atoms.

used instead of the experimental ones. Only the results for molecule *A* are shown (Fig. 4) since molecule *B* gave virtually identical results (r.m.s. deviation = 0·002 e). Several (C–)H groups are clearly activated, *i.e.* the H atom bears a moderate positive charge while the C atom is strongly positive thus providing an excellent electrostatic potential to catch any negative atom or ion [*e.g.* O(14), O(2′), Cl^-]. The close contacts with H(10*AA*), H(11*BA*) and H(1′*B*) should not be considered as hydrogen bonds as the C atoms involved carry a negative charge.

The result of the different packing of molecules *A* and *B* is reflected in the higher equivalent isotropic thermal parameters of molecule *B* (the average is 22% higher amounting to some 0·0080 Å^2). Indeed, the *B* molecule lacks the restricting environment present for the *A* molecule about the methyl groups C(10) and C(11),

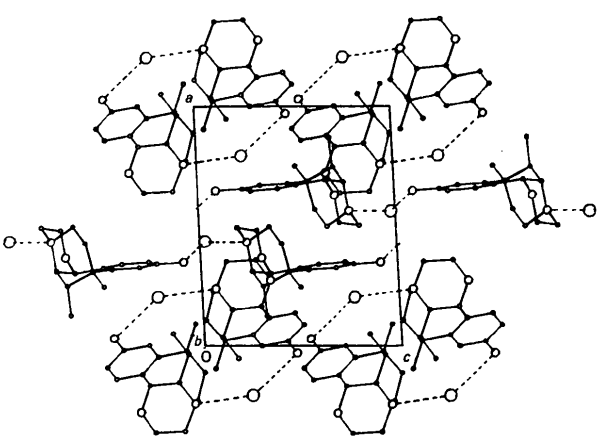

Fig. 3. Packing of the crystal. The most important hydrogen bonds are indicated by dashed lines.

while the tight packing of morpholine and phenol is similar for both molecules.

Apart from the rigid-body motion of the molecules, internal motions are also present. They can be discerned by means of a general rigid-bond test (Rosenfield, Trueblood & Dunitz, 1978). In this test, differences in mean square displacement amplitudes (MSDA) are calculated for each pair of atoms in the molecule. For a rigid molecule these differences should be close to zero. Gross violation of this condition of equality is observed for those intramolecular distances involving C(3) that are roughly perpendicular to the plane of the piperidine ring. In contrast, along distances within the plane of the ring, differences in MSDA's are close to the average for all bonded atom pairs (Table 4). From this, torsional oscillations involving C(3) can be inferred. Consequently, bond lengths about C(3) will be badly underestimated.

When the title compound is compared with the classical 6,7-benzomorphans in which no epoxyethano bridge is present, major changes are observed in the piperidinium ring. While the sum of the bond angles about N(2) is quite similar, the endocyclic angle C(1)—N(2)—C(3) is increased by some 4° along with a similar decrease of the C(1)—N(2)—C(12) angle. The origin of this deformation lies probably in the marked flattening of the piperidinium ring caused by serious sterical repulsion between the C(3) methylene and the C(13) methylene of the morpholinium ring. Indeed, the endocyclic torsion angles about N(2) are also reduced by some 10°. Apart from this unfavourable interaction, other *syn*-diaxial interactions still occur due to the presence of the aromatic substituent on the morpholinium ring. As a result the endocyclic angle about O(14) is increased by some 3·5° together with a decrease of the C(1)—C(8)—O(14)—C(13) torsion angle by 8° when compared with morpholinium rings in well-defined structures in which *syn*-diaxial interactions are absent, such as molindone (Olson, Cheung, Morgan, Blount, Todaro, Berger, Davidson & Boff, 1981), moxnidazole (Goldberg, 1982) or moclobemide (Durant, Van der Brempt, Bufkens & Evrard, 1986).

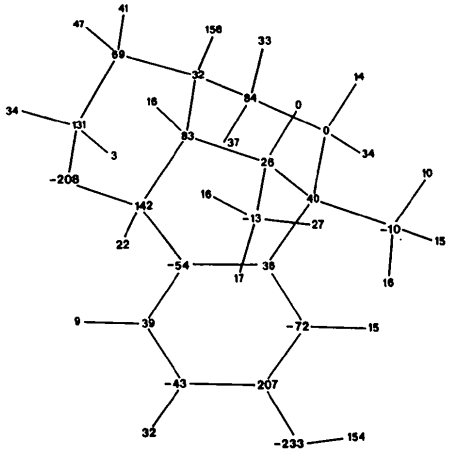

Fig. 4. Net atomic charges resulting from *CNDO*/2 calculation for molecule *A* (charges × 10^3).

Table 4. *Evidence for torsional oscillations about* C(3) (*all amplitudes* × 10^4 Å^2)

	Molecule *A*	Molecule *B*
Average Δ(MSDA) for bonded atom pairs:	23 (16)	25 (18)
For non-bonded atom pairs:		
(*a*) perpendicular to the piperidinium ring		
Δ(MSDA) between C(3) and C(1′)	65	128
C(2′)	54	95
C(3′)	52	103
C(4′)	64	77
C(6)	67	86
C(7)	69	73
gives an average of	62 (7)	94 (20)
(*b*) in the plane of the piperidinium ring		
Δ(MSDA) between C(3) and C(1)	10	58
C(5)	42	27
C(9)	28	41
gives an average of	27 (16)	42 (16)

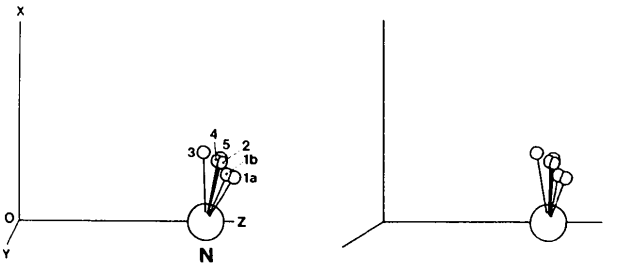

Fig. 5. Stereoscopic view of the orientation of the N proton [local coordinate system defined by the aromatic ring: C(7)—C(6) = *x* axis, C(7)—C(3′) = −*y* axis, *z* axis perpendicular to the *xy* plane]. Molecules: (1*a*) = Mr3159*A*, (1*b*) = Mr3159*B*, (2) = Mr2034, (3) = Mr2549, (4) = bremazocine, (5) = ketazocine.

The pharmacological inactivity of the title compound is possibly related to some of the structural modifications introduced by the epoxyethano bridge. Because of the marked flattening of the piperidinium ring the distance between the centre of the aromatic ring and N(2) is changed. The values of 4·308 and 4·335 Å (for *A* and *B* respectively) are significantly shorter than the characteristic 4·48 (5) Å (mean of 17 observations in our series of substituted 6,7-benzomorphans). Moreover, the orientation of the N proton with respect to the aromatic ring is also somewhat different from that of the typical κ-opioid 6,7-benzomorphans (Fig. 5). Here again, proton positions have been obtained from an *MMP*2 optimization. Whether such a moderate misalignment of the proton is sufficient to explain complete inactivity remains doubtful. *Ab initio* molecular-orbital calculations on model systems of amines have shown that a bend of some 10° from optimal orientation can occur at the expense of only a few kJ mol^{-1} (Kolb & Scheiner, 1984). A third, and perhaps the most important, difference involves the C(1)—N(2)—C(12)—C(13) torsion angle. Because of the morpholinium ring

this is (+)-synclinal in the title compound. However, in classical 6,7-benzomorphans, conformations are restricted to the range between antiperiplanar and (−)-synclinal due to the unfavourable interactions between the C(3) and C(13) methylenes. Accordingly the C(13) methylene of the title compound occupies a volume that is normally free. It is conceivable that this volume exceeds the local boundaries of the receptor, thus leading to a global misalignment of the drug molecule. In this way, O(14) will be unable to form a hydrogen bond to the hypothetical common binding moiety in the receptor responsible for κ-opioid activity. The rather promising results from a fit between the title compound and ketazocine in free space thus make little sense in the physical environment of the receptor.

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Structure of 1-Pyrenebutanoic Acid

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Abstract. $C_{20}H_{16}O_2$, $M_r = 288{\cdot}34$, monoclinic, $P2_1/a$, $a = 12{\cdot}236\ (17)$, $b = 5{\cdot}018\ (6)$, $c = 23{\cdot}827\ (29)$ Å, $\beta = 92{\cdot}26\ (11)°$, $V = 1461{\cdot}76\ (3{\cdot}26)$ Å^3, $Z = 4$, $D_x = 1{\cdot}310\ (2)$ g cm^{-3}, $\lambda(\text{Cu } K\alpha) = 1{\cdot}54178$ Å, $\mu = 5{\cdot}79$ cm^{-1}, $F(000) = 608{\cdot}00$, room temperature. Data collected from twinned crystal; $h = \text{mod}(6)$ reflections overlapping. $R = 0{\cdot}087$ for 936 reflections with $I > 3\sigma(I)$ and $h = \text{mod}\ (6)$ reflections excluded. Molecules related by the centre of inversion form hydrogen-bonded dimers, H···O = 1·64 (1) Å, O–H···O = 149 (1)°. The atoms participating in the hydrogen bond form an eight-membered ring which is almost flat

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