Short Communication

The Absolute Configuration of Ketamine – A General Anaesthetic. The Crystal Structure of the (*R,R*)-Tartrate Salt of (−)-(*S*)-Ketamine

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Ketamine hydrochloride, (±)-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride, Fig. 1, which was approved for clinical use in 1970, is a potent, rapid-action general anaesthetic with a short duration of action. Intravenous administration produces surgical anaesthesia within 30 s and lasts as long as 10 min.[1-4] The (+)-enantiomer is predominantly responsible for the desired hypnotic and analgesic action, whereas the (−)-isomer is the main source of unwanted side-effects such as CNS-stimulatory actions.[5]

To the best of our knowledge, the absolute stereostructures of the enantiomers of ketamine hydrochloride have not been substantiated in the literature. However, in 1982 the configurations were claimed to be (−)-(*R*)* and (+)-(*S*) *when studied by physical chemistry techniques*[4] (stated as *Unpublished data* in Ref. 4). A forthcoming paper on the issue was announced.[6]

To obtain unequivocal configurational assignments of the enantiomers of this important drug, we have carried out a crystal structure analysis of the (*R,R*)-tartrate salt of (−)-ketamine.

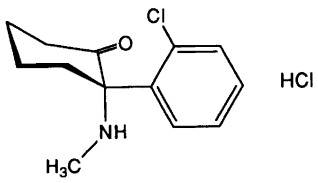

Fig. 1. (+)-(*S*)-Ketamine hydrochloride.

Experimental

Optical resolution of (±)-ketamine base was carried out as previously described employing the tartaric acids as resolving agents.[7] The resolution was monitored by chiral liquid chromatography on Enantiopac™ (Pharmacia LKB) as described by Bishop *et al.*[8] except for minor alterations: 5 mM phosphate buffer, pH 7.2, and ambient temperature. Under these conditions the tartrate salt is cleaved and the percentage of each isomer in the mother liquor is easily measured. Tartaric acid itself is eluted later and does not interfere with the ketamine peaks. (+)-Ketamine

Table 1. Final fractional coordinates and equivalent temperature factors with estimated standard deviations for non-hydrogen atoms in the (*R,R*)-tartrate salt of (−)-(*S*)-ketamine [(−)-(*S*)-2-(2-chlorophenyl)-2-(methylammonio)cyclohexanone (*R,R*)-tartrate].

Atom	*x*	*y*	*z*	U_{eq}/Å^{2} [a]
Cl	0.02547(17)	0.04452(11)	0.24049(5)	0.027
O1	0.0800(4)	−0.1587(3)	0.1424(1)	0.021
OW1	0.3580(4)	0.1580(2)	0.5058(1)	0.019
O2	−0.3432(4)	−0.0012(3)	0.3657(1)	0.021
OW2	0.8855(4)	0.1833(3)	0.9918(1)	0.021
O3	−0.3477(4)	0.1241(3)	0.4395(1)	0.022
O4	0.0122(4)	0.1315(3)	0.4503(1)	0.020
O5	−0.0459(4)	−0.1193(3)	0.4516(1)	0.025
O6	0.3154(4)	0.0018(3)	0.3657(1)	0.019
O7	0.3082(4)	−0.0985(3)	0.4494(1)	0.022
N	0.0058(5)	0.0228(3)	0.0751(1)	0.017
C1	−0.2201(6)	0.0827(4)	0.1511(2)	0.017
C2	−0.1573(7)	0.1153(4)	0.2067(2)	0.020
C3	−0.2325(7)	0.2056(4)	0.2367(2)	0.026
C4	−0.3757(7)	0.2701(4)	0.2122(2)	0.026
C5	−0.4391(7)	0.2409(4)	0.1574(2)	0.022
C6	−0.3630(7)	0.1495(4)	0.1275(2)	0.019
C7	−0.1436(7)	−0.0172(4)	0.1160(2)	0.017
C8	−0.2916(7)	−0.0749(4)	0.0764(2)	0.021
C9	−0.4461(7)	−0.1306(4)	0.1114(2)	0.024
C10	−0.3657(7)	−0.2240(4)	0.1499(2)	0.026
C11	−0.2158(7)	−0.1745(4)	0.1895(2)	0.025
C12	−0.0699(6)	−0.1188(4)	0.1518(2)	0.018
C13	0.1587(7)	0.0915(4)	0.0996(2)	0.023
C14	−0.2664(6)	0.0639(4)	0.4039(2)	0.015
C15	−0.0578(6)	0.0661(4)	0.4031(2)	0.018
C16	0.0237(6)	−0.0548(4)	0.4040(2)	0.017
C17	0.2350(6)	−0.0502(4)	0.4073(2)	0.017

[a] $U_{eq} = (U_{11} + U_{22} + U_{33})/3$.

* Ketamine base in ethanol and ketamine hydrochloride in water exhibit opposite signs in their optical rotations.[7]

hydrochloride showed $[\alpha]_D^{25} + 91.2°$ (*c* 0.3, H_2O); lit.[7] $[\alpha]_D^{25} + 92.48°$ (*c* 2, H_2O).

Results and discussion

An X-ray crystal structure investigation of the title compound was undertaken to establish the absolute configurations of (+)- and (−)-ketamine.

(R,R)-*Tartrate Salt of (−)-(S)-ketamine [(−)-(S)-2-(2-chlorophenyl)-2-(methylammonio)cyclohexanone* (R,R)-*tartrate.* The crystals of the (*R,R*)-tartrate of (−)-ketamine, $C_{13}H_{17}ClNO^+C_4O_6H_5^-\cdot 2H_2O$, belong to the orthorhombic system with space group $P2_12_12_1$, cell dimensions a = 7.245(4), b = 11.637(5), c = 22.993(8) Å, and Z = 4 (D_x = 1.44 g cm^{-3}). Using $2\Theta_{max} = 50°$ and MoK_α radiation, and choosing an observed–unobserved cut-off at 2.5σ(I), a total of 1715 observed reflections were recorded on an automatic diffractometer at ca. −130 °C. No corrections for absorption or secondary extinction were applied (crystal size: 1.0×0.7×0.02 mm). The structure was solved by direct methods[9] and refined by full-matrix least-squares techniques.[10] Weights in least-squares were calculated from the standard deviations in intensities, σ(I), taken as $\sigma(I) = [C_1 + (0.02C_2)^2]^{1/2}$, where C_1 is the total number of counts and C_2 the net count. Anisotropic temperature factors were used for non-hydrogen atoms. The maximum r.m.s. amplitudes of thermal vibration range from 0.14 to 0.20 Å. Hydrogen atom positions were calculated and refined with isotropic temperature factors. The R-value arrived at was 4.49 % (R_w = 4.24 %). Final fractional coordinates with estimated standard deviations for the non-hydrogen atoms are listed in Table 1. Bond distances and bond angles, with

Table 2. Bond distances (Å) and bond angles (°) with estimated standard deviations for the (*R,R*)-tartrate salt of (−)-(*S*)-ketamine [(−)-(*S*)-2-(2-chlorophenyl)-2-(methylammonio)-cyclohexanone (*R,R*)-tartrate].

Distance		Distance	
Cl–C2	1.743(5)	O1–C12	1.201(6)
O2–C14	1.288(6)	O3–C14	1.227(6)
O4–C15	1.420(6)	O5–C16	1.418(6)
O6–C17	1.273(6)	O7–C17	1.239(6)
N–C7	1.508(6)	N–C13	1.478(6)
C1–C2	1.408(7)	C1–C6	1.403(7)
C1–C7	1.520(7)	C2–C3	1.370(7)
C3–C4	1.399(8)	C4–C5	1.384(7)
C5–C6	1.381(7)	C7–C8	1.559(7)
C7–C12	1.537(7)	C8–C9	1.523(7)
C9–C10	1.518(7)	C10–C11	1.528(8)
C11–C12	1.513(7)	C14–C15	1.512(7)
C15–C16	1.526(7)	C16–C17	1.533(7)
Angle		**Angle**	
C7–N–C13	117.8(4)	C2–C1–C6	116.1(4)
C2–C1–C7	124.8(4)	C6–C1–C7	119.2(4)
Cl–C2–C1	121.5(4)	Cl–C2–C3	116.1(4)
C1–C2–C3	122.4(5)	C2–C3–C4	120.2(5)
C3–C4–C5	118.8(5)	C4–C5–C6	120.6(5)
C1–C6–C5	122.0(5)	N–C7–C1	110.9(4)
N–C7–C8	105.2(4)	N–C7–C12	108.8(4)
C1–C7–C8	112.9(4)	C1–C7–C12	115.5(4)
C8–C7–C12	102.7(4)	C7–C8–C9	112.4(4)
C8–C9–C10	109.3(5)	C9–C10–C11	110.5(4)
C10–C11–C12	108.5(4)	O1–C12–C7	121.0(4)
O1–C12–C11	124.8(5)	C7–C12–C11	113.2(4)
O2–C14–O3	125.8(5)	O2–C14–C15	115.6(4)
O3–C14–C15	118.6(4)	O4–C15–C14	110.8(4)
O4–C15–C16	110.1(4)	C14–C15–C16	111.8(4)
O5–C16–C15	111.2(4)	O5–C16–C17	109.6(4)
C15–C16–C17	110.8(4)	O6–C17–O7	127.4(5)
O6–C17–C16	115.9(4)	O7–C17–C16	116.7(4)

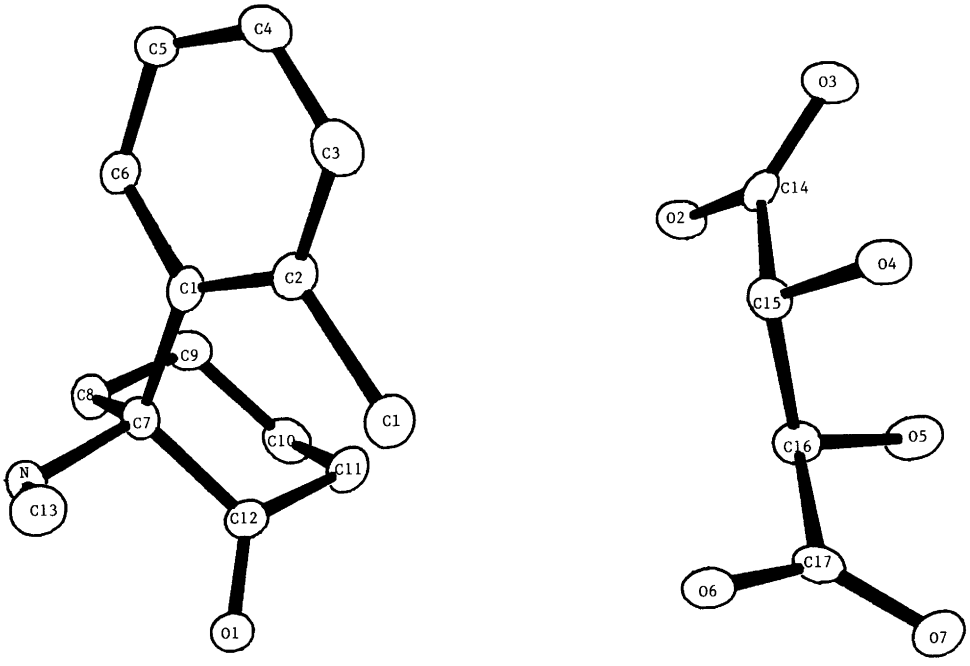

Fig. 2. Perspective drawing of the (*R,R*)-tartrate salt of (−)-(*S*)-ketamine showing the numbering of the atoms.

estimated standard deviations are given in Table 2. Fig. 2 is a perspective drawing of the molecule showing the numbering of atoms and the (*S*)-configuration of the (−)-ketamine moiety of the (*R,R*)-tartrate salt.

Lists of thermal parameters, hydrogen atom parameters, and observed and calculated structure factors are available from P. Groth on request.

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