Acta Chemica Scandinavica A 28 (1974) 1162—1166

The Crystal Structure of (±)-*erythro*-2-(2,5-Dimethoxyphenyl)-2-hydroxy-1-methylethylammonium Chloride

MARTIN VAHL GABRIELSEN and ALEX MEHLSEN SØRENSEN

The Royal Danish School of Pharmacy, Chemical Laboratory C, 2100 Copenhagen Ø, Denmark

Methoxamine chloride, (±)-*erythro*-2-(2,5-dimethoxyphenyl)-2-hydroxy-1-methylethylammonium chloride, $C_{11}H_{17}NO_3$.HCl crystallizes in the space group $P2_1/c$ with $a = 14.208(11)$ $b = 9.466(7)$, $c = 9.683(9)$ Å, $\beta = 98.99(12)°$, $Z = 4$. The crystal structure was determined from three-dimensional diffractometer collected X-ray diffraction data, and refined to a final R value of 0.049 by full-matrix least-squares methods. The *erythro* configuration has been confirmed. The structure is stabilized by a maximum number of hydrogen bonds.

Methoxamine is chemically closely related to nor-ephedrine, pharmacologically it is a sympatomimethicum with entirely alpha-adrenergic activity. The general acceptance of the *erythro* configuration for methoxamine has been based on studies on the optical rotation of this and related compounds [1] and the probably stereospecific, catalytic reduction of the corresponding isonitrosopropiophenone to methoxamine.[2,3]

As this evidence for the configuration was not considered conclusive, an X-ray investigation of the structure was carried out.

EXPERIMENTAL

Crystals suitable for X-ray diffraction intensity measurements were grown by slow evaporation at room temperature of an aqueous solution. The unit-cell dimensions were determined from least-squares refinement for the theta values for 36 reflections. The crystal density was measured by flotation in a mixture of chlorobenzene and bromobenzene. The X-ray intensity data were obtained from a crystal with dimensions $0.2 \times 0.4 \times 0.5$ mm mounted on a Nonius three-circle automatic diffractometer using graphite monochromatized Mo$K\alpha$ radiation ($\lambda = 0.7107$ Å). The crystal was mounted with the crystal b-axis and the goniometer ϕ-axis parallel, the ω-scan technique with a fixed scan range of 1.0° and a scan speed of 1.2 deg./min was employed, and background intensity was measured for half the scanning time at the scan range limits. The intensity of one reference reflection was measured after every 25 reflections. Out of 2309 independent reflections in the range $2.5° \leq \theta \leq 25°$, 1578 with an intensity greater than three times their corresponding estimated standard deviation were considered to be observed. The intensity data were corrected for Lorentz and polarization effects. The computations were carried out on a GIER and an IBM 360/75 computer using *The X-Ray System*,[4] *ORTEP* [5] and diffractometer input and output data reduction programs written by one of the authors (A.M.S.). X-Ray atomic scattering factors used were those listed in International Tables for X-Ray Crystallography (1962).

CRYSTAL DATA

Methoxamine chloride, (±)-*erythro*-2-(2,5-dimethoxyphenyl)-2-hydroxy-1-methylethylammonium chloride, $C_{11}H_{17}NO_3$.HCl, M = 247.72, Monoclinic, $a = 14.208(11)$, $b = 9.466(7)$, $c = 9.683(9)$ Å, $\beta = 98.99(12)°$, $V = 1286$ Å^3, $D_m = 1.26$ g cm^{-3}, $Z = 4$, $D_c = 1.28$ g cm^{-3}. Linear absorption coefficient λ(Mo$K\alpha$) = 0.7107 Å: $\mu = 2.9$ cm^{-1}. Space group $P2_1/c$.

STRUCTURE DETERMINATION

From a three-dimensional, sharpened, origin removed Patterson synthesis approximate positions of the chlorine and the hydrogen bonded nitrogen (N) and oxygen (O3) atoms were postulated. An electron density map

Table 1. Final positional and thermal (Å²) parameters. The temperature expression for non-hydrogen atoms is of the form: exp $\{-2\pi^2 (h^2a^{*2}U_{11}+k^2b^{*2}U_{22}+\cdots+2klb^*c^*U_{23})\}$, and for hydrogen atoms of the form: exp $\{-2\pi^2U(2\sin\theta/\lambda)^2\}$. Estimated standard deviations of the parameters are given in parentheses.

	x/a	y/b	z/c	$U_{11}\times 100$	$U_{22}\times 100$	$U_{33}\times 100$	$U_{12}\times 100$	$U_{13}\times 100$	$U_{23}\times 100$
Cl	0.0526(1)	0.1083(1)	0.3279(1)	7.77(5)	4.03(4)	3.99(4)	1.79(4)	1.55(4)	0.55(3)
O(1)	0.2093(2)	0.0666(2)	−0.2030(2)	8.25(15)	5.06(12)	4.62(12)	−1.89(11)	0.94(11)	0.93(10)
O(2)	0.4520(2)	0.0289(4)	0.2977(3)	7.16(17)	12.17(25)	8.67(20)	−0.48(17)	−2.10(15)	−2.37(19)
O(3)	0.1244(2)	−0.1156(2)	0.1402(2)	7.46(13)	3.83(10)	4.02(10)	−0.67(10)	2.15(10)	−0.56(9)
N	0.0560(2)	−0.2842(3)	−0.0805(3)	5.63(14)	3.55(13)	3.46(12)	0.41(10)	0.81(11)	−0.12(10)
C(1)	0.2485(2)	−0.0119(3)	0.0275(3)	5.35(16)	3.30(13)	4.37(14)	−0.16(12)	0.88(12)	−0.88(12)
C(2)	0.2728(2)	0.0675(3)	−0.0818(3)	6.02(18)	3.94(15)	5.23(16)	−0.83(13)	1.64(14)	−0.61(13)
C(3)	0.3576(3)	0.1406(4)	−0.0614(4)	7.37(24)	6.04(22)	7.41(24)	−2.24(17)	2.53(20)	−0.75(18)
C(4)	0.4190(3)	0.1296(5)	0.0633(5)	5.72(21)	7.51(25)	9.08(29)	−1.83(18)	1.62(20)	−2.62(23)
C(5)	0.3969(3)	0.0484(4)	0.1689(4)	5.55(19)	6.82(21)	6.66(21)	−0.23(17)	0.10(17)	−1.98(19)
C(6)	0.3108(2)	−0.0218(3)	0.1514(4)	6.09(19)	4.77(17)	5.28(17)	0.08(14)	0.59(15)	−0.94(15)
C(7)	0.1527(2)	−0.0836(3)	0.0102(3)	5.31(15)	3.21(14)	3.51(13)	−0.24(12)	0.87(12)	−0.10(11)
C(8)	0.1534(2)	−0.2237(3)	−0.0661(3)	5.24(15)	3.44(14)	3.18(13)	−0.27(11)	0.77(11)	−0.11(11)
C(9)	0.2241(3)	−0.3286(4)	0.0056(4)	6.75(22)	4.03(16)	5.86(20)	−1.24(15)	0.14(16)	1.02(16)
C(10)	0.2222(4)	0.1616(4)	−0.3112(4)	9.91(29)	4.87(18)	6.18(22)	−0.25(19)	2.54(22)	1.35(17)
C(11)	0.5403(3)	0.0967(8)	0.3244(7)	6.07(26)	14.24(52)	11.30(41)	0.00(29)	−0.98(26)	−4.76(41)

	x/a	y/b	z/c	$U\times 100$		x/a	y/b	z/c	$U\times 100$
H(31)	0.371(3)	0.196(5)	−0.140(6)	7	H(102)	0.280(4)	0.142(6)	−0.340(6)	7
H(41)	0.475(4)	0.169(6)	0.073(5)	7	H(103)	0.225(3)	0.243(6)	−0.274(5)	7
H(61)	0.294(3)	−0.082(5)	0.221(5)	6	H(111)	0.568(5)	0.059(7)	0.419(8)	10
H(71)	0.104(3)	−0.025(4)	−0.046(4)	4	H(112)	0.582(5)	0.064(7)	0.265(7)	10
H(81)	0.163(2)	−0.207(4)	−0.158(4)	4	H(113)	0.531(4)	0.208(8)	0.320(7)	10
H(91)	0.208(3)	−0.348(5)	0.099(5)	5	H(1N)	0.013(3)	−0.235(5)	−0.148(4)	4
H(92)	0.292(3)	−0.294(4)	0.006(5)	5	H(2N)	0.037(3)	−0.288(4)	0.001(5)	4
H(93)	0.220(3)	−0.413(5)	−0.051(5)	5	H(3N)	0.050(3)	−0.379(5)	−0.106(4)	4
H(101)	0.159(3)	0.151(5)	−0.394(5)	7	H(03)	0.108(3)	−0.039(5)	0.185(4)	5

phased on these atoms showed four likely positions for carbon atoms; the nine remaining non-hydrogen atoms of the methoxamine ion appeared clearly in a subsequent electron density map phased from the contributions of those atoms whose positions had been located.

Full matrix least-squares refinement (minimizing $\sum w(|F_o|-|F_c|)^2$, $w=1$) using individual isotropic temperature factors converged at $R=0.19$. Individual anisotropic thermal parameters were introduced and after three cycles of refinement a difference Fourier synthesis was calculated from structure factors in the range $\sin\theta/\lambda \leq 0.35$. Approximate positions of all the hydrogen atoms were found in the eighteen largest peaks (electron density of 0.2 – 0.5 e Å^{-3}). Individual isotropic thermal parameters, approximately equal to those calculated for the corresponding heavier atoms, were assigned to the hydrogen atoms.

Full-matrix least-squares refinement on the positional parameters of all atoms and individual anisotropic thermal parameters for all non-hydrogen atoms converged at $R=0.049$ (weighted $R=0.061$, average and maximum values of shift error were 0.05 and 0.3, resp.). In the last stages of the refinement empirical weights were introduced to make $w(|F_o|-|F_c|)^2$ independent of $|F_o|$ and $\sin\theta$. The weighting scheme chosen was: $w=axy$ where $a=1$ for $|F_o| \leq 25$ else $a=0.5$, $x=1$ for $\sin\theta > 0.28$ else $x=\sin\theta/0.28$ and $y=1$ for $|F_o| < 9.0$ else $y=9.0/|F_o|$. Final positional and thermal parameters are given in Table 1. Tables of the structure factors are available on request.

Full-matrix least-squares refinement carried out as for the *erythro* configuration of the structure above but interchanging the coordinates of the nitrogen and the terminal side chain carbon atoms converged at $R=0.057$. A difference Fourier map showed a peak (0.25 e Å^{-3}) at the postulated position of the carbon atom and a hole (−0.35 e Å^{-3}) at the postulated position of the nitrogen atom.

DISCUSSION

The assumed *erythro* configuration of methoxamine is confirmed by the X-ray structure determination. Final R-values for the postulated *erythro*- and *threo*-configurations, respectively, are 4.9 and 5.7 %. Further evidence for the *erythro*-form is the presence of three short *inter*atomic distances between nitrogen and chlorine atoms, whereas the three shortest distances between the carbon atom C(9) and chlorine atoms are 3.82, 4.52 and 5.12 Å.

The *p*-dimethoxyphenyl part of the ion is approximately planar apart from four hydrogen atoms, two from each methyl group, which straddle the benzene ring. The methyl groups are as distant as possible from the extended aminoethyl side-chain. The plane of the benzene ring is almost perpendicular to the plane containing the atoms C(1), C(7), C(8), and N. The hydroxy group, the methyl group [C(9)], and the methoxy group at C(5) are situated on the same side of the latter plane.

Some data defining the conformation of the methoxamine ion are listed in Table 2; the geometry of the ion is illustrated by Figs. 1 and 2.

Bond distances and valency angles, uncorrected for thermal motion, are given in Table 3. The bond lengths are close to normally

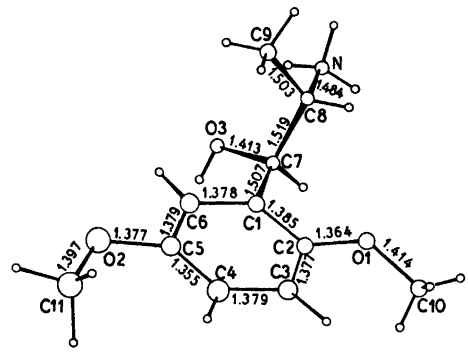

Fig. 1. Methoxamine ion, interatomic distances.

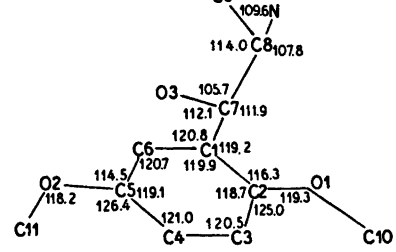

Fig. 2. Methoxamine ion, interatomic angles.

Table 2. Conformation of the methoxamine ion.

Benzene ring. Distances of atoms from least squares plane. The equation is in direct (unit cell) space.

Equation: $-7.116x + 7.488y + 4.118z + 1.755 = 0$

Atom	Deviation (Å)	Atom [a]	Deviation (Å)
C(1)	0.010	C(10)	0.102
C(2)	−0.018	C(11)	−0.030
C(3)	0.010	O(1)	−0.072
C(4)	0.004	O(2)	−0.019
C(5)	−0.011	H(31)	0.01
C(6)	0.003	H(41)	−0.05
C(7) [a]	0.084	H(61)	−0.04

[a] The coordinates of these atoms did not contribute to the least squares matrix.

Torsion angles (°) involving non-hydrogen atoms

C(3)−C(2)−O(1)−C(10)	+9.7	C(1)−C(7)−C(8)−C(9)	−59.3
C(4)−C(5)−O(2)−C(11)	+0.5	C(1)−C(7)−C(8)−N	178.8
C(6)−C(1)−C(7)−O(3)	−21.3	O(3)−C(7)−C(8)−C(9)	+62.9
C(6)−C(1)−C(7)−C(8)	+97.4	O(3)−C(7)−C(8)−N	−59.0

accepted values. Some valency angles in the *p*-dimethoxybenzene system deviate significantly from the ideal values, possibly a consequence of the compact planar atomic arrangement.

The packing of the molecules is depicted in Fig. 3. A feature common for this and similar compounds [6-8] is the existence of a maximum number of hydrogen bonds between the halide and substituted ammonium ions.

The chlorine ions form continuous layers in the (100) planes. The onium and hydroxy groups in the methoxamine ions are directed towards these layers, so that an infinite methoxamine ion−chloride ion−methoxamine ion "sandwhich" is formed through the crystal. Each chloride ion is hydrogen bonded in a roughly tetrahedral manner to one hydroxy and three onium groups in four different methoxamine ions. There are no significantly close approaches between non-hydrogen bonded atoms. A summary of the geometry of the close contacts is shown in Table 3.

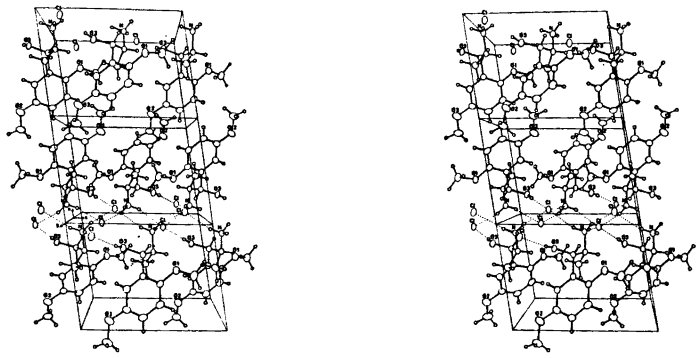

Fig. 3. Stereoscopic pair of figures showing the crystal structure of methoxamine chloride, as seen along the *b*-axis.

Table 3. Interatomic distances (Å) and angles (deg.).

Bond distances

C(1)–C(2)	1.385(4)	C(3)–H(31)	0.96(5)
C(2)–C(3)	1.377(5)	C(4)–H(41)	0.87(5)
C(3)–C(4)	1.379(6)	C(6)–H(61)	0.94(5)
C(4)–C(5)	1.355(6)	C(7)–H(71)	0.98(4)
C(5)–C(6)	1.379(5)	C(8)–H(81)	0.93(4)
C(6)–C(1)	1.378(4)	C(9)–H(91)	0.98(5)
C(1)–C(7)	1.507(4)	C(9)–H(92)	1.02(5)
C(7)–C(8)	1.519(4)	C(9)–H(93)	0.97(5)
C(8)–C(9)	1.503(4)	C(10)–H(101)	1.11(5)
C(2)–O(1)	1.364(4)	C(10)–H(102)	0.93(6)
C(10)–O(1)	1.414(5)	C(10)–H(103)	0.85(6)
C(5)–O(2)	1.377(5)	C(11)–H(111)	1.00(7)
C(11)–O(2)	1.397(6)	C(11)–H(112)	0.94(7)
C(7)–O(3)	1.413(4)	C(11)–H(113)	1.06(7)
C(8)–N	1.484(4)		

The hydrogen bond system

A–H···B	B equipoint	A–H	A···B	H···B	∠AHB
N–H(1N)···Cl	$(-x, -y, -z)$	0.95(4)	3.120(4)	2.20(4)	165(4)
N–H(2N)···Cl	$(-x, y-\frac{1}{2}, \frac{1}{2}-z)$	0.88(5)	3.252(4)	2.44(5)	153(3)
N–H(3N)···Cl	$(x, -y-\frac{1}{2}, z-\frac{1}{2})$	0.93(5)	3.192(3)	2.27(5)	174(3)
O(3)–H(O3)···Cl	(x, y, z)	0.89(4)	3.068(3)	2.20(5)	165(4)

Valency angles [a]

C(6)–C(1)–C(2)	119.9(3)	O(2)–C(5)–C(6)	114.5(4)
C(6)–C(1)–C(7)	120.8(3)	C(5)–C(6)–C(1)	120.7(3)
C(7)–C(1)–C(2)	119.2(2)	C(1)–C(7)–C(8)	111.9(2)
C(1)–C(2)–C(3)	118.7(3)	C(1)–C(7)–O(3)	112.1(2)
C(1)–C(2)–O(1)	116.3(3)	O(3)–C(7)–C(8)	105.7(2)
O(1)–C(2)–C(3)	125.0(3)	C(7)–C(8)–C(9)	114.0(2)
C(2)–C(3)–C(4)	120.5(4)	C(7)–C(8)–N	107.8(2)
C(3)–C(4)–C(5)	121.0(4)	N–C(8)–C(9)	109.6(3)
C(4)–C(5)–C(6)	119.1(3)	C(2)–O(1)–C(10)	119.3(3)
C(4)–C(5)–O(2)	126.4(4)	C(5)–O(2)–C(11)	118.2(4)

[a] All angles involving hydrogen atoms are within three times their estimated standard deviations from the expected values.

Acknowledgements. The authors express their gratitude to Professor, dr. phil. Bodil Jerslev for her stimulating interest in this work, and to Dr. Bengt Öhrner, Apotekens Centrallaboratorium, Sweden, for providing a sample of the NFN standard of methoxamine chloride.

REFERENCES

1. Baltzly, R. and Mehta, N. B. *J. Med. Chem. 11* (1968) 833.
2. Baltzly, R. and Buck, J. S. *J. Amer. Chem. Soc. 62* (1940) 164.
3. Baltzly, R. and Buck, J. S. *J. Amer. Chem. Soc. 64* (1942) 3040.
4. Stewart, J. M., Kundell, F. A. and Baldwin, J. C. *X-Ray 70 Crystal Structure Calculation System*, Computer Science Center, University of Maryland, July 1970.
5. Johnson, C. K. *ORTEP, A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustration*, Oak Ridge National Laboratory, Oak Ridge 1965.
6. Phillips, D. C. *Acta Crystallogr. 7* (1954) 159.
7. Carlström, D. and Bergin, R. *Acta Crystallogr. 23* (1967) 313.
8. Bergin, R. and Carlström D. *Acta Crystallogr. B 24* (1968) 1506.

Received July 5, 1974.