Operation of Long-Range Substituent Effects in Rigid Opiates: Protonated and Unprotonated Oxymorphone

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Abstract □ The structure of protonated oxymorphone (amine salt) was determined by an X-ray crystallographic study. Significant differences were found with the previously determined structure of unprotonated oxymorphone (free base). Upon protonation on nitrogen, an elongation of the N—C bond occurred, accompanied by subtle changes in bond lengths and angles distant from the site of protonation. These changes in geometry are interpreted as a reflection of long-range substituent effects.

Keyphrases □ Oxymorphone—protonated and unprotonated, operation of long-range effects in rigid opiates □ Opiates—operation of long-range substituent effects, protonated and unprotonated oxymorphone □ Crystallography, X-ray—determination of structure of protonated and unprotonated oxymorphone

The existence of long-range substituent effects in morphines was proposed in 1979 (1). The anomalous variations in the pKa values of variously substituted morphines (2) were interpreted as the evidence for the existence of these effects. Additional evidence was sought to support the existence of these effects in morphines, including the X-ray evidence which is expected to show that a substituent introduced in the morphine molecule causes changes in bond lengths and angles, not only locally but throughout the entire molecule (1), and the voltammetric evidence, which is expected to demonstrate that the electron transfer from the lone electron pair of the nitrogen of morphines is affected by remote substitution. The data on voltammetric behavior of morphines recently published (3) may constitute the latter evidence[1]. The authors report here the X-ray evidence.

Early X-ray crystallographic studies of morphines were performed on morphine (4) and codeine (5) with the objective of determining their molecular structure and absolute stereochemistry, respectively. More recently, refined structures of morphine (6) and some of its pharmacologically important derivatives, such as naloxone (7) and oxymorphone (8), have been obtained. The latter studies responded to the needs of medicinal chemists who attempted to explain the pharmacological effects of morphine agonists and antagonists in terms of the geometric (9,10) and stereoelectronic (11–18) features of these molecules. After the publication of the refined structures of morphine (6) and naloxone (7), medicinal and quantum chemists started using these structures as an approximation of the structures of other morphine derivatives whose X-ray structures had not been determined (11–13, 15–17). Such approximations were widely used and did not stimulate additional X-ray work in the morphine field.

The approximate geometries were derived from the known geometries using three assumptions: (*a*) The geometry of a morphine does not change upon protonation of nitrogen (12, 15). Thus, the X-ray structure of morphine amine salt was used in place of the structure of the corresponding free base (12). (*b*) In morphines that differ only in the substituent on nitrogen, the geometry of *N*-nor moieties is the same (12, 13, 15–17). For example, the geometry of the *N*-nor moiety of nalorphone was assumed to be the same as that of morphine (12); in the same way, the geometries of the *N*-nor moieties of oxymorphone (13, 16, 17), nalmexone, naltrexone, and nalbuphine (16, 17) were derived from the geometry of naloxone. (*c*) Introduction of the substituent at C-2 and at the phenolic and alcoholic oxygens of morphine does not change its basic geometry (11). Therefore, skeletal structures of 2-amino morphine, codeine, heroin, and 6-acetyl morphine were assumed to be the same (11).

Justification of assumption *a* seems to be difficult when considering the IR data of amines and their salts, which suggests longer N—C bonds in protonated amines (19–21). The validity of these assumptions is challenged by the existence of long-range substituent effects in morphines (1): the introduction of a substituent in a rigid molecule like morphine is likely to cause distortions of bond angles and torsional angles, not only locally, but throughout the entire molecule. The geometry changes caused by long-range substituent effects are typically very small. However, it has been demonstrated recently that even very small differences in geometry significantly influence the results of quantum chemical calculations of oxymorphone (18). These results suggest that the use of exact (X-ray) structures of morphines is preferred to the use of approximate (slightly inaccurate) structures for quantum chemical studies of morphines.

The objective of this study was to test experimentally

Table I—Crystal Data

Crystal Parameter	Experimental or Calculated Value of Parameter
Molecular formula	$C_{17}H_{19}NO_4 \cdot HCl \cdot H_2O \cdot C_2H_6O$
Molecular weight	401.89
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a	10.586 (4) Å
b	18.671 (5) Å
c	9.361 (3) Å
V_c [a]	1850.21 Å^3
Z [b]	4
D_c [c]	1.443 g cm^{-3}
D_o [d]	1.343 g cm^{-3}
$F(000)$ [e]	856
μ [f]	2.5 cm^{-1}
λ(molybdenum K_α) [g]	0.71069 Å

[a] Calculated volume of the unit cell. [b] Number of asymmetric units in the cell. [c] Calculated density. [d] Observed density. [e] $F(000)$ is equal to the total number of electrons in the cell. [f] Linear absorption coefficients. [g] X-ray wavelength of molybdenum K_α line.

[1] Presented at the International Conference on Conformational Analysis, Durham, N.H., June 1981.

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Table II—Positional Parameters × 10^4 [a]

Atom[b]	x	y	z	B_{equiv}[c]
C1	5274 (4)	1407 (2)	7072 (4)	3.54 (18)
C2	5009 (4)	1048 (2)	5854 (5)	3.60 (18)
C3	4430 (4)	1377 (2)	4740 (4)	3.28 (16)
C4	4090 (4)	2080 (2)	4910 (4)	3.03 (16)
C5	3886 (4)	3235 (2)	4427 (4)	3.27 (18)
C6	5191 (4)	3421 (2)	3869 (4)	3.55 (19)
C7	5934 (4)	3948 (2)	4691 (5)	3.88 (18)
C8	6045 (4)	3699 (2)	6192 (5)	3.68 (19)
C9	4809 (4)	3345 (2)	8339 (4)	3.00 (17)
C10	5304 (4)	2580 (2)	8439 (4)	3.51 (18)
C11	4956 (4)	2120 (2)	7230 (4)	3.13 (17)
C12	4336 (4)	2422 (2)	6143 (4)	2.89 (16)
C13	3862 (4)	3186 (2)	6024 (4)	2.83 (16)
C14	4769 (4)	3659 (2)	6862 (4)	2.83 (17)
C15	2529 (4)	3236 (2)	6617 (4)	3.38 (18)
C16	2499 (4)	3042 (2)	8152 (4)	3.77 (19)
C17	3439 (5)	3261 (2)	10464 (5)	4.45 (21)
N1	3500 (3)	3432 (2)	8944 (3)	3.12 (14)
O1	4221 (3)	1046 (2)	3488 (3)	4.15 (14)
O2	3559 (3)	2529 (1)	3936 (3)	3.39 (12)
O3	5613 (3)	3128 (2)	2857 (3)	4.76 (15)
O4	4284 (3)	4355 (1)	7096 (3)	3.29 (12)
CL1	2013 (1)	4846 (1)	9700 (1)	4.62 (5)
OW1	713 (3)	5075 (2)	6825 (4)	4.91 (15)
OS1	3127 (4)	1514 (2)	896 (4)	6.12 (18)
CS1	3303 (7)	841 (3)	336 (7)	6.92 (32)
CS2	2526 (7)	731 (4)	−886 (8)	8.24 (38)

[a] Numbers in parentheses are the estimated standard deviations (*SD*) of the last digits. [b] Atom labeling is shown in Fig. 1. $S = CH_3CH_2OH$. $W = H_2O$. [c] B_{equiv} is defined in Ref. 27.

Table III—Anisotropic Thermal Parameters × 10^3 [a,b]

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C1	53 (3)	38 (2)	44 (2)	4 (2)	−2 (2)	4 (2)
C2	46 (3)	37 (2)	54 (2)	5 (2)	2 (2)	1 (2)
C3	43 (2)	36 (2)	46 (2)	−3 (2)	5 (2)	−6 (2)
C4	33 (2)	42 (2)	40 (2)	0 (2)	0 (2)	0 (2)
C5	51 (3)	37 (2)	36 (2)	8 (2)	−8 (2)	−2 (2)
C6	51 (3)	42 (2)	43 (2)	15 (2)	1 (2)	11 (2)
C7	47 (3)	46 (2)	54 (2)	−2 (2)	6 (2)	8 (2)
C8	47 (3)	42 (2)	51 (2)	−4 (2)	−2 (2)	0 (2)
C9	39 (3)	35 (2)	40 (2)	1 (2)	−6 (2)	−1 (2)
C10	51 (3)	42 (2)	41 (2)	8 (2)	−9 (2)	2 (2)
C11	40 (2)	39 (2)	40 (2)	5 (2)	2 (2)	2 (2)
C12	39 (2)	29 (2)	41 (2)	3 (2)	3 (2)	0 (2)
C13	35 (2)	33 (2)	40 (2)	2 (2)	−3 (2)	0 (2)
C14	34 (2)	34 (2)	40 (2)	0 (2)	−2 (2)	−1 (2)
C15	34 (3)	44 (2)	50 (2)	4 (2)	−5 (2)	−1 (2)
C16	50 (3)	48 (2)	45 (2)	−3 (2)	4 (2)	−5 (2)
C17	67 (3)	57 (3)	46 (2)	2 (2)	0 (2)	7 (2)
N1	46 (2)	35 (2)	37 (2)	−2 (2)	1 (2)	0 (1)
O1	60 (2)	49 (2)	49 (2)	6 (2)	−8 (2)	−14 (1)
O2	49 (2)	38 (1)	42 (1)	5 (1)	−9 (1)	−2 (1)
O3	71 (2)	61 (2)	48 (2)	11 (2)	16 (2)	−1 (2)
O4	51 (2)	31 (1)	43 (1)	4 (1)	−3 (1)	1 (1)
CL1	63 (1)	60 (1)	52 (1)	18 (1)	−1 (1)	−14 (1)
OW1	66 (2)	59 (2)	61 (2)	−3 (2)	−3 (2)	−8 (2)
OS1	109 (3)	55 (2)	68 (2)	20 (2)	−9 (2)	0 (2)
CS1	116 (5)	68 (3)	79 (4)	26 (4)	−7 (4)	−6 (3)
CS2	114 (6)	98 (5)	101 (4)	23 (4)	−7 (5)	−28 (4)

[a] The anisotropic temperature factor has the form: $\exp -2\pi(U_{11}h^2a^{*2} + \ldots + 2U_{12}hka^*b^* + \ldots)$. [b] Numbers in parentheses are the estimated *SD* of the last digit.

the validity of assumption *a*: to establish, by an X-ray crystallographic study, whether protonation of nitrogens influences the geometry of morphines. The results of this study would also test the validity of the long-range substituent concept in morphines. Since the X-ray structure of an unprotonated morphine derivative, oxymorphone, has already been reported (8), the protonated oxymorphone (amine salt) was chosen as the subject of the X-ray structure determination.

EXPERIMENTAL

A single crystal of oxymorphone hydrochloride[2] (4,5α-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one hydrochloride), suitable for X-ray analysis, was grown from 95% ethanol after slow evaporation. The size of the crystal used for data collection measured ~0.25 × 0.3 × 0.4 mm. The crystals were clear, colorless prisms.

Weissenberg and precision photographs showed the crystal to be orthorhombic and have systematic extinctions HOO:H=2*n* OKO:K=2*n* OOL:L=2*n* indicating space group $P2_12_12_1$ (number 19). The density was measured by flotation in a mixture of toluene and bromotrichloromethane. The crystal was mounted on a $P2_1$ automatic diffractometer[3] equipped with an incident beam graphite-crystal monochromator. All measurements were made at 25(±2)° using molybdenum K_α radiation. The unit-cell constants and the orientation matrix to be used in data collection were obtained from a least-square refinement of 15 centered general reflections. Crystal data are listed in Table I.

Data Collection—The diffraction data were collected by the θ–2θ scan technique at room temperature with graphite monochromated molybdenum K_α radiation. The scan rate varied from 2 to 10°/min, dependent on the intensity of diffraction maxima (scan width was based on $\Delta\theta = 1.00 + 0.15 \tan\theta$). A decay of ~50% was noted for the three standard reflections ($\bar{4},\bar{2},2;\bar{2},1,2;0,\bar{1},4$) monitored for every 50 reflections over the period of collection.

A total of 2172 reflections was collected, comprising the quadrant of reciprocal space where *h*, *k*, and *l* are each nonnegative. Of the 2172 reflections collected, 1710 were classified as observed for $|F_o|^2 > 3\sigma(|F_o|^2)$, where $|F_o|$ is the observed structure factor amplitude corrected for Lorentz and polarization effects.

Structure Determination and Refinement—The diffractometer data were reduced and corrected for decay using a program from the CRYSP programs (22). The structure was solved by direct methods using the MULTAN 74 program (23). The probable phase set, as determined by statistics and based on three origin and three starting reflections, produced an *E*-map containing 19 of the 27 heavy atoms in the structure. The remaining atoms were located in difference Fourier maps using the program set CRYM (24).

Full matrix least-square refinement on the heavy atom positions minimizing the quantity $\Sigma\omega(F_o^2 - F_c^2)^2$, where $\omega = 1/\sigma^2(F_o^2)$, was followed by the calculation of all hydrogen atom positions except for the hydroxyl hydrogen atoms and methyl hydrogen atoms which were located in difference Fourier maps. At this point, two cycles of isotropic full matrix least-squares resulted in an *R* value, $[= \Sigma(||F_o| - |F_c||)/\Sigma|F_o|]$

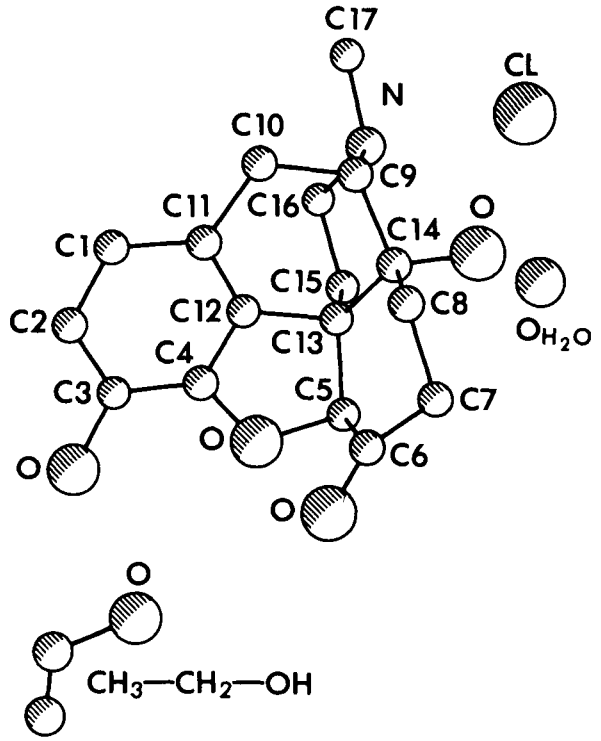

Figure 1—*Oxymorphone·HCl·H_2O·C_2H_5OH*

[2] Endo Laboratories, Inc.
[3] Syntex.

Table IV—Positional Parameters × 10^3 and Isotropic Thermal Parameters for the Hydrogen Atoms

Atom	x	y	z	B_{iso}
H1	573	117	780	4.54
H2	518	54	581	4.60
H5	333	359	409	4.27
H7A	554	440	467	4.88
H7B	677	399	430	4.88
H8A	654	402	672	4.68
H8B	641	323	620	4.68
H9	554	358	885	4.00
H10A	494	238	927	4.51
H10B	618	260	851	4.51
H15A	201	291	611	4.38
H15B	223	371	651	4.38
H16A	262	254	825	4.77
H16B	169	317	853	4.77
H17A	420	349	1074	5.45
H17B	262	345	1071	5.45
H17C	394	287	1068	5.45
NH	331	394	876	4.12
HO4	385	451	639	4.29
OWHA	91	499	761	5.91
OWHB	121	489	663	5.91
HS1A	314	49	102	7.92
HS1B	420	80	5	7.92
HS2A	268	28	−131	9.24
HS2B	274	110	−161	9.24
HS2C	168	79	−64	9.24
HOS1	385	159	127	7.12
HO1	464	71	342	5.15

0.112. Further full matrix least-square analysis of 245 variables—coordinates and anisotropic temperature factors for 27 heavy atoms, a secondary extinction parameter (25) and a scale factor—led to a final R value of 0.068 and a goodness-of-fit [$= \Sigma\omega(F_o^2 - F_c^2)^2/M - S)^{1/2}$] for $M = 2172$ reflections and $S = 245$ parameters of 9.7. (In this analysis the coordinates and isotropic temperature factors for 27 hydrogen atoms were held constant). The ωR value [$= [\Sigma\omega(F_o^2 - F_c^2)^2/\Sigma\omega F_o^4]^{1/2}$] was 0.117 and the R factor for the 3σ data set was 0.056. The estimated standard deviations were computed from the inverse matrix of the last full matrix, least-squares cycle. All shifts in parameters were less than their estimated standard deviations in the final refinement cycle. The scattering factors and anomalous dispersion terms for chlorine were taken from a published source[4], the scattering factors for hydrogen were taken from Stewart *et al.* (26).

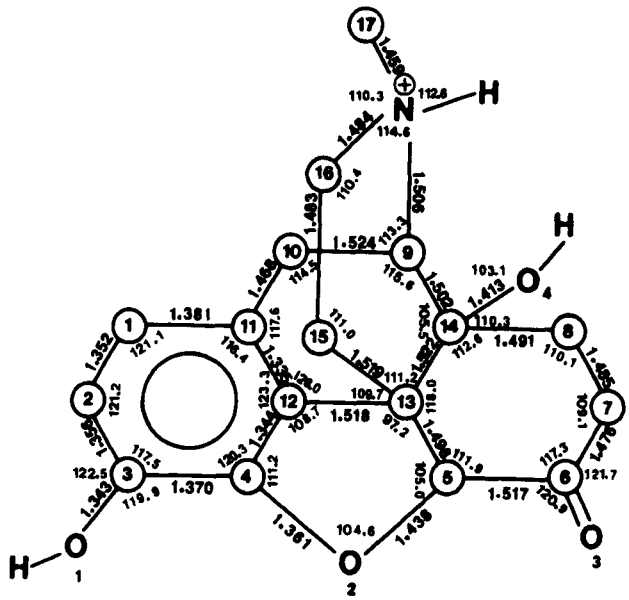

Figure 2—*Bond lengths and bond angles in protonated oxymorphone (oxymorphone·HCl·H_2O·C_2H_5OH). The estimated standard deviations are 0.005–0.006 Å for C—C, C—O, and C—N bonds, and 0.3–0.4° for C—C—(C,O,N) angles.*

[4] The International Tables for X-ray Crystallography (1962).

Table V—Interatomic Distances [Å] [a]

Bond	a [b]	b [c]	a − b	σ	(a−b)/σ [d]
C1—C2	1.352 (6)	1.406 (5)	−0.054	0.008	6.9
C2—C3	1.356 (6)	1.378 (5)	−0.022	0.008	2.8
C3—C4	1.370 (5)	1.376 (4)	−0.006	0.006	0.9
C4—C12	1.344 (5)	1.380 (4)	−0.036	0.006	5.6
C11—C12	1.335 (5)	1.375 (5)	−0.040	0.007	5.6
C1—C11	1.381 (6)	1.381 (4)	0		
C12—C13	1.518 (5)	1.493 (4)	0.025	0.006	3.9
C13—C5	1.498 (5)	1.547 (4)	−0.049	0.006	7.7
C5—C6	1.517 (6)	1.522 (4)	−0.005	0.007	0.7
C4—O2	1.361 (4)	1.392 (4)	−0.031	0.006	5.5
C5—O2	1.438 (5)	1.475 (3)	−0.037	0.006	6.4
C3—O1	1.343 (5)	1.375 (3)	−0.032	0.006	5.5
C6—C7	1.476 (6)	1.501 (4)	−0.025	0.007	3.5
C7—C8	1.485 (6)	1.522 (5)	−0.037	0.008	4.7
C8—C14	1.491 (6)	1.515 (4)	−0.024	0.007	3.3
C14—C13	1.522 (5)	1.548 (4)	−0.026	0.006	4.1
C14—C9	1.502 (5)	1.548 (5)	−0.046	0.007	6.5
C9—C10	1.524 (5)	1.545 (5)	−0.021	0.007	2.9
C10—C11	1.468 (5)	1.520 (5)	−0.052	0.007	7.3
C13—C15	1.519 (6)	1.539 (4)	−0.020	0.007	2.8
C15—C16	1.483 (6)	1.520 (4)	−0.037	0.007	5.1
C16—N	1.484 (5)	1.467 (4)	0.017	0.006	2.6
N—C17	1.459 (5)	1.464 (4)	−0.005	0.006	0.8
C14—O4	1.413 (4)	1.427 (4)	−0.014	0.006	2.5
C6—O3	1.182 (5)	1.221 (4)	−0.039	0.006	6.1
N—C9	1.506 (5)	1.474 (4)	0.032	0.006	5.0

[a] Numbers in parentheses are the estimated *SD* of the last digit. [b] Oxymorphone·HCl·H_2O·C_2H_5OH. [c] Oxymorphone·H_2O (8). [d] If $(a - b)/\sigma \geq 5$, the difference in bond lengths, $a - b$, is significant.

Table VI—Bond Angles [a]

Angle	a [b]	b [c]	a − b	σ	(a − b) /σ [d]
C4—C12—C13	108.7 (3)	109.2 (3)	−0.5	0.4	1.2
C4—C12—C11	123.3 (4)	122.9 (3)	0.4	0.5	0.8
C4—C3—C2	117.5 (4)	117.1 (3)	0.4	0.5	0.8
C4—C3—O1	119.9 (4)	119.3 (3)	0.6	0.5	0.8
C3—C2—C1	121.2 (4)	121.5 (3)	−0.3	0.5	0.6
C3—C4—C12	120.3 (4)	121.0 (3)	−0.7	0.5	1.4
O1—C3—C2	122.5 (3)	123.6 (3)	−1.1	0.4	2.6
C2—C1—C11	121.1 (4)	121.1 (2)	0		
C1—C11—C12	116.4 (4)	116.3 (3)	0.1	0.5	0.2
C1—C11—C10	125.8 (4)	126.6 (3)	−0.8	0.5	1.6
C11—C12—C13	128.0 (3)	127.9 (3)	0.1	0.4	0.2
C11—C10—C9	114.5 (3)	114.4 (3)	0.1	0.4	0.2
C12—C4—O2	111.2 (3)	111.6 (3)	−0.4	0.4	0.9
C12—C13—C15	109.7 (3)	109.3 (2)	0.4	0.4	1.1
C12—C13—C14	107.4 (3)	108.6 (3)	−1.2	0.4	2.9
C12—C11—C10	117.6 (4)	117.0 (3)	0.6	0.5	1.2
C12—C13—C5	97.2 (3)	98.3 (2)	−1.1	0.4	3.1
C10—C9—C14	115.6 (3)	114.2 (2)	1.4	0.4	3.9
C10—C9—N	113.3 (3)	116.0 (3)	−2.7	0.4	6.4
C9—C14—C13	105.5 (3)	105.5 (2)	0		
C9—N—C16	114.6 (3)	113.7 (2)	0.9	0.4	2.5
C9—N—C17	112.6 (3)	114.0 (3)	−1.4	0.4	4.1
C9—C14—C8	112.4 (3)	113.9 (3)	−1.5	0.4	3.6
C9—C14—O4	103.1 (3)	108.8 (2)	−5.7	0.4	15.8
C14—C13—C5	118.0 (3)	117.4 (2)	0.6	0.4	1.7
C14—C13—C15	111.2 (3)	109.5 (2)	1.7	0.4	4.7
C14—C8—C7	110.1 (4)	111.1 (3)	−1.0	0.5	2.0
O4—C14—C8	110.3 (3)	107.0 (3)	3.3	0.4	7.9
O4—C14—C13	112.5 (3)	110.7 (3)	1.8	0.4	4.3
C13—C14—C8	112.6 (3)	111.0 (2)	1.6	0.4	4.4
C13—C15—C16	111.0 (3)	111.3 (3)	−0.3	0.4	0.7
C13—C5—C6	111.9 (3)	113.7 (2)	−1.8	0.4	5.0
C13—C5—O2	105.0 (3)	104.5 (2)	0.5	0.4	1.4
C5—C6—C7	117.3 (4)	117.1 (2)	0.2	0.4	0.4
C5—O2—C4	104.6 (3)	104.0 (2)	0.6	0.4	1.7
C5—C6—O3	120.9 (4)	120.6 (3)	0.3	0.5	0.6
C5—C13—C15	112.1 (3)	112.9 (2)	−0.8	0.4	2.2
C6—C7—C8	109.1 (3)	111.0 (3)	−1.9	0.4	4.5
C6—C5—O2	108.6 (3)	108.6 (2)	0		
O3—C6—C7	121.7 (3)	122.3 (3)	−0.6	0.4	1.4
C15—C16—N	110.4 (3)	110.4 (2)	0		
C14—C9—N	106.1 (3)	105.5 (3)	0.6	0.4	1.4
C16—N—C17	110.3 (3)	109.7 (3)	0.6	0.4	1.4

[a] Numbers in parentheses are the estimated *SD* of the last digit. [b] Oxymorphone ·HCl·H_2O·C_2H_5OH. [c] Oxymorphone ·H_2O (8). [d] If $(a - b)/\sigma \geq 5$, the difference in bond angles, $a - b$, is significant.

Table VII—Torsional Angles [a]

Torsional Angle	a [b]	b [c]	a − b	σ	a − b /σ [d]
Ring A					
C1—C2—C3—C4	1.9 (6)	0.6 (5)	1.3	0.8	1.6
C2—C3—C4—C12	0.3 (6)	−3.6 (4)	−3.9	0.7	5.6
C3—C4—C12—C11	2.8 (6)	6.0 (5)	−3.2	0.8	4.0
C4—C12—C11—C1	−4.1 (6)	−4.9 (5)	0.8	0.8	1.0
C12—C11—C1—C2	2.4 (6)	1.8 (4)	0.6	0.7	0.9
C11—C1—C2—C3	0.5 (6)	0.3 (5)	0.2	0.8	0.3
Ring B					
C4—O2—C5—C13	−35.1 (4)	−32.7 (3)	−2.4	0.5	4.8
O2—C5—C13—C12	34.3 (4)	33.8 (3)	0.5	0.5	1.0
C5—C13—C12—C14	−23.2 (4)	−23.8 (3)	0.6	0.5	1.2
C13—C12—C4—O2	3.0 (4)	4.8 (3)	−1.8	0.5	3.6
C12—C4—O2—C5	20.0 (4)	18.0 (3)	2.0	0.5	4.0
Ring C					
C9—C10—C11—C12	4.7 (5)	9.1 (4)	−4.4	0.6	7.3
C10—C11—C12—C13	−4.2 (6)	−8.5 (5)	4.3	0.8	5.4
C11—C12—C13—C14	31.4 (5)	34.0 (4)	−2.6	0.6	4.3
C12—C13—C14—C9	−55.3 (4)	−56.2 (3)	0.9	0.5	1.8
C13—C14—C9—C11	61.9 (4)	61.9 (3)	0		
C14—C9—C10—C11	−35.6 (5)	−37.8 (4)	2.2	0.6	3.7
Ring D					
C5—C6—C7—C8	55.6 (5)	50.1 (4)	5.5	0.6	9.2
C6—C7—C8—C14	−62.6 (4)	−60.6 (4)	−2.0	0.6	3.3
C7—C8—C14—C13	55.8 (4)	56.5 (4)	−0.7	0.6	1.2
C8—C14—C13—C5	−40.8 (5)	−42.7 (4)	1.9	0.6	3.2
C14—C13—C5—C6	30.8 (5)	31.5 (4)	−0.7	0.6	1.2
C13—C5—C6—C7	−38.9 (5)	−35.2 (4)	−3.7	0.6	6.2
Ring E					
C9—C14—C13—C15	64.8 (4)	63.0 (3)	1.8	0.5	3.6
C14—C13—C15—C16	−57.0 (4)	−55.0 (3)	−2.0	0.5	4.0
C13—C15—C16—N	48.8 (4)	50.0 (3)	−1.2	0.5	2.4
C15—C16—N—C9	−53.8 (4)	−57.6 (3)	3.8	0.5	7.6
C16—N—C9—C14	62.5 (4)	66.4 (3)	−3.9	0.5	7.8
N—C9—C14—C13	−64.5 (4)	−66.7 (3)	2.2	0.5	4.4

[a] Numbers in parentheses are the estimated *SD* of the last digit. [b] Oxymorphone ·HCl·H_2O·C_2H_5OH. [c] Oxymorphone ·H_2O (8). [d] If (a − b)/σ ≥ 5, the difference in torsional angles, a − b, is significant.

Detailed information about the crystal structure of oxymorphone·HCl·H_2O·C_2H_5OH is given in Tables I–VII: crystal data (Table I), coordinates and B_{equiv} for nonhydrogen atoms (Table II), anisotropic thermal parameters (Table III), positional parameters and B_{iso} for hydrogen atoms (Table IV), interatomic distances (Table V), bond angles (Table VI), and torsional angles (Table VII).

The molecular structure of oxymorphone·HCl·H_2O·C_2H_5OH is depicted in Fig. 1, with bond lengths and bond angles shown in Fig. 2. For the purpose of comparison, the geometry of unprotonated oxymorphone (8) is also shown (Fig. 3).

RESULTS AND DISCUSSION

Inspection of Figs. 2 and 3 and Table V reveals some significant[5] differences in bond lengths of protonated and unprotonated oxymorphone. Thus, the N—C-9 is longer by 0.032 (6) Å in protonated oxymorphone (Scheme II) than in the unprotonated analog (Scheme III). The elongation of the N—C bond upon protonation is not unexpected in light of the IR data of amines and their salts[6] and is consistent with the previously described elongation of the N—C bonds of cyclazocine upon protonation (28).

Several C—C bonds are considerably shorter (0.036–0.054 Å) in the protonated than in the unprotonated molecule: C-1–C-2, C-10–C-11, C-5–C-13, C-9–C-14, C-11–C-12, and C-4–C-12. Significant differences in several C—O bonds are also observed. Comparison of bond angles for protonated and unprotonated oxymorphone (Table VI) reveals several small but significant differences of up to ~6 degrees. Similarly, several torsional angles of these two molecules differ for up to ~6 degrees (Table VII).

Observed changes in bond lengths, angles, and torsional angles distant from the site of protonation are interpreted as a reflection of long-range substituent effects in oxymorphone (1). Protonation leads to a formal positive electric charge on nitrogen, which can be transmitted further throughout the molecule *via* long-range inductive and electrostatic field effects (1). The elongation of the N—C bond upon protonation may introduce a local strain and conformational distortion which may be transmitted through the entire molecule by a slight flexing of bond and torsional angles (conformational transmission effect); in this way, the strain is shared by the whole structure (1).

While long-range effects are expected to influence the geometry of the entire molecule, the exact location and magnitude of the geometric changes are difficult to predict; observed changes therefore appear to be erratic. For this reason, extrapolation of the geometric changes observed here, upon protonation of oxymorphone to predictions of geometries of other morphine derivatives, is extremely difficult.

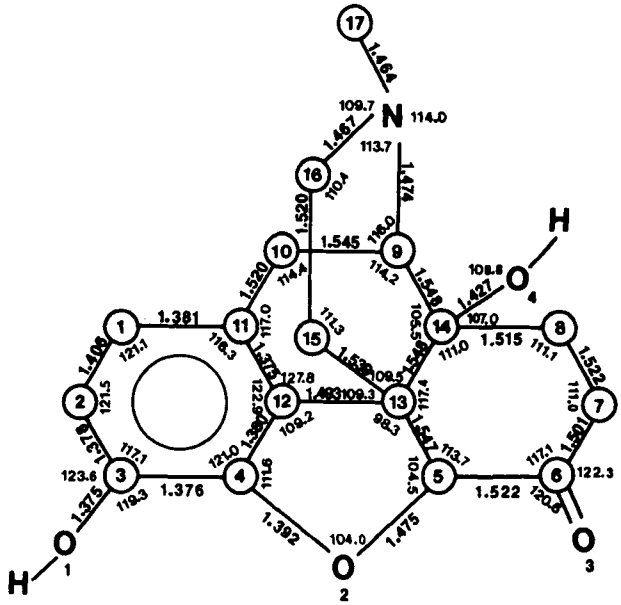

Figure 3—*Bond lengths and bond angles in unprotonated oxymorphone (oxymorphone·H_2O) (8). The estimated standard deviations are 0.004–0.005 Å for C—C, C—O, and C—N bonds, and 0.2–0.3° for C—C—(C,O,N) angles.*

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[5] Significant differences are those which are >5σ. $\sigma = (\sigma_a^2 + \sigma_b^2)^{1/2}$, where σ_a and σ_b are standard deviations of the property measured (bond lengths, bond angles, *etc.*) of protonated and unprotonated oxymorphone.

[6] The N—H stretching frequencies of protonated amines (amine salts) are lower than those of their respective free bases (19–21). Since the frequency is directly related to the square root of the force constant of the bond (29), the lower frequency indicates a weaker and probably longer bond.

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Medicated Tampons: Intravaginal Sustained Administration of Metronidazole and *In Vitro–In Vivo* Relationships

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Abstract □ The technical feasibility of utilizing tampons as a drug delivery system for prolonged intravaginal drug administrations was studied. Several commercially available brands of tampons were examined. The methodology for the incorporation of various doses of metronidazole, an antitrichomonas agent, in tampons was described. The sustained-release profile of metronidazole from these medicated tampons was characterized. Intravaginal administration of metronidazole *via* the medicated tampons was investigated in rhesus monkeys and human volunteers, and *in vitro–in vivo* correlations were established. The biopharmaceutics of intravaginal absorption of metronidazole *via* medicated tampons was analyzed in comparison with a vaginal solution formulation.

Keyphrases □ Metronidazole—intravaginal sustained administration in medicated tampons, *in vitro–in vivo* relationships □ Tampons—intravaginal sustained administration of metronidazole, *in vitro–in vivo* relationships □ Intravaginal administration—sustained metronidazole in tampons, *in vitro–in vivo* relationships

Tampons are made of cotton and/or cellulose and are commonly used for intravaginal insertion to absorb menstrual discharge (1). Numerous brands of vaginal tampons are commercially available. Their characteristics of high fluid absorbability and retention have been recommended for the absorption of extensive vaginal discharge in trichomonas-infected women.

Metronidazole[1] has been shown to be an effective antiprotozoal agent with a broad spectrum of activity against anaerobes (2–6). It is selectively absorbed by and produces cytotoxicity in anaerobes (6–8). Its efficacy in the treatment of *Trichomonas vaginalis* has been well documented (9). The idea of developing a medicated tampon to combine the therapeutic efficacy of metronidazole and the high fluid absorbability of tampon for trichomonas-infected women is thus generated.

Additionally, a high incidence of toxic shock syndrome was recently reported in menstruating women who used tampons, especially one brand[2] (10). Continuing epidemiological and microbiological studies at the Center for Disease Control have firmly related the pathogenesis of toxic shock syndrome to the infection of *Staphylococcus aureus* isolated from the vaginas of patients who suffered from toxic shock syndrome (98 *versus* 7% in the unmatched controls). On the other hand, no *S. aureus* could be recovered from the unused tampons, including those from tampon boxes used by the patients (10). The incidence of toxic shock syndrome further suggests the need to develop a medicated tampon, which administers an antistaphylococcal agent in the vagina in a controlled manner for a prolonged period of time, to protect the user from *S. aureus* infection.

The objective of this investigation is to evaluate the technical feasibility of using the tampon as an intravaginal drug delivery system. In this report, the methodology for

[1] Flagyl (SC-10295), Searle Laboratories, Division of G. D. Searle & Co., Skokie, IL 60077.

[2] Rely tampons.

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