The strychnine is protonated at N(2). The values of the bond angles about N(2) are in good agreement with the corresponding values in strychnine sulfonic acid tetrahydrate.

A view of the crystal structure of strychnine hydrochloride along the *c* axis (Fig. 2), reveals the nature of the packing and the hydrogen-bonding arrangement. The structure is stabilized by a three-dimensional network of hydrogen bonds. The N—H···Cl-type hydrogen bonds which contribute to this network are N(2)···Cl(1) [2·987 (5) Å in molecule *A*] and N(2)···Cl(2) [3·064 (5) Å in molecule *B*]. The water molecules between the strychnine molecules are involved in hydrogen bonding of the O—H···Cl and O—H···O types; although one of the H atoms attached to O(3) could not be located, O(3)···Cl(2) [3·181 (6) Å] was assumed to be a hydrogen bond, and others are O(3)···O(4) 2·816 (8), O(4)···Cl(1) 3·129 (6), O(5)···Cl(1) 3·184 (7) Å. The bonds are of complex zigzag configuration. This three-dimensional hydrogen-bond network, which represents the main type of intermolecular interaction, apparently accounts for the somewhat high melting point of the compound.

The authors thank Dr T. Banerjee, Physics Department, Calcutta University, and Dr S. Chaudhuri, Bose Institute, for many valuable discussions and Dr A. De, Physics Department, Calcutta University, for his assistance during the course of this work.

References

BANERJEE, T. & CHAUDHURI, S. (1986). *Can. J. Chem.* **64**, 876–880.

CREMER, D. & POPLE, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)

MANSKE, R. H. E. & HOLMES, H. L. (1950). *The Alkaloids*, Vol. 1, p. 376. New York: Academic Press.

SAKE GOWDA, D. S., CARTZ, L. & NATARAJAN, S. (1973). *Acta Cryst.* **B29**, 2760–2770.

SHELDRICK, G. M. (1976). *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England.

Acta Cryst. (1989). C**45**, 1797–1802

Structure and Conformational Analysis of the Opioid Antagonist (−)-(1*R*,5*R*,9*R*)-5,9-Diethyl-2-(3-furylmethyl)-2′-hydroxy-6,7-benzomorphan (Mr2266)*†

BY C. L. VERLINDE, N. M. BLATON, O. M. PEETERS AND C. J. DE RANTER‡

Instituut voor Farmaceutische Wetenschappen, Katholieke Universiteit, Van Evenstraat 4, *B*-3000 *Leuven, Belgium*

(*Received* 19 *January* 1989; *accepted* 23 *March* 1989)

Abstract. $C_{21}H_{27}NO_2$, $M_r = 325·449$, monoclinic, $P2_1$, $a = 16·3916\,(7)$, $b = 12·7460\,(5)$, $c = 8·9806\,(5)$ Å, $\beta = 107·191\,(4)°$, $V = 1792·5\,(2)$ Å^3, $Z = 4$, $D_m = 1·22\,(2)$, $D_x = 1·206$ Mg m^{-3}, $\lambda(\mathrm{Cu}\ K\alpha) = 1·54178$ Å, $\mu(\mathrm{Cu}\ K\alpha) = 0·566$ mm^{-1}, $F(000) = 704$, $T = 291$ K, final $R = 0·048$ for 4225 observed reflections. The two molecules present in the asymmetric unit adopt a different conformation with respect to the *N*-side chain. Starting from the asymmetric carbon and proceeding along the allyl moiety the conformations are antiperiplanar/(−)-anticlinal for molecule 1 and antiperiplanar/(+)-synclinal for molecule 2. The furyl rings engage in aromatic–aromatic interactions which are compared with results from a theoretical study from the literature. Finally, the 3-furyl geometry is evaluated through a Cambridge Structural Database search and *CNDO*/2 calculations.

Introduction. In a search for new opioid antagonists within a series of *N*-furylmethyl-substituted 6,7-benzomorphans the title compound was characterized as a pure antagonist about as potent as naloxone (Merz, Langbein, Stockhaus, Walther & Wick, 1974). Depending upon the furyl substitution pattern, the action profile could resemble that of a mixed antagonist(agonist) in the *N*-(2-furylmethyl) derivative, that of a mixed agonist–antagonist in the *N*-(3-methylfurfuryl) derivative, or that of a pure

---

[*] *Chemical Abstracts* name: (−)-(2*R*,6*R*,11*R*)-6,11-diethyl-3-(3-furylmethyl)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-8-ol.

[†] Structural Studies of Substituted 6,7-Benzomorphan Compounds. XV. Part XIV: Verlinde, Blaton, De Ranter & Peeters (1989).

[‡] To whom correspondence should be addressed.

0108-2701/89/111797-06$03.00

agonist in the *N*-(2-methyl-3-methylfuryl) derivative. The alkyl substitution pattern at positions 5 and 9 had little influence on these profiles, but modified the potencies of the drugs.

Following the suggestion that there might be different opioid receptor types (Martin, Eades, Thompson, Huppler & Gilbert, 1976), the title compound, by then well known by its code name Mr2266, was tested *in vitro* in electrically stimulated organ models (Lord, Waterfield, Hughes & Kosterlitz, 1977). It was shown to be about equipotent as an antagonist at the μ- and κ-receptor types, and an order of magnitude less potent at the δ-receptor type. The fact that is was a more potent antagonist at the κ opioid receptor type than naloxone, was at the basis of a popular misconception. Indeed, in 1986 one could still read that 'Mr2266 is a selective κ-antagonist' (Casy & Parfitt, 1986). Really selective κ-antagonists such as binaltorphimine have only been designed quite recently in the class of the bimorphinans (Portoghese, Lipkowski & Takemori, 1987).

Through a comparison of the electronic and conformational features within the aforementioned *N*-furylmethyl-6,7-benzomorphan series two important factors for antagonist activity have been identified (Cheney, Zichi & Miller, 1983): (1) the availability of a suitably localized LUMO resembling that of the allyl in naloxone; (2) the absence of a bulky *cis* moiety in the allyl-like substituent. In that study a molecular mechanics evaluation of the *N*-side chain of the protonated drugs localized four local energy minima, differing by less than 4 kJ mol^{-1}. Calculations on the free base molecules were omitted as a close correspondence between energy minima of free base and protonated naloxone had emerged from an earlier study (Cheney & Zichi, 1981).

However, the relevance of a conformational analysis on the isolated molecule can be questioned, mainly because of the large susceptibility of the furyl ring to undergo perturbations by neighbouring aromatic groups in the real receptor environment. Furthermore, the consequences of the rigid-rotation approximation (*i.e.* with fixed bond lengths and bond angles) adopted in that study are not clear. Therefore, it seemed worthwhile to investigate the conformational behaviour of such molecules in a real environment through a crystal structure analysis, although it is not implied that the crystal environment is directly related to the binding site of the receptor.

Experimental. Colourless crystals obtained at room temperature from an equimolar ehtyl acetate–ethanol solution. Density measured by flotation in *n*-heptane/CCl_4, $\sim 0{\cdot}5 \times 0{\cdot}4 \times 0{\cdot}15$ mm, Hilger & Watts computer-controlled four-circle diffractometer, Ni-filtered Cu $K\alpha$ radiation, $\omega/2\theta$-scan technique ($2\theta_{\max} = 140°$, $\overline{19} \le h \le 19$, $\overline{15} \le k \le 15$, $0 \le l \le 10$), cell dimensions by least-squares refinement of the 2θ angles of 23 reflections with $39 < 2\theta < 50°$, space group $P2_1$ from systematic absences $0k0$ for k odd (optically active compound). Four standard reflections (400, 040, $10\overline{2}$ and $24\overline{3}$) monitored after each 50 reflections did not reveal a significant change in intensity. 6337 independent reflections measured, $R_{\rm int} = 0{\cdot}026$, 4225 observed reflections [$I > 3\sigma(I)$], Lorentz-polarization corrections, absorption corrections by the method of North, Phillips & Mathews (1968) with transmission factors between 0·999 and 0·926, scattering factors from Cromer & Mann (1968), and Stewart, Davidson & Simpson (1965) for hydrogen.

The structure of the benzomorphan skeleton of the *A* molecule was revealed by *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) but, although well oriented, it was misplaced in the unit cell. Subsequently *DIRDIF* (Beurskens, Bosman, Doesburg, Gould, van den Hark, Prick, Noordik, Beurskens & Parthasarathi, 1981) produced the correct translation vector and solved the remaining part of the structure. 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; final refinement by full-matrix least squares. Hydrogen positions from ΔF synthesis included in refinement with fixed isotropic temperature factors equal to those of their parent atoms; final $R = 0{\cdot}048$, $wR = 0{\cdot}059$ and $S = 0{\cdot}14$ for 594 parameters, $w = (30{\cdot}0 + |F_o| + 0{\cdot}001|F_o|^2)^{-1}$; $(\Delta/\sigma)_{\rm ave} = 0{\cdot}13$, $(\Delta/\sigma)_{\max} = 1{\cdot}76$ (only the phenol hydrogens have values larger than one; they were located from the lower end of the ΔF), $-0{\cdot}40 \le$ final $\Delta\rho \le 0{\cdot}44$ e Å^{-3}.

Discussion. The atomic numbering scheme is given in Fig. 1 and atomic parameters are listed in Table 1. The two molecules in the asymmetric unit are labelled *A* and *B* respectively. Bond lengths, bond angles

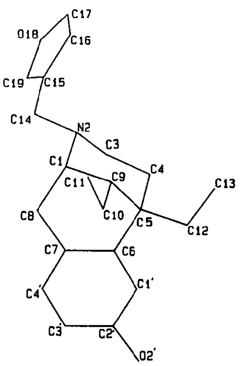

Fig. 1. Atomic numbering scheme.

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

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

	x	y	z	B_{eq}(Å^2)
C(1′A)	5600 (2)	5299*	5280 (4)	2·8 (1)
C(2′A)	5246 (2)	4868 (5)	6369 (4)	2·9 (1)
O(2′A)	5337 (2)	5434 (4)	7704 (3)	3·8 (1)
O(3′A)	4824 (3)	3914 (5)	6058 (5)	3·5 (1)
C(4′A)	4741 (3)	3433 (5)	4650 (5)	3·4 (1)
C(1A)	5154 (2)	3922 (5)	734 (5)	2·7 (1)
N(2A)	4501 (2)	4686 (4)	− 171 (3)	2·5 (1)
C(3A)	4335 (3)	5542 (5)	814 (5)	2·9 (1)
C(4A)	5154 (3)	6093 (5)	1666 (5)	2·9 (1)
C(5A)	5856 (2)	5338 (5)	2622 (4)	2·6 (1)
C(6A)	5515 (2)	4813 (4)	3849 (4)	2·5 (1)
C(7A)	5065 (2)	3858 (5)	3519 (4)	3·0 (1)
C(8A)	4912 (3)	3277 (5)	1982 (5)	3·2 (1)
C(9A)	5998 (3)	4510 (5)	1464 (5)	2·9 (1)
C(10A)	6759 (3)	3756 (6)	2166 (6)	4·2 (2)
C(11A)	7049 (4)	3208 (6)	942 (8)	5·4 (2)
C(12A)	6667 (3)	5980 (6)	3391 (5)	3·6 (2)
C(13A)	7156 (4)	6405 (7)	2317 (7)	4·9 (2)
C(14A)	3697 (3)	4152 (5)	− 973 (6)	3·3 (1)
C(15A)	3055 (2)	4883 (5)	− 2020 (5)	3·2 (1)
C(16A)	3124 (3)	5571 (6)	− 3216 (6)	4·0 (2)
C(17A)	2364 (3)	6035 (5)	− 3792 (6)	4·3 (2)
O(18A)	1803 (2)	5691 (5)	− 3050 (4)	5·3 (1)
C(19A)	2241 (3)	4981 (6)	− 1973 (6)	4·3 (2)
C(1′B)	10870 (2)	3025 (5)	15518 (4)	2·7 (1)
C(2′B)	10580 (2)	2573 (5)	16659 (4)	3·0 (1)
O(2′B)	10645 (2)	3154 (4)	17990 (3)	3·6 (1)
C(3′B)	10252 (3)	1565 (5)	16466 (5)	3·4 (1)
C(4′B)	10165 (3)	1061 (5)	15059 (5)	3·3 (1)
C(1B)	10459 (2)	1561 (5)	11030 (4)	2·6 (1)
N(2B)	9791 (2)	2287 (4)	10099 (3)	2·6 (1)
C(3B)	9604 (3)	3139 (5)	11053 (5)	3·0 (1)
C(4B)	10406 (3)	3743 (5)	11855 (5)	3·1 (1)
C(5B)	11126 (2)	3032 (5)	12856 (4)	2·6 (1)
C(6B)	10811 (2)	2508 (4)	14109 (4)	2·6 (1)
C(7B)	10413 (2)	1525 (5)	13864 (4)	2·6 (1)
C(8B)	10249 (3)	943 (5)	12327 (5)	3·0 (1)
C(9B)	11289 (2)	2184 (5)	11727 (5)	2·7 (1)
C(10B)	12045 (2)	1457 (5)	12510 (5)	3·4 (1)
C(11B)	12253 (4)	681 (7)	11391 (7)	5·4 (2)
C(12B)	11925 (3)	3704 (5)	13594 (6)	3·6 (2)
C(13B)	12387 (4)	4155 (6)	12471 (8)	4.7 (2)
C(14B)	9004 (2)	1712 (5)	9311 (5)	3·0 (1)
C(15B)	8370 (2)	2334 (5)	8054 (5)	3·3 (1)
C(16B)	7463 (3)	2258 (6)	7633 (7)	4·7 (2)
C(17B)	7148 (4)	2939 (6)	6496 (6)	5·3 (2)
O(18B)	7778 (2)	3463 (5)	6136 (4)	5·1 (1)
C(19B)	8524 (3)	3082 (6)	7118 (6)	4·4 (2)

Parameter kept fixed for origin definition.

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

C(1′A)—C(2′A)	1·389 (6)	C(1′B)—C(2′B)	1·377 (7)
C(1′A)—C(6A)	1·396 (6)	C(1′B)—C(6B)	1·404 (7)
C(2′A)—O(2′A)	1·369 (6)	C(2′B)—O(2′B)	1·383 (6)
C(2′A)—C(3′A)	1·386 (9)	C(2′B)—C(3′B)	1·383 (9)
C(3′A)—C(4′A)	1·376 (7)	C(3′B)—C(4′B)	1·386 (7)
C(4′A)—C(7A)	1·388 (8)	C(4′B)—C(7B)	1·387 (7)
C(1A)—N(2A)	1·497 (7)	C(1B)—N(2B)	1·488 (6)
C(1A)—C(8A)	1·534 (8)	C(1B)—C(8B)	1·528 (7)
C(1A)—C(9A)	1·540 (7)	C(1B)—C(9B)	1·539 (6)
N(2A)—C(3A)	1·479 (8)	N(2B)—C(3B)	1·470 (8)
N(2A)—C(14A)	1·469 (6)	N(2B)—C(14B)	1·471 (6)
C(3A)—C(4A)	1·508 (7)	C(3B)—C(4B)	1·510 (7)
C(4A)—C(5A)	1·550 (7)	C(4B)—C(5B)	1·547 (7)
C(5A)—C(6A)	1·530 (7)	C(5B)—C(6B)	1·524 (7)
C(5A)—C(9A)	1·548 (8)	C(5B)—C(9B)	1·559 (8)
C(5A)—C(12A)	1·539 (7)	C(5B)—C(12B)	1·541 (7)
C(6A)—C(7A)	1·408 (8)	C(6B)—C(7B)	1·401 (8)
C(7A)—C(8A)	1·521 (7)	C(7B)—C(8B)	1·519 (7)
C(9A)—C(10A)	1·552 (8)	C(9B)—C(10B)	1·540 (7)
C(10A)—C(11A)	1·493 (10)	C(10B)—C(11B)	1·519 (10)
C(12A)—C(13A)	1·525 (10)	C(12B)—C(13B)	1·541 (10)
C(14A)—C(15A)	1·509 (7)	C(14B)—C(15B)	1·513 (7)
C(15A)—C(16A)	1·417 (8)	C(15B)—C(16B)	1·425 (7)
C(15A)—C(19A)	1·352 (7)	C(15B)—C(19B)	1·344 (9)
C(16A)—C(17A)	1·337 (8)	C(16B)—C(17B)	1·323 (10)
C(17A)—O(18A)	1·358 (8)	C(17B)—O(18B)	1·347 (9)
O(18A)—C(19A)	1·363 (8)	O(18B)—C(19B)	1·368 (6)
C(2′A)—C(1′A)—C(6A)	121·6 (3)	C(2′B)—C(1′B)—C(6B)	121·8 (5)
C(1′A)—C(2′A)—O(2′A)	116·6 (5)	C(1′B)—C(2′B)—O(2′B)	117·6 (5)
C(1′A)—C(2′A)—C(3′A)	119·5 (4)	C(1′B)—C(2′B)—C(3′B)	120·1 (4)
O(2′A)—C(2′A)—C(3′A)	123·8 (5)	O(2′B)—C(2′B)—C(3′B)	122·3 (4)
C(2′A)—C(3′A)—C(4′A)	118·9 (5)	C(2′B)—C(3′B)—C(4′B)	118·5 (4)
C(3′A)—C(4′A)—C(7A)	122·9 (5)	C(3′B)—C(4′B)—C(7B)	122·2 (5)
N(2A)—C(1A)—C(8A)	116·6 (4)	N(2B)—C(1B)—C(8B)	117·0 (3)
N(2A)—C(1A)—C(9A)	108·9 (5)	N(2B)—C(1B)—C(9B)	108·9 (5)
C(8A)—C(1A)—C(9A)	110·1 (3)	C(8B)—C(1B)—C(9B)	109·1 (3)
C(1A)—N(2A)—C(3A)	112·5 (3)	C(1B)—N(2B)—C(3B)	112·1 (3)
C(1A)—N(2A)—C(14A)	111·0 (5)	C(1B)—N(2B)—C(14B)	110·8 (5)
C(3A)—N(2A)—C(14A)	109·8 (4)	C(3B)—N(2B)—C(14B)	110·2 (3)
N(2A)—C(3A)—C(4A)	110·7 (4)	N(2B)—C(3B)—C(4B)	110·7 (4)
C(3A)—C(4A)—C(5A)	113·3 (5)	C(3B)—C(4B)—C(5B)	112·6 (5)
C(4A)—C(5A)—C(6A)	107·5 (3)	C(4B)—C(5B)—C(6B)	108·6 (3)
C(4A)—C(5A)—C(9A)	106·6 (3)	C(4B)—C(5B)—C(9B)	106·0 (3)
C(4A)—C(5A)—C(12A)	108·7 (5)	C(4B)—C(5B)—C(12B)	109·3 (5)
C(6A)—C(5A)—C(9A)	110·2 (5)	C(6B)—C(5B)—C(9B)	109·7 (5)
C(6A)—C(5A)—C(12A)	111·1 (3)	C(6B)—C(5B)—C(12B)	110·9 (3)
C(9A)—C(5A)—C(12A)	112·5 (4)	C(9B)—C(5B)—C(12B)	112·1 (3)
C(1′A)—C(6A)—C(5A)	120·7 (4)	C(1′B)—C(6B)—C(5B)	120·8 (5)
C(1′A)—C(6A)—C(7A)	118·7 (4)	C(1′B)—C(6B)—C(7B)	117·8 (4)
C(5A)—C(6A)—C(7A)	120·5 (4)	C(5B)—C(6B)—C(7B)	121·3 (4)
C(4′A)—C(7A)—C(6A)	118·3 (4)	C(4′B)—C(7B)—C(6B)	119·3 (4)
C(4′A)—C(7A)—C(8A)	118·5 (5)	C(4′B)—C(7B)—C(8B)	118·8 (5)
C(6A)—C(7A)—C(8A)	123·2 (4)	C(6B)—C(7B)—C(8B)	121·9 (4)
C(1A)—C(8A)—C(7A)	113·2 (5)	C(1B)—C(8B)—C(7B)	115·0 (5)
C(1A)—C(9A)—C(5A)	108·8 (4)	C(1B)—C(9B)—C(5B)	108·7 (3)
C(1A)—C(9A)—C(10A)	112·7 (5)	C(1B)—C(9B)—C(10B)	111·8 (5)
C(5A)—C(9A)—C(10A)	114·3 (3)	C(5B)—C(9B)—C(10B)	113·0 (3)
C(9A)—C(10A)—C(11A)	112·5 (4)	C(9B)—C(10B)—C(11B)	113·4 (3)
C(5A)—C(12A)—C(13A)	116·8 (4)	C(5B)—C(12B)—C(13B)	116·5 (4)
N(2A)—C(14A)—C(15A)	112·2 (5)	N(2B)—C(14B)—C(15B)	114·1 (5)
C(14A)—C(15A)—C(16A)	131·1 (4)	C(14B)—C(15B)—C(16B)	126·5 (5)
C(14A)—C(15A)—C(19A)	123·4 (5)	C(14B)—C(15B)—C(19B)	128·6 (4)
C(16A)—C(15A)—C(19A)	105·5 (5)	C(16 B)—C(15B)—C(19B)	104.9 (4)
C(15A)—C(16A)—C(17A)	107·0 (5)	C(15B)—C(16B)—C(17B)	107·4 (6)
C(16A)—C(17A)—O(18A)	110·8 (5)	C(16B)—C(17B)—O(18B)	111·0 (5)
C(17A)—O(18A)—C(19A)	105·8 (4)	C(17B)—O(18B)—C(19B)	105·8 (5)
C(15A)—C(19A)—O(18A)	110·9 (5)	C(15B)—C(19B)—O(18B)	111·0 (5)

	Molecule A	Molecule B
C(1)—N(2)—C(14)—C(15)	− 174·4 (4)	− 166·4 (4)
C(3)—N(2)—C(14)—C(15)	60·5 (5)	68·9 (5)
C(4)—C(5)—C(12)—C(13)	− 71·2 (6)	− 68·5 (6)
C(9)—C(5)—C(12)—C(13)	46·5 (7)	48·7 (6)
C(6)—C(5)—C(12)—C(13)	170·5 (5)	171·7 (5)
C(5)—C(9)—C(10)—C(11)	− 161·8 (5)	− 175·6 (5)
C(1)—C(9)—C(10)—C(11)	73·1 (6)	61·4 (6)
N(2)—C(14)—C(15)—C(16)	52·4 (8)	− 147·1 (5)
N(2)—C(14)—C(15)—C(19)	− 128·7 (6)	31·4 (8)

and selected torsion angles are given in Table 2. An *ORTEP* stereopair (Johnson, 1965) of the *A* molecule is shown in Fig. 2.* Through use of a least-squares fit procedure using the program *BMFIT* (Nyburg, 1974) on the atoms of the fused-ring skeleton, *i.e.* without the substituents on N(2), C(5) and C(9), a close similarity between molecules *A* and *B* is observed (r.m.s. deviation = 0·044 Å). In fact, this fused-ring skeleton is analogous to that observed for Mr1526 (Peeters, De Ranter & Blaton, 1982), another benzomorphan studied in the neutral form.

The ring connecting the phenol and piperidine adopts a conformation halfway between half-chair and half-boat [puckering parameters for the sequence

---

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, bond lengths and angles involving H atoms, torsion angles and least-squares-planes data have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52072 (47 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

C(1)—C(8)—C(7)—C(6)—C(5)—C(9) according to Cremer & Pople (1975): $\varphi = 134{\cdot}5\,(8)$, $\theta = 130{\cdot}3\,(6)^\circ$ for *A*, $\varphi = 133{\cdot}0\,(7)$, $\theta = 127{\cdot}3\,(5)^\circ$ for *B*] in contrast to the half-boat which prevails in the protonated benzomorphans (Verlinde, 1988).

The conformations of the ethyl groups on C(5) and C(9) are quite similar in both molecules: C(5)—C(9)—C(10)—C(11) and C(6)—C(5)—C(12)—C(13) are antiperiplanar, and the C(5)—C(12)—C(13) valence angle has opened up to 116·8 (5) and 116·5 (5)° respectively. This widening is a consequence of unfavourable *syn*-diaxial interactions between the methyl C(13) group and the H(9) and H(4*A*) on the piperidine ring. However, in 5-ethyl-9,9-dimethyl-substituted benzomorphans, such as bremazocine (Verlinde, Blaton, De Ranter & Peeters, 1984), the 9β-methyl simply prevents the antiperiplanar form, and the 5-ethyl is forced into the (+)-synclinal conformation while the valence angle is further widened to about 119°, as a result of steric interactions with the C(10) methylene. An *MM*2 force-field calculation (Allinger & Flanagan, 1983) was performed to test if the (+)-synclinal form is energetically acceptable for the title compound. The antiperiplanar form was found more stable by 6·3 kJ mol^{-1} while the 5-ethyl torsion angle was well reproduced at 172·2°.

An important aspect of the title compound is the conformation of its *N*-side chain. Referring to the torsion angles C(1)—N(2)—C(14)—C(15) and N(2)—C(14)—C(15)—C(19) respectively, molecule *A* is in an antiperiplanar/(−)-anticlinal conformation while molecule *B* adopts an antiperiplanar/(+)-synclinal conformation. It is thus almost as if the furyl in molecule *A* has been rotated by 180° to yield molecule *B*. These two conformations correspond roughly to two of the four equi-energetic minima found in the potential-energy surface calculated by the *MM*2 force field, shown in Fig. 3 (two-dimensional 30° grid search; energy minimization within 1·0 kJ mol^{-1} for each of the 144 conformations, but with the furyl geometry kept rigid as the parametrization is lacking). These minima virtually coincide with the minima calculated by Cheney, Zichi & Miller (1983). The minima corresponding to the C(1)—N(2)—C(14)—C(15) (−)-synclinal arrangement are not present in the crystal as the accessibility of the piperidine N would be hampered by one of the *ortho* furyl hydrogens, thus preventing the formation of a hydrogen bond. That the observed conformations do not match exactly the calculated minima is probably due to packing forces in the crystal as the energy minima are quite shallow (Fig. 3). Indeed, both furyls present in the asymmetric unit make numerous short contacts (Table 3 and Fig. 4). For verification, all hydrogen positions have been 'normalized': hydrogens were moved along the observed C—H bond direction until a standard value of 1·08 Å (Allen, Kennard, Watson, Brammer, Orpen & Taylor, 1987) was reached. These close contacts are in excellent agreement with recent studies describing the aromatic–aromatic interaction in proteins (Burley & Petsko, 1985; Gould, Gray, Taylor & Walkinshaw, 1985). They represent edge-to-face interactions of furyl–furyl and furyl–phenyl (as can be seen from the interplanar angles) resulting from Coulombic attraction between the δ(+) hydrogen atoms of one ring and the π cloud of the other one. The aforementioned authors concluded that a typical aromatic–aromatic interaction has an energy between −4 and −8 kJ mol^{-1}. Hence, it should be no surpise that the observed side chain conformations are somewhat different from the calculated ones.

Apart from perturbing the *N*-side chain torsion angles, the furyl stacking apparently also has an effect on the exocyclic 3-furyl valence angles. While the endocyclic angles in *A* and *B* differ only by 0·6° (a value within the e.s.d.'s), C(14)—C(15)—C(16) differs by 4·6° and C(14)—C(15)—C(19) by 5·2°. Whether such large changes of the exocyclic 3-furyl bond angles are common was investigated through a CSD search (Allen *et al.*, 1979) (Table 4 and Fig. 5).

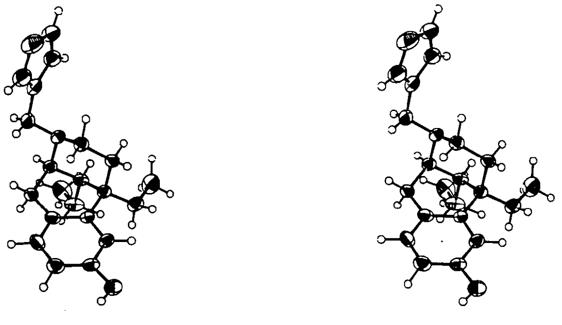

Fig. 2. Stereoscopic view of the *A* molecule with 50% probability anisotropic displacement ellipsoids for the non-hydrogen atoms.

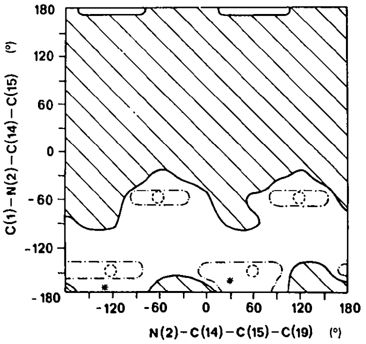

Fig. 3. Conformational potential-energy surface for Mr2266; contours: 2·1 (dashed line), 4·2 (dot and dash line) and 12·5 kJ mol^{-1} (unbroken line); the conformations adopted in the crystal are indicated with asterisks.

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

Furyl short contacts (numbering as in Fig. 4)

	a	*b*	*c*
(1) H(17*A*)···C(17*B*^{i})	2·92 (8)	2·80	85·3 (2)
(2) H(16*A*)···C(2′*A*^{ii})	2·92 (5)	2·80	88·8 (2)
(3) C(19*A*)···H(1′*B*^{iii})	2·81 (6)	2·74	87·8 (2)
(4) H(17*B*)···C(4′*A*)	2·92 (5)	2·80	75·4 (2)
···C(7*A*)	2·92 (5)	2·80	
(5) H(19*B*)···C(2′*B*^{ii})	2·86 (6)	2·76	77·7 (2)
···O(2′*B*^{ii})	2·57 (5)	2·47	77·7 (2)

Hydrogen bonds (numbering as in Fig. 4)

D(onor)-H···*A*(cceptor)	*D*H	H*A*	*DA*	< *DHA*
(6) O(2′*A*)—H(2′*A*)···N(2′*A*^{ii})	0·82 (6)	2·02 (6)	2·824 (6)	166 (5)
(7) O(2′*B*)—H(2′*B*)···N(2′*B*^{iv})	0·81 (6)	2·08 (6)	2·886 (6)	168 (5)

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

Notes: (*a*) contact distance (Å); (*b*) normalized contact distance (Å); (*c*) interplanar angle between furyl mean plane and mean plane of the contact.

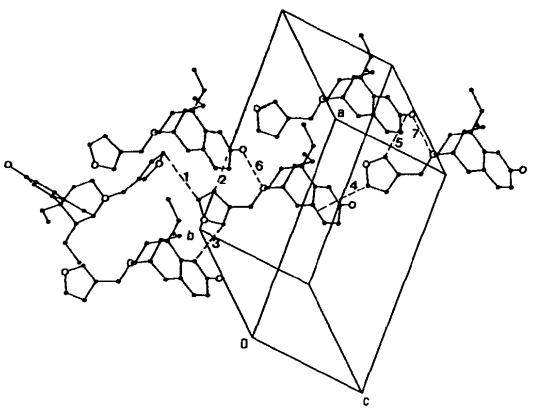

Fig. 4. Crystal packing of Mr2266. Hydrogen bonds and short contacts are indicated by dashed lines and are identified in Table 3.

Also, the structure was compared to that of furan as obtained from a very accurate microwave determination (Mata, Martin & Sørensen, 1978); the X-ray diffraction study of furan (Fourme, 1972) was not of sufficient quality (Verlinde & De Ranter, 1989). For the CSD search stringent criteria were imposed: (i) *R* ≤ 0·05, (ii) reported mean estimated standard deviation for C—C bond lengths ≤ 0·005 Å, (iii) no element present heavier than oxygen, (iv) no disorder. Bond lengths are not included in the discussion as they are substantially affected by libration effects and asphericity shifts. However, bond angles are much less affected and are quite accurate (Domenicano & Vaciago, 1979). While the endocyclic bond angles of molelule *A* are in complete agreement with the CSD search values (r.m.s. deviation = 0·1°), those of the *B* molecule differ somewhat more (r.m.s. deviation = 0·4°) although remaining well within the limits of the e.s.d.'s. From comparison with the structure of furan itself it is clear that the C(3)-substitution influences the ring geometry. A decrease in the *ipso* angle is accompanied by an increase of both *ortho* angles, while the angle about the oxygen atom is also affected. Analogous observations for benzene derivatives have been interpreted in terms of inductive and resonance effects (Domenicano & Murray-Rust, 1979), and in terms of VSEPR theory (Domenicano, 1985).

Table 4. *CSD entries included in 3-furyl statistics*

AXHNOM	Ahmed, Ng & Fallis (1978)
BEBSIK	Kraus, Kypke, Bokel, Grimminger, Sawitzki & Schwinger (1982)
CEDZOA	Busby, Day, Day, Wheeler, Wheeler & Day (1983)
CIHWOF	Blount, Chan, Clardy, Manchard & Pezzanite (1984)
COHJAK	Eguren, Fayos, Perales, Sarona & Rodriguez (1984)
DUMJUQ	Goddard & Akhtar (1986)
GNAPHA	Martinez-Ripoll *et al.*, (1981)
MZRRNE10	Marquez, Rabanal, Valverde, Eguren, Perales & Fayos (1980)

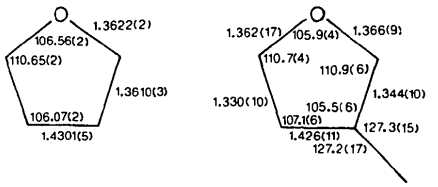

Fig. 5. Comparative geometry (Å and °) of furan (MW) and 3-furyl (CSD, nine observations, see Table 4).

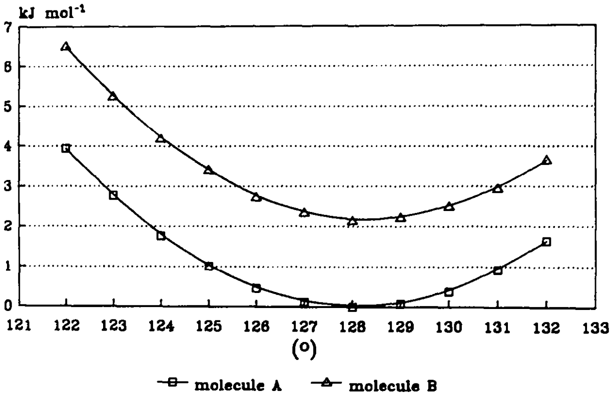

Fig.6. *CNDO*/2 optimization of the C(14)—C(15)—C(19) angle in the 3-ethylfuran fragment.

From the CSD search it appears that the exocyclic valence angles of the *B* molecule are fairly normal. Those of the *A* molecule, however, differ by 3·9° from the CSD mean value. The CSD search also reveals that these angles are easily modified by the environment since the e.s.d. calculated from the nine observations (1·6°) is about three times as large as the e.s.d.'s of the individual observations. So, these differences may result from environmental effects (Taylor & Kennard, 1983). As a final check *CNDO*/2 calculations (Pople & Segal, 1966) were set up to determine the optimized valence angle for both observed orientations of the furyl (Fig. 6). The title molecule was mimicked by 3-(*N*,*N*-dimethylaminomethyl)furan built from the CSD geometry of the 3-furyl fragment, furyl hydrogen geometry was taken from the microwave study by Mata, Martin &

Sørensen (1978), and a CSD compilation (Allen *et al.*, 1987) provided parameters for the rest of the structure. For both orientations a minimum at 128° was found for the equivalent of the C(14)—C(15)—C(19) angle, which matches the CSD mean value. The angle observed for molecule *A* is 123·4°, which is about 2·3 kJ mol^{-1} above the energy minimum. This could easily be overcome by the energy gained from the favourable aromatic–aromatic interactions.

Some of these interactions are in agreement with the model features for opioid antagonistic action proposed by Cheney, Zichi & Miller (1983): C(17) and C(19) prove to be excellent sites for interaction along π^* molecular orbitals (Table 3: short contacts 1 and 3). On the other hand, the present crystal structure demonstrates that the furyl hydrogens can also engage in favourable interactions (Table 3: short contacts 1, 2, 4 and 5). They have probably been overlooked in the modelling study because of the limited basis sets used in the *ab initio* FSGO (floating spherical Gaussian orbital) calculations in which CH linkages are represented by a single Gaussian. The present study thus warns against the use of oversimplified theoretical models.

The authors thank Dr H. Merz, Boehringer Ingelheim, for providing the title compound.

References

Ahmed, F. R., Ng, A. S. & Fallis, A. G. (1978). *Can. J. Chem.* **56**, 1020–1025.

Allen, F. H., Bellard, S., Brice, M. D., Cartwright, B. A., Doubleday, A., Higgs, H., Hummelink, T., Hummelink-Peters, B. G., Kennard, O., Motherwell, W. D. S., Rodgers, J. R. & Watson, D. G. (1979). *Acta Cryst.* B**35**, 2331–2339.

Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, A. G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans.* 2, pp. S1–S19.

Allinger, N. L. & Flanagan, H. L. (1983). *J. Comput. Chem.* **4**, 399–403.

Beurskens, P. T., Bosman, W. P., Doesburg, H. M., Gould, R. O., van den Hark, Th. E. M., Prick, P. A. J., Noordik, J. H.,. Beurskens, G. & Parthasarathi, V. (1981). *DIRDIF*. Tech. Rep. 1981/2. Crystallography Laboratory, Toernooiveld, 6525 ED Nijmegen, The Netherlands.

Blount, J. F., Chan, W. R., Clardy, J., Manchard, P. S. & Pezzanite, J. O. (1984). *J. Chem. Res.* (*S*), pp. 114–115.

Burley, S. K. & Petsko, G. A. (1985). *Science*, **229**, 23–28.

Busby, M. C., Day, V. W., Day, R. O., Wheeler, D. M. S., Wheeler, M. M. & Day, C. S. (1983). *Proc. R. Ir. Acad. Sect. B*, **83**, 21–31.

Casy, A. F. & Parfitt, R. T. (1986). *Opioid Analgesics. Chemistry and Receptors*, p. 427. New York: Plenum.

Cheney, B. V. & Zichi, D. A. (1981). *Int. J. Quantum Chem. Quantum Biol. Symp.* **8**, 201–219.

Cheney, B. V., Zichi, D. A. & Miller, A. B. (1983). *Int. J. Quantum Chem. Quantum Biol. Symp.* **10**, 43–59.

Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.

Cromer, D. T. & Mann, J. B. (1968). *Acta Cryst.* A**24**, 321–324.

Domenicano, A. (1985). In *Lecture Notes, International School of Crystallography, Static and Dynamic Implications of Precise Structural Information*, edited by A. Domenicano, I. Hargittai & P. Murray-Rust, pp. 315–330. Rome: CNR.

Domenicano, A. & Murray-Rust, P. (1979). *Tetrahedron Lett.* **24**, 2283–2286.

Domenicano, A. & Vaciago, A. (1979). *Acta Cryst.* B**35**, 1382–1388.

Eguren, L., Fayos, J., Perales, A., Sarona, G. & Rodriguez, B. (1984). *Phytochemistry*, **23**, 466–467.

Fourme, R. (1972). *Acta Cryst.* B**28**, 2984–2991.

Goddard, R. & Akhtar, F. (1986). *Acta Cryst.* C**42**, 1217–1220.

Gould, R. O., Gray, A. M., Taylor, P. & Walkinshaw, M. D. (1985). *J. Am. Chem. Soc.* **107**, 5921–5927.

Johnson, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee, USA.

Kraus, W., Kypke, K., Bokel, M., Grimminger, W., Sawitzki, G. & Schwinger, G. (1982). *Justus Liebigs Ann. Chem.* pp. 87–98.

Lord, J. A. H., Waterfield, A. A., Hughes, J. & Kosterlitz, H. W. (1977). *Nature* (*London*), **267**, 495–499.

Main, P., Fiske, S. J., Hull, S. E., Lessinger, L., Germain, G., Declercq, J.-P. & Woolfson, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

Marquez, C., Rabanal, R. M., Valverde, S., Eguren, L., Perales, A. & Fayos, J. (1980). *Tetrahedron Lett.* **21**, 5039–5042.

Martin, W. R., Eades, C. G., Thompson, J. A., Huppler, R. E. & Gilbert, P. E. (1976). *J. Pharmacol. Exp. Ther.* **197**, 517–532.

Martinez-Ripoll, M., Fayos, J., Rodriguez, B., Garcia-Alvarez, M. C., Savona, G., Piozzi, F. P., Paternostro, M. & Hanson, J. R. (1981). *J. Chem. Soc. Perkin Trans* 1, pp. 1186–1190.

Mata, F., Martin, M. C. & Sørensen, G. O. (1978). *J. Mol. Struct.* **48**, 157–163.

Merz, H., Langbein, A., Stockhaus, K., Walther, G. & Wick, H. (1974). In *Narcotic Antagonists. Advances in Biochemical Psychopharmacology*, Vol. 8, edited by M. C. Braude, L. S. Harris, E. L. May, J. P. Smith & J. E. Villarreal, pp. 91–107. New York: Raven Press.

North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.

Nyburg, S. C. (1974). *Acta Cryst.* B**30**, 251–253.

Peeters, O. M., De Ranter, C. J. & Blaton, N. M. (1982). *Acta Cryst.* B**38**, 3055–3059.

Pople, J. A. & Segal, G. A. (1966). *J. Chem. Phys.* **44**, 3289–3296.

Portoghese, P. S., Lipkowski, A. W. & Takemori, A. E. (1987). *Life Sci.* **40**, 1287–1292.

Stewart, J. M., Machin, P. A., Dickinson, C., Ammon, H. L., Heck, H. & Flack, H. (1976). The *XRAY76* system. Tech. Rep. TR-446. Computer Science Center, Univ. of Maryland, College Park, Maryland, USA.

Stewart, R. F., Davidson, E. R. & Simpson, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

Taylor, R. & Kennard, O. (1983). *Acta Cryst.* B**39**, 517–525.

Verlinde, C. L. (1988). *κ-Opioids in the 6,7-Benzomorphan Series: X-ray Crystallography, Conformational Analysis and Pharmacophore Modelling.* Doctoral Dissertation, Univ. of Leuven, Belgium.

Verlinde, C. L., Blaton, N. M., De Ranter, C. J. & Peeters, O. M. (1984). *Acta Cryst.* C**40**, 1759–1761.

Verlinde, C. L., Blaton, N. M., De Ranter, C. J. & Peeters, O. M. (1989). *Acta Cryst.* C**45**, 799–803.

Verlinde, C. L. & De Ranter, C. J. (1989). *J. Mol. Struct.* (*Theochem*), **187**, 161–167.