Acta Cryst. (1992). C**48**, 1627–1630

Crystal Structure of a Calcium Channel Antagonist: 4-(2,4-Dichlorophenyl)-*N*,*N*,*N*′,*N*′-tetraethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxamide

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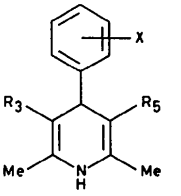
(*Received* 24 *September* 1991; *accepted* 31 *January* 1992)

Abstract. $C_{23}H_{31}Cl_2N_3O_2.H_2O$, $M_r = 470.4$, monoclinic, $P2_1/n$, $a = 14.686$ (5), $b = 7.590$ (2), $c = 23.578$ (6) Å, $\beta = 107.47$ (1)°, $V = 2507$ (1) Å^3, $Z = 4$, $D_m = 1.213$ (2) (flotation), $D_x = 1.25$ g cm^{-3}, λ(Mo $K\alpha$) = 0.71069 Å, $\mu = 2.84$ cm^{-1}, $F(000) = 1000$, $T = 293$ K, $R = 0.051$, $wR = 0.055$ for 3814 observed [$I \geq 3\sigma(I)$] reflections. The structure of the title compound is similar to that of the reported analogous structures. The dihydropyridine ring is in a shallow boat conformation. Deviation from planarity in the dihydropyridine ring (defined as the sum of the numeric values of the six intra-ring torsion angles) is 75.09 (2)°. The 2,4-dichlorophenyl ring is normal to the dihydropyridine ring. The presence of the water molecule has completely changed the hydrogen-bonding pattern from that observed in all other analogous structures.

Introduction. Many derivatives of 1,4-dihydropyridine (DHP) (Table 1) exhibit high affinity for calcium channel receptors and may act as agonists or antagonists, depending on the nature of the derivative, the physiological state of the channel and, in some cases, the side of the membrane containing the channel receptor to which the compound is added (Kokubun & Reuter, 1984). Triggle and co-workers (Triggle, Shefter & Triggle, 1980; Fossheim, Svarteng, Mostagd, Romming, Shefter & Triggle, 1982; Langs & Triggle, 1985) have determined crystal structures of some DHPs and identified some important structural requirements for biological activity (Janis & Triggle, 1983) which include: (*a*) structural integrity of the DHP ring, (*b*) no substitution on the N atom at position 1, (*c*) the 2,6 position to have dialkyl substitutents and the 3,5 positions to have diester substituents, and (*d*) an aryl substitutent, preferably a substituted phenyl group, at the 4 position of the DHP ring.

In light of the above findings, it was considered interesting to study the crystal structure of the title compound (23), which is expected to be as active as nifedipine (9) even though it has amide substituents at C(3) and C(5) instead of esters which are characteristic of nifedipine and its related compounds. Also, the 4-phenyl ring has chloro substitution at *ortho* and *para* positions, *para* substitution alone being reported to have a detrimental effect.

Table 1. *Crystallographically studied derivatives of 1,4-dihydropyridine*



	R_3	R_5	X
(1)	$COOCH_3$	$COOCH_3$	H
(2)	$COOCH_3$	$COOCH_3$	3-NO_2
(3)	$COOCH_3$	$COOCH_3$	4-NO_2
(4)	$COOCH_3$	$COOCH_3$	2,4-$(NO_2)_2$
(5)	$COOCH_3$	$COOCH_3$	4-CH_3
(6)	$COOCH_3$	$COOCH_3$	3-CH_3
(7)	$COOCH_3$	$COOCH_3$	2,3,4,5,6-$(F)_6$
(8)	$COOCH_3$	$COOCH_3$	4-$N(CH_3)_2$
(9)	$COOCH_3$	$COOCH_3$	2-NO_2 (Ni fedipine)
(10)	$COOCH_3$	$COOCH_3$	3-CN
(11)	$COOC_2H_5$	$COOC_2H_5$	H
(12)*	$COOC_4H_7NCH_2C_6H_5$	$COOCH_3$	2-NO_2
(13)*	$COOC_4H_7NCH_2C_6H_5$	$COOCH_3$	2-NO_2
(14)	$COOCH(CH_3)_2$	$COO(CH_2)_2OCH_3$	3-NO_2 (Ni modipine)
(15)	$COOCH_3$	$COOCH_2CH_3$	2,3-CH_2O_2 (Oxodipine)
(16)	$COOCH_2CH_3$	$COOCH_3$	2,3-$(Cl)_2$ (Felodipine)
(17)	$COOCH_3$	$COOCH_3$	2-$CH(F)_3$
(18)	NO_2	$COOCH_3$	2-$CH(F)_3$
(19)	$CO_2C_2H_5$	$CO_2C_2H_5$	$CH_3C_3ONC_6H_5$
(20)	$COOCH_3$	$COOCH_3$	C_5H_4N
(21)	$COCH_3$	$COCH_3$	C_5H_4N
(22)	$COOCH_2CH_3$	$COOCH_2CH_3$	-
(23)	$CON(CH_2CH_3)_2$	$CON(CH_2CH_2)_2$	2,4$(Cl)_2$

References: (1)–(6) Fossheim, Svarteng, Mostagd, Romming, Shefter & Triggle (1982); (7)–(10) Triggle, Shefter & Triggle (1980); (11) Hempel & Gupta (1978); (12)–(13) Tamazwa, Arima, Kojima, Isomura, Okada, Fujita, Furuya, Takenaka, Inagaki & Terai (1986); (14) Wang, Herbette & Rhodes (1989); (15) Fonseca, Martínez-Carrera & García-Blanco (1986); (16) Fossheim (1986); (17) Fossheim (1985); (18) Langs & Triggle (1985); (19) Schauer, Anderson, Natale & Quincy (1986); (20) Krajewski, Urbanczyk-Lipkowska & Gluzinski (1977*a*); (21) Krajewski, Urbanczyk-Lipkowska & Gluzinski (1977*b*); (22) Fortier, Fraser, Moore, Park, Whitney & Marks (1985); (23) present work.

* HCl and HBr salts.

Experimental. The title compound was provided by Dr Y. S. Sadanandam and Dr (Mrs) Meera Shetty, Organic Chemistry Division, IICT Hyderabad. A

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crystal (0.25 × 0.20 × 0.15 mm) was obtained by recrystallization from aqueous *N,N*-dimethylacetamide, and used for data collection on a Siemens *R*3*m* diffractometer with graphite-monochromated Mo $K\alpha$ radiation. Cell constants were determined from least-squares fitting to the setting angles for 25 reflections ($2\theta_{av} = 22°$). Data were collected for $3.5 \le 2\theta \le 48°$, $-15 \le h \le 15$, $0 \le k \le 8$, $0 \le l \le 25$, using $\theta/2\theta$ scans. Two check reflections monitored periodically showed no significant variation. Data were corrected for Lorentz and polarization effects but not for absorption. Of 4219 measured reflections, 3815 were observed [$I \ge 3\sigma(I)$] and used in further calculations. The structure was solved by direct methods, all non-H atoms being refined anisotropically. Positions of all H atoms were obtained from a $\Delta\rho$ map and were included in the final cycles of refinement with isotropic thermal parameters and allowed to ride on their parent atoms. Full-matrix weighted $\{w = [\sigma^2(F) + gF^2]^{-1}$, $g = 9.5 \times 10^{-4}$ (refined)} least-squares refinement on F yielded $R = 0.051$ and $wR = 0.057$, $S = 1.48$ at convergence. Maximum shift/e.s.d. was 0.01 over the last cycle, with the largest peak in the final difference Fourier synthesis at 0.32 e Å^{-3} and the minimum at -0.27 e Å^{-3}. Atomic scattering factors used were those in *SHELXTL-Plus* (Sheldrick, 1990). Software for the diffractometer was provided with the Siemens *R*3*m* four-circle diffractometer, *SHELXTL-Plus* was used for structure solution, refinement and graphical representation. Geometric calculations and crystal packing were computed using the program *PARST* (Nardelli, 1983).

Discussion. The structure and conformation of the title compound together with the numbering scheme are shown in Fig. 1. Final atomic coordinates and equivalent isotropic thermal parameters for all non-H atoms are given in Table 2,* while bond lengths and angles are listed in Table 3.

Bond distances and angles do not differ significantly from the respective values found in nifedipine and its analogues, all of which possess varying degrees of biological activity (Triggle, Shefter & Triggle, 1980; Fossheim, Svarteng, Mostagd, Romming, Shefter & Triggle, 1982; Wang, Herbette & Rhodes, 1989; Fossheim, 1986). Several crystallographic studies have correlated the pharmacological effects with the degree of puckering of DHP rings (Triggle, Shefter & Triggle, 1980; Fossheim, Svarteng, Mostagd, Romming, Shefter & Triggle, 1982). In the title compound also, the 1,4-DHP ring adopts a shallow boat configuration {ΔC_s[C(4)] = 0.21 (Duax, Weeks & Rohrer, 1976)} with N(1) and C(4) −0.150 (2) and −0.2.44 (2) Å respectively from the four-atom plane through C(2), C(3), C(5) and C(6). The degree of puckering of the 1,4-DHP ring can be gauged from the values of the torsion angles about the intra-ring bonds (Table 4), and the ring distortion is reflected in the magnitude of the torsion angles about the ring bonds emerging from the atoms N(1) and C(4). The torsion angles about the C(4) ring bonds are in all cases greater than those about the N(1) bonds (Table 4), indicating that the puckering is always greater at C(4).

Table 2. *Fractional coordinates and equivalent isotropic thermal parameters* (Å^2 × 10^3) *with e.s.d.'s in parentheses*

$U_{eq} = (1/3)\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
Cl(1)	0.2474 (1)	−0.5582 (1)	0.6726 (1)	90 (1)
Cl(2)	0.0988 (1)	0.0835 (1)	0.6748 (1)	83 (1)
N(1)	0.4374 (1)	−0.2472 (2)	0.5046 (1)	44 (1)
C(2)	0.3548 (2)	−0.3430 (3)	0.4788 (1)	41 (1)
C(21)	0.3267 (2)	−0.3465 (3)	0.4123 (1)	55 (1)
C(3)	0.3097 (1)	−0.4266 (3)	0.5130 (1)	41 (1)
C(31)	0.2343 (2)	−0.5614 (3)	0.4892 (1)	46 (1)
O(32)	0.2506 (1)	−0.7169 (2)	0.5063 (1)	60 (1)
N(33)	0.1504 (1)	−0.5169 (3)	0.4491 (1)	58 (1)
C(34)	0.1167 (2)	−0.3346 (4)	0.4371 (1)	67 (1)
C(35)	0.0445 (2)	−0.2832 (5)	0.4689 (1)	88 (1)
C(36)	0.0856 (2)	−0.6585 (5)	0.4201 (1)	79 (1)
C(37)	0.1160 (3)	−0.7465 (5)	0.3720 (1)	111 (2)
C(4)	0.3437 (1)	−0.4105 (4)	0.5804 (1)	40 (1)
C(5)	0.4468 (2)	−0.3472 (3)	0.6013 (1)	40 (1)
C(51)	0.5010 (1)	−0.4046 (3)	0.6626 (1)	45 (1)
O(52)	0.5111 (1)	−0.5647 (2)	0.6734 (1)	60 (1)
N(53)	0.5393 (1)	−0.2835 (3)	0.7050 (1)	51 (1)
C(54)	0.5196 (2)	−0.0931 (3)	0.6992 (1)	56 (1)
C(55)	0.4530 (2)	−0.0311 (4)	0.7331 (1)	72 (1)
C(56)	0.6014 (2)	−0.3469 (5)	0.7621 (1)	68 (1)
C(57)	0.7000 (2)	−0.3921 (5)	0.7604 (1)	90 (1)
C(6)	0.4872 (1)	−0.2671 (3)	0.5645 (1)	41 (1)
C(61)	0.5877 (2)	−0.1975 (3)	0.5807 (1)	51 (1)
C(7)	0.2793 (1)	−0.2909 (3)	0.6034 (1)	39 (1)
C(8)	0.2634 (2)	−0.1168 (3)	0.5836 (1)	48 (1)
C(9)	0.2087 (2)	−0.0007 (3)	0.6045 (1)	54 (1)
C(10)	0.1673 (2)	−0.0585 (3)	0.6463 (1)	54 (1)
C(11)	0.1796 (2)	−0.2297 (3)	0.6670 (1)	54 (1)
C(12)	0.2351 (2)	−0.3430 (3)	0.6452 (1)	48 (1)
O(W)	0.5541 (1)	−0.1873 (2)	0.4233 (1)	59 (1)

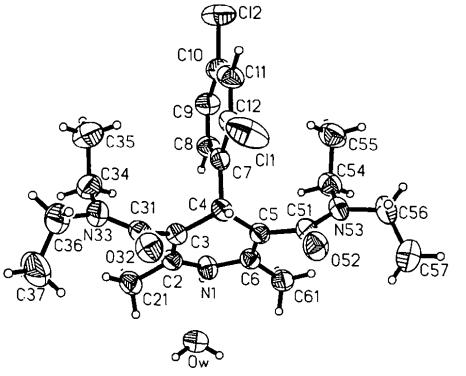


Fig. 1. The structure of the title compound. The ellipsoids are shown at 50% probability level.

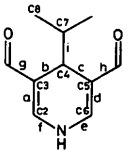
* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55117 (17 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: CR0394]

Table 3. *Bond lengths* (Å) *and bond angles* (°) *with e.s.d.'s in parentheses*

Cl(1)—C(12)	1.745 (2)	Cl(2)—C(10)	1.740 (3)
N(1)—C(2)	1.389 (3)	N(1)—C(6)	1.390 (2)
C(2)—C(21)	1.496 (3)	C(2)—C(3)	1.346 (3)
C(3)—C(31)	1.488 (3)	C(3)—C(4)	1.520 (3)
C(31)—O(32)	1.247 (3)	C(31)—N(33)	1.350 (3)
N(33)—C(34)	1.468 (4)	N(33)—C(36)	1.463 (4)
C(34)—C(35)	1.521 (5)	C(36)—C(37)	1.495 (5)
C(4)—C(5)	1.522 (3)	C(4)—C(7)	1.523 (3)
C(5)—C(51)	1.491 (3)	C(5)—C(6)	1.336 (3)
C(51)—O(52)	1.241 (3)	C(51)—N(53)	1.350 (3)
N(53)—C(54)	1.472 (3)	N(53)—C(56)	1.463 (3)
C(54)—C(55)	1.511 (5)	C(56)—C(57)	1.501 (5)
C(6)—C(61)	1.504 (3)	C(7)—C(8)	1.397 (3)
C(7)—C(12)	1.391 (4)	C(8)—C(9)	1.379 (3)
C(9)—C(10)	1.376 (4)	C(10)—C(11)	1.381 (3)
C(11)—C(12)	1.386 (3)		

C(2)—N(1)—C(6)	120.8 (2)	N(1)—C(2)—C(3)	120.4 (2)
N(1)—C(2)—C(21)	113.5 (2)	C(21)—C(2)—C(3)	126.1 (2)
C(2)—C(3)—C(4)	121.5 (2)	C(2)—C(3)—C(31)	122.8 (2)
C(31)—C(3)—C(4)	115.0 (2)	C(3)—C(31)—N(33)	120.7 (2)
C(3)—C(31)—O(32)	118.7 (2)	O(32)—C(31)—N(33)	120.6 (2)
C(31)—N(33)—C(36)	118.2 (2)	C(31)—N(33)—C(34)	123.7 (2)
C(34)—N(33)—C(36)	117.9 (2)	N(33)—C(34)—C(35)	113.1 (2)
N(33)—C(36)—C(37)	112.5 (3)	C(3)—C(4)—C(7)	112.1 (2)
C(3)—C(4)—C(5)	110.3 (2)	C(5)—C(4)—C(7)	111.1 (2)
C(4)—C(5)—C(6)	121.7 (2)	C(4)—C(5)—C(51)	114.4 (2)
C(51)—C(5)—C(6)	123.4 (2)	C(5)—C(51)—N(53)	120.1 (2)
C(5)—C(51)—O(52)	118.8 (2)	O(52)—C(51)—N(53)	121.1 (2)
C(51)—N(53)—C(56)	117.6 (2)	C(51)—N(53)—C(54)	125.0 (2)
C(54)—N(53)—C(56)	117.3 (2)	N(53)—C(54)—C(55)	113.4 (2)
N(53)—C(56)—C(57)	112.9 (2)	N(1)—C(6)—C(5)	120.6 (2)
C(5)—C(6)—C(61)	126.1 (2)	N(1)—C(6)—C(61)	113.3 (2)
C(4)—C(7)—C(12)	123.7 (2)	C(4)—C(7)—C(8)	120.3 (2)
C(8)—C(7)—C(12)	116.0 (2)	C(7)—C(8)—C(9)	122.8 (2)
C(8)—C(9)—C(10)	118.8 (2)	Cl(2)—C(10)—C(9)	120.6 (2)
C(9)—C(10)—C(11)	120.9 (2)	Cl(2)—C(10)—C(11)	118.4 (2)
C(10)—C(11)—C(12)	118.8 (2)	C(7)—C(12)—C(11)	122.6 (2)
Cl(1)—C(12)—C(11)	116.8 (2)	Cl(1)—C(12)—C(7)	120.6 (2)

Table 4. *Selected torsion angles* (°) *for* 1,4-*dihydropyridine derivatives*



	a	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*i*	*O*
(1)	10.6	−29.3	27.7	−6.7	−16.3	14.1	−177.7	4.1	−81.5	104.7
(2)	6.5	−24.1	24.4	−7.0	−14.2	14.4	−177.8	7.1	−57.8	90.6
(3)	6.6	−23.2	24.2	−8.6	−11.1	12.1	165.7	13.0	−39.5	85.8
(4)	9.2	−17.3	12.9	−0.4	−9.9	5.3	−174.2	5.5	−77.0	55.0
(5)	6.6	−23.3	23.9	−7.7	−12.4	13.0	157.8	15.9	−42.8	86.9
(6)	7.1	−25.1	25.3	−7.6	−14.2	14.4	173.5	11.4	−58.2	93.7
(7*A*)	3.1	−13.5	15.2	−6.2	−6.2	7.9	−9.4	13.3	−56.7	52.1
(7*B*)	4.8	−16.1	18.0	−8.4	−5.1	7.0	8.1	5.3	−62.8	59.4
(8)	10.5	−29.0	27.1	−5.6	−17.5	14.8	175.4	11.8	−90.1	104.5
(9)	10.6	−22.0	17.9	−2.9	−11.3	7.4	−169.9	9.1	−73.5	72.1
(10)	10.3	−31.1	29.4	−7.0	−18.3	16.4	174.2	4.3	−96.3	112.5
(11)	9.4	−32.8	33.4	−10.6	−17.5	18.1	169.3	2.0	−29.3	121.8
(12)	−10.0	−8.0	20.0	−20.0	5.0	11.0	−4.0	−11.0	51.0	74.0
(13)	−19.0	−7.3	30.2	−30.9	8.9	18.0	176.5	4.0	88.0	114.3
(14)	8.0	23.5	22.4	−6.0	−12.9	11.9	12.2	3.9	127.2	84.7
(15)	−3.5	15.9	−16.8	−5.4	9.5	−10.4	−164.2	−4.8	61.2	61.6
(16)	3.8	−14.2	15.5	−6.3	−6.2	7.6	2.0	−0.1	−61.4	53.6
(17)	4.2	−16.5	17.8	−6.9	−7.9	9.3	−174.7	4.0	−64.0	62.6
(18)	−7.5	12.6	−9.5	1.7	5.2	−2.3	–	169.9	65.4	38.8
(19)	−7.0	18.4	−17.6	5.3	8.9	−8.0	8.0	5.0	66.7	65.2
(20)	4.8	−20.8	22.1	−7.2	−12.0	13.2	−11.2	2.9	−64.4	80.1
(21)	3.4	−21.9	24.7	−8.9	−12.5	15.5	179.2	7.3	−66.4	86.9
(22)	−5.6	19.7	−20.5	7.2	9.7	10.5	7.6	−14.9	–	73.1
(23)	3.8	−19.3	19.2	−3.5	−14.8	14.6	113.9	−111.4	−57.4	75.1

g is C(4)—C(3)—C(31)—O(32), *h* is C(4)—C(5)—C(51)—O(52) and *i* is C(5)—C(4)—C(7)—C(12); *O* is the sum of the numeric values of the six intra-ring torsion angles (*a*–*f*). References are as given in Table 1.

Owing to the lack of comparable pharmacological data it is not known how well the title compound will fit the previously published regression line (Fossheim, Svarteng, Mostagd, Romming, Shefter & Triggle, 1982), relating 1,4-DHP ring puckering and the ability to inhibit contractile response in smooth muscle preparations. Deviations from planarity in the 1,4-DHP ring, defined as the sum of the numeric value of the six intra-ring torsion angles, range from 38.8 to 121.8° in the 1,4-DHP derivatives (Table 4). The corresponding value in the title compound is 75.1° and that in nifedipine is 72.1° (Triggle, Shefter & Triggle, 1980).

The orientation of the dichlorophenyl ring relative to the 1,4-DHP ring, characterized by the torsion angle C(3)—C(4)—C(7)—C(8), is −57.4 (3)°. Similar orientation of the phenyl ring is preferred in all the investigated phenyl-substituted derivatives (Table 4). It is probable that in this way the steric strain, which is imposed by the phenyl substitutent and the groups at the 3 and 5 positions, is minimized (Fossheim, 1986). The present conformation, where the 2,4-dichloro substitutents point away from the 1,4-DHP ring, has been found in the solid state as well as in solution for 2,3-dichloro substitutions (Fossheim, 1986; Berntsson & Carter, 1981).

The conformations of carbonyl groups at C(3) and C(5) of the 1,4-DHP ring observed in several 1,4-DHP derivatives are described by the torsion angles provided in Table 4, where it can be seen that the carbonyl group at position 5 is always in a synperiplanar (*sp*) conformation, while that at position 3 is in antiperiplanar (*ap*) or *sp* conformation. Interestingly in the title compound, though both the carbonyl groups are twisted in the same direction, these are neither in *sp* nor in *ap* orientation, but are synclinal (*sc*) to the respective ring double bonds [C(2)—C(3)—C(31)—O(32) = 113.9 (3), C(6)—C(5)—C(51)—O(52) = −111.4 (3)°]. This is the first report of this type of orientation in a 1,4-DHP analogue and may be attributed to the presence of the water molecule which forms hydrogen bonds with the above-mentioned carbonyl O atoms.

The molecular packing viewed down the *b* axis is shown in Fig. 2. It is worth noting here that the O atom O(*W*) of the water molecule has taken part in forming both an intramolecular hydrogen bond with N(1) [N(1)···O(*W*) = 2.965 (3) Å, N(1)—H···O(*W*) = 136.5 (2)°] and intermolecular bonds with O(32) and O(52) of the neighbouring molecule [O(*W*)···O(32) ($-x+1$, $-y-1$, $-z+1$) = 2.94 (2) Å, O(32)···H(1)O(*W*)—O(*W*) = 178.8 (2)°; O(*W*)···O(52) ($-x+1$, $-y-1$, $-z+1$) = 2.890 (2) Å, O(52)···H(2)O(*W*)—O(*W*) = 174.3 (2)°] thus acting as an acceptor as well as a donor, respectively. This pattern of hydrogen bonding is distinctly different from

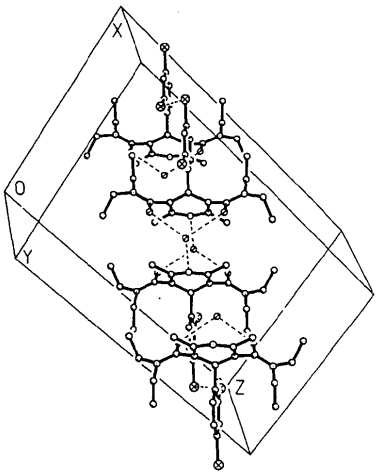


Fig. 2. The unit cell of the title compound looking down the *b* axis. C, O and N atoms are represented by crossed, dashed, and dotted circles respectively. Broken lines represent hydrogen bonds.

that in all the reported similar structures, where N1 is involved in forming an intermolecular hydrogen bond with the neighbouring carbonyl O atom(s). This shows that the presence of the water molecule in the title compound has totally altered its hydrogen bonding.

We thank Dr Y. S. Sadanandam and Dr (Mrs) Meera Shetty, Organic Chemistry Division, IICT, Hyderabad, for supplying the compound, and Miss Madhavi Bhogaraju for assistance.

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Structure of 5β,10α,10β-Triethylthebaine Hydrochloride

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(*Received* 18 *November* 1991; *accepted* 21 *January* 1992)

Abstract. (−)-6,7,8,14-Tetradehydro-4,5α-epoxy-5β,10α,10β-triethyl-3,6-dimethoxy-17-methylmorphinan hydrochloride, $C_{25}H_{34}NO_3^+.Cl^-$, M_r = 432.00, monoclinic, $P2_1$, a = 9.304 (2), b = 10.987 (2), c = 11.833 (2) Å, β = 109.65 (1)°, V = 1139.2 Å^3, Z = 2, D_x = 1.26 g cm^{-3}, λ(Mo $K\alpha$) = 0.71073 Å, μ = 1.986 cm^{-1}, $F(000)$ = 464, T = 293 K, R = 0.064 for 2966 observed reflections. The piperidine ring is in a chair conformation. In contrast to other morphinan derivatives, the *N*-methyl group is in an axial position. Apparently, the ethyl group at the 10β position forces the *N*-methyl group into this position.

Introduction. Compounds obtained through appropriate modification of the Diels–Alder adducts of the opium alkaloid (−)-thebaine (1) are well known for their high analgesic potency (Bentley, 1971). In order to investigate the influence of a 5β-alkyl substituent on the course of the Diels–Alder reaction and its influence on the analgesic potency of the adducts,

0108-2701/92/091630-04$06.00