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The Absolute Configuration of (+)-2-Benzyl-2-[*N*-(α-phenylethyl)amino]cyclohexanone Hydrochloride

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Abstract. $C_{21}H_{25}NO.HCl$, $M_r = 343.90$, orthorhombic, $P2_12_12_1$, $a = 8.588\,(1)$, $b = 11.700\,(1)$, $c = 18.130\,(2)$ Å, $V = 1821.7\,(4)$ Å^3, $Z = 4$, $D_x = 1.254$ Mg m^{-3}, λ(Mo $K\alpha$) = 0.71069 Å, $\mu = 2.139$ mm^{-1}, $F(000) = 736$, $T = 293$ K, final $R = 0.037$ for 3192 observed reflections. Condensation of 2-(benzyloxy)cyclohexanone with (*R*)-1-phenylethylamine yields, by rearrangement, an unexpected reaction product mixture of (αR,2*S*)- and (αR,2*R*)-2-benzyl-2-[*N*-(α-phenylethyl)amino]cyclohexanone hydrochlorides. The absolute configuration of one of the epimers, (+)-2-benzyl-2-[*N*-(α-phenylethyl)amino]cyclohexanone hydrochloride, is elucidated as (αR,2*S*) by X-ray structure analysis, showing the cyclohexanone ring in the chair conformation with the benzyl group in an axial and the α-phenylethylamino group in an equatorial position. N—H(Cl) hydrogen bonds are found along [100].

Introduction. An efficient synthesis of optically active *cis*-2-alkoxy and 2-aryloxycyclohexanamines has been reported (Lauktien & Frahm, 1990). The unexpected title compound, (+)-2-benzyl-2-[*N*-(α-phenylethyl)amino]cyclohexanone hydrochloride (3), was isolated after condensation and rearrangement

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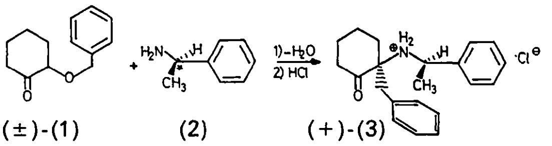
from 2-(benzyloxy)cyclohexanone when reacted with optically pure (*R*)-1-phenylethylamine (2). Diastereomeric separation was carried out by means of fractional crystallization from acetone with a diastereomeric excess of >98% which was proved by ^1H and ^{13}C NMR spectroscopy. Compound (3) possesses a close structural relationship to ketamine (Ketanest®), a general anaesthetic with an analgesic side effect (Dinnendahl & Fricke, 1983).



Experimental. Colourless crystal from ethanol, 0.41 × 0.44 × 0.31 mm {m.p. = 464–467 K, $[\alpha]_D^{20°C} = +111.6°$ (ethanol, $0.3\ g\ dm^{-3}$)}. Rigaku AFC-6*R* diffractometer, rotating anode, Mo *Kα* radiation, graphite monochromator. Lattice parameters from angular settings of 25 independent reflections ($30 < 2\theta < 40°$). 13 165 intensities were measured by the *ω*-scan technique to $(\sin\theta/\lambda)_{max} = 0.7\ Å^{-1}$, $\pm h$, $-k$, l up to $h = 12$, $k = 16$, $l = 26$. Three standard reflections were measured every 200 reflections with an intensity variation of 0.4%. 5316 unique reflections were measured, 2124 of which were unobserved [$F < 3\sigma(F)$]. $R_{int} = 0.034$ based on intensities (Friedel pairs not merged). The structure was solved by direct methods using *MITHRIL* (Gilmore, 1984) and refined on $|F|$ by full-matrix least-squares calculations using anisotropic temperature factors for the non-H atoms. Scattering factors and anomalous-dispersion coefficients were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV). H atoms were calculated or taken from difference Fourier maps and refined for positional parameters and isotropic thermal vibrations. 321 parameters were refined, yielding $R = 0.037$, $wR = 0.028$, $S = 2.63$ (omitting unobserved reflections) with $w = [\sigma^2(F) + (0.0045|F|)^2]$. The final values were $\Delta/\sigma = 0.017$, $\Delta\rho_{max} = 0.43$, $\Delta\rho_{min} = -0.20\ e\ Å^{-3}$.

In order to establish the absolute configuration of the molecule, both enantiomorphs were refined separately yielding two identical parameter sets with $R = 0.037$, $wR = 0.028$, $S = 2.63$ for the (+) antipode and $R = 0.039$, $wR = 0.031$, $S = 2.78$ for the (−) antipode. A decision in favour of the (+) antipode was tested by comparing the reflections $\bar{3}\bar{1}4$, $\bar{1}\bar{2}7$, $2,2,\overline{10}$, $\bar{5},\bar{2},14$, $1,11,\bar{5}$ with ratios $F(h)_{obs}/F(\bar{h})_{obs}$ of 1.11, 1.19, 1.14, 1.14, 1.14. The corresponding ratios $F(h)_{calc}/F(\bar{h})_{calc}$ for the chosen enantiomer are 1.13, 1.11, 1.14, 1.09, 1.10 and for the optical antipode are 0.89, 0.90, 0.89, 0.92, 0.91. Therefore, the (+) antipode with (*αR*,2*S*) configuration is the most likely. All calculations were performed using the *TEXSAN* (Molecular Structure Corporation, 1989) single-crystal analysis software package.

Discussion. The configuration in this compound is of importance in further evaluation of its pharmacological behaviour. For this reason, so as to determine unambiguously the absolute configuration, additional measurements were made by means of the three-beam interaction method developed by Hümmer, Weckert & Bondza (1989). The method allows the determination of triplet phase invariants $\Phi = -\varphi(h) + \varphi(g) + \varphi(h-g)$, where the φ's are the structure-factor phases involved with an accuracy of about 45°, *i.e.* the phase octant with centres at $\Phi = 0°$ mod 45° can be determined. Thus, the best selectors for fixing the absolute configuration by this method would be triplet phases near 90 or $-90° = 270°$. Several triplet-phase relationships were measured with Cu radiation from a rotating-anode generator. Fig. 1 gives two typical examples. By comparison of the three-beam diffraction profiles of the two centrosymmetrically related three-beam cases $0/h/g$ and $0/-h/-g$, the triplet phases can unambiguously be evaluated. In the examples of Fig. 1, $\Phi =$

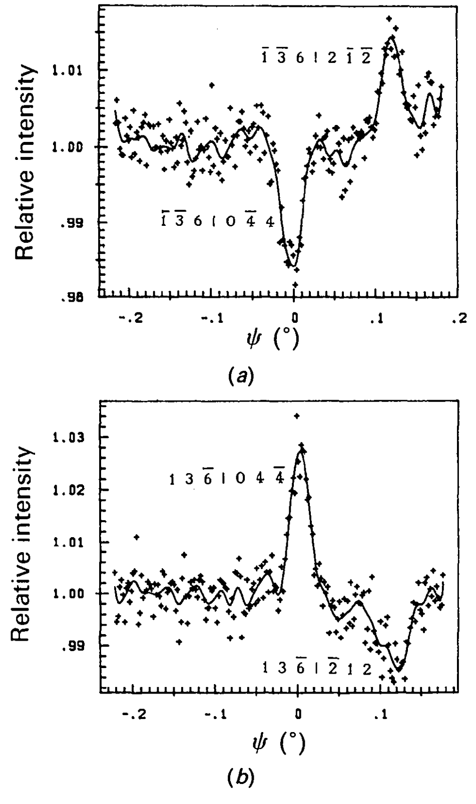


Fig. 1. *ψ*-scan profiles for the three-beam cases with (*a*) primary reflection $h = \bar{1}\bar{3}6$, secondary reflections $g = 0\bar{4}4$ and $g' = 2\bar{1}\bar{2}$, and (*b*) their centrosymmetric related reflections. The solid line is calculated by a spline data-smoothing routine using generalized cross validation by Craven & Wahba (1979).

Table 1. *Comparison of calculated and experimentally determined triplet phases* (°)

Φ_{calc} refers to the (+) enantiomer with (*αR*,2*S*) configuration.

h,g	Φ_{calc}	Φ_{exp}
032,124	112	135
032,113	103	90
136,044	92	90
136,212	−102	−90
321,310	−51	−45

Table 2. *Positional and isotropic or equivalent isotropic thermal parameters* (Å²)

For non-H atoms $B_{eq} = (8\pi^2/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	*y*	*z*	B_{iso}/B_{eq}
Cl	0.11134 (6)	0.59331 (4)	0.49305 (3)	3.98 (2)
O	0.3519 (2)	0.7225 (1)	0.62446 (7)	4.07 (7)
N	0.2557 (2)	0.8548 (1)	0.51739 (8)	2.64 (7)
C(1)	0.3211 (2)	0.8170 (2)	0.6444 (1)	3.2 (1)
C(2)	0.2179 (2)	0.8955 (2)	0.5958 (1)	2.77 (8)
C(3)	0.2578 (3)	1.0227 (2)	0.6045 (1)	3.5 (1)
C(4)	0.2992 (3)	1.0582 (2)	0.6822 (1)	4.2 (1)
C(5)	0.4300 (3)	0.9867 (3)	0.7133 (2)	4.9 (1)
C(6)	0.3775 (3)	0.8629 (2)	0.7180 (1)	4.8 (1)
C(7)	0.0445 (2)	0.8646 (2)	0.6094 (1)	3.3 (1)
C(α)	0.1600 (2)	0.8904 (2)	0.4512 (1)	2.89 (9)
C(β)	0.2340 (3)	0.8342 (2)	0.3845 (1)	3.7 (1)
C(1′)	−0.0294 (2)	0.9018 (2)	0.6798 (1)	3.04 (9)
C(2′)	−0.1039 (3)	1.0071 (2)	0.6829 (2)	4.6 (1)
C(3′)	−0.1735 (3)	1.0468 (3)	0.7451 (2)	6.1 (2)
C(4′)	−0.1680 (3)	0.9835 (3)	0.8068 (2)	6.8 (2)
C(5′)	−0.1015 (3)	0.8759 (3)	0.8068 (1)	6.6 (2)
C(6′)	−0.0309 (3)	0.8340 (3)	0.7415 (1)	4.2 (1)
C(1″)	0.1427 (2)	1.0187 (2)	0.4428 (1)	3.1 (1)
C(2″)	−0.0035 (3)	1.0680 (2)	0.4463 (1)	4.0 (1)
C(3″)	−0.0202 (4)	1.1842 (2)	0.4367 (2)	5.5 (1)
C(4″)	0.1078 (4)	1.2518 (2)	0.4239 (2)	5.6 (1)
C(5″)	0.2528 (3)	1.2030 (2)	0.4180 (1)	4.9 (1)
C(6″)	0.2698 (3)	1.0861 (2)	0.4268 (1)	3.8 (1)
H(1)	0.249 (2)	0.777 (2)	0.514 (1)	3.2 (4)
H(2)	0.360 (2)	0.871 (1)	0.507 (1)	3.8 (4)

90° for $0/\bar{1}\bar{3}6/0\bar{4}4$ and $0/13\bar{6}/\bar{2}12$ and $\Phi = -90°$ for $0/13\bar{6}/04\bar{4}$ and $0/\bar{1}\bar{3}6/2\bar{1}\bar{2}$. The results of these measurements, summarized in Table 1, lead to the safe conclusion that the (+) enantiomer has an (*αR*,2*S*) configuration.

It should be noted that the three-beam diffraction method works without the use of anomalous-dispersion effects. Therefore, it is particularly suited to the determination of the absolute structure of light-atom compounds. The atomic coordinates and equivalent isotropic displacement parameters are given in Table 2* and bond distances and angles in Table 3. An *ORTEP* (Johnson, 1965) drawing of a single molecule of (3) is depicted in Fig. 2, clearly showing the (*αR*,2*S*) configuration.

Table 3. *Interatomic distances* (Å), *bond angles* (°), *torsion angles* (°) *and hydrogen-bond geometry* (Å, °)

O—C(1)	1.193 (2)	C(α)—C(1″)	1.517 (3)
N—C(2)	1.534 (2)	C(1′)—C(2′)	1.389 (3)
N—C(α)	1.513 (2)	C(1′)—C(6′)	1.372 (3)
N—H(1)	0.92 (2)	C(2′)—C(3′)	1.358 (4)
N—H(2)	0.94 (2)	C(3′)—C(4′)	1.343 (4)
C(1)—C(2)	1.551 (3)	C(4′)—C(5′)	1.382 (4)
C(1)—C(6)	1.518 (3)	C(5′)—C(6′)	1.418 (4)
C(2)—C(3)	1.535 (3)	C(1″)—C(2″)	1.382 (3)
C(2)—C(7)	1.552 (3)	C(1″)—C(6″)	1.377 (3)
C(3)—C(4)	1.513 (3)	C(2″)—C(3″)	1.378 (3)
C(4)—C(5)	1.510 (4)	C(3″)—C(4″)	1.374 (4)
C(5)—C(6)	1.519 (4)	C(4″)—C(5″)	1.374 (4)
C(7)—C(1′)	1.490 (3)	C(5″)—C(6″)	1.385 (3)
C(α)—C(β)	1.515 (3)		

C(2)—N—C(α)	122.4 (1)	N—C(α)—C(β)	106.6 (2)
C(2)—N—H(1)	111 (1)	N—C(α)—C(1″)	113.9 (2)
C(2)—N—H(2)	109 (1)	C(β)—C(α)—C(1″)	113.0 (2)
C(α)—N—H(1)	101 (1)	C(7)—C(1′)—C(2′)	119.3 (2)
C(α)—N—H(2)	108 (1)	C(7)—C(1′)—C(6′)	122.3 (2)
H(1)—N—H(2)	104 (2)	C(2′)—C(1′)—C(6′)	118.4 (2)
O—C(1)—C(2)	120.2 (2)	C(1′)—C(2′)—C(3′)	122.7 (3)
O—C(1)—C(6)	121.6 (2)	C(2′)—C(3′)—C(4′)	119.2 (3)
C(2)—C(1)—C(6)	118.2 (2)	C(3′)—C(4′)—C(5′)	121.1 (3)
N—C(2)—C(1)	102.8 (2)	C(4′)—C(5′)—C(6′)	119.4 (3)
N—C(2)—C(3)	110.4 (1)	C(1′)—C(6′)—C(5′)	119.1 (3)
N—C(2)—C(7)	106.1 (2)	C(α)—C(1″)—C(2″)	119.8 (2)
C(1)—C(2)—C(3)	112.9 (2)	C(α)—C(1″)—C(6″)	120.7 (2)
C(1)—C(2)—C(7)	108.7 (2)	C(2″)—C(1″)—C(6″)	119.4 (2)
C(3)—C(2)—C(7)	115.1 (2)	C(1″)—C(2″)—C(3″)	120.0 (3)
C(2)—C(3)—C(4)	114.5 (2)	C(2″)—C(3″)—C(4″)	120.4 (2)
C(3)—C(4)—C(5)	111.7 (2)	C(3″)—C(4″)—C(5″)	119.9 (2)
C(4)—C(5)—C(6)	109.2 (2)	C(4″)—C(5″)—C(6″)	119.8 (3)
C(1)—C(6)—C(5)	112.5 (2)	C(1″)—C(6″)—C(5″)	120.4 (2)
C(2)—C(7)—C(1′)	118.4 (2)		

C(1)—C(2)—C(3)—C(4)	−37.9 (2)	C(3)—C(4)—C(5)—C(6)	−62.8 (3)
C(2)—C(1)—C(6)—C(5)	−41.7 (3)	C(1)—C(6)—C(5)—C(4)	55.4 (3)
C(3)—C(2)—C(1)—C(6)	32.1 (2)	C(2)—C(3)—C(4)—C(5)	54.9 (3)

D—H···*A*	H···*A*	*D*···*A*	*D*—H···*A*
N—H(1)···Cl	2.48 (2)	3.330 (1)	155 (2)
N—H(2)···Cl^{i}	2.19 (2)	3.120 (2)	168 (2)

Symmetry code: (i) $\frac{1}{2}+x, \frac{3}{2}-y, 1-z$.

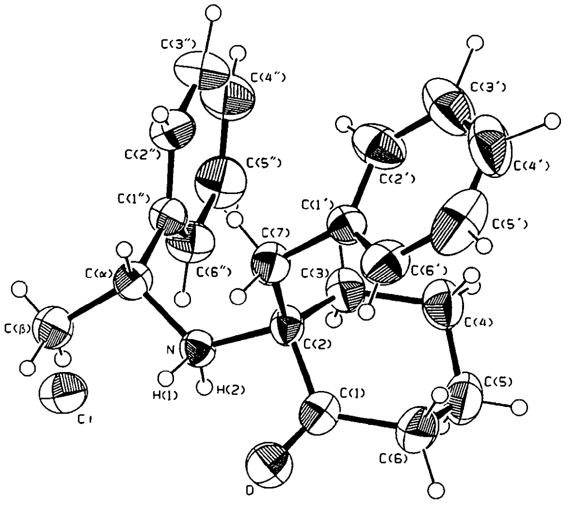


Fig. 2. *ORTEP* drawing of $C_{21}H_{25}NO.HCl$.

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* Lists of structure factors, anisotropic thermal parameters, H-atom parameters and least-squares-planes data have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55653 (25 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: BX0563]

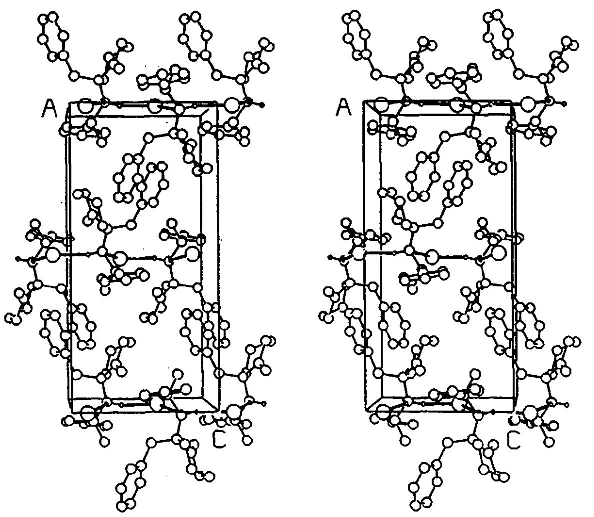

Fig. 3. Stereoscopic view of an arrangement of (+)-(3) molecules in the unit cell showing N—H(Cl) hydrogen bonds along [100].

The cyclohexanone ring is in the chair conformation. C(2), C(3), C(5) and C(6) are almost coplanar within 0.07 Å and C(1) and C(4) deviate by 0.65 and 0.40 Å, respectively, from this plane. The benzyl group is in the axial and the α-phenylethylamino group in the equatorial position. The benzyl group and the carbonyl group are on opposite sides of the C(2), C(3), C(5), C(6) plane. The dihedral angle between this least-squares plane 1 and the least-squares plane 2 [C(1′), C(2′), C(3′), C(4′), C(5′), C(6′)] is 62.96° and that between plane 1 and the least-squares plane 3 [C(1″), C(2″), C(3″), C(4″), C(5″), C(6″)] is 118.71°. Planes 2 and 3 form a dihedral angle of 63.27°.

The packing of the molecules is presented in Fig. 3, showing clearly the sandwich structure of adjoining benzyl groups and the N—H(Cl) hydrogen bonds along [100].

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Structure of 1,1,1,7,7,7-Hexafluoro-2,6-dihydroxy-2,6-bis(trifluoromethyl)-4-heptanone

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Abstract. $C_9H_6F_{12}O_3$, $M_r = 390.13$, monoclinic, $P2_1/c$, $a = 11.724\,(1)$, $b = 10.265\,(1)$, $c = 11.350\,(2)$ Å, $\beta = 99.39\,(1)°$, $V = 1347.6\,(3)$ Å^3, $Z = 4$, $D_m = 1.923\,(2)$, $D_x = 1.923$ Mg m^{-3}, λ(Cu $K\alpha$) = 1.54184 Å, $\mu = 2.28$ mm^{-1}, $F(000) = 768$, $T = 295$ K, final $R_f = 0.073$, $wR = 0.063$ for 1510 observations with $I \geq 2.5\sigma(I)$. The structure consists of discrete molecules arranged in pairs with weak dipolar interactions between the functional groups. Within each molecule there are hydrogen bonds between the ketonic carbonyl O atom and both of the alcohol functions, forming two six-membered rings.

Introduction. It is well established that highly fluorinated alcohols form strong hydrogen bonds (Willis, 1988, and references therein). We have recently shown that in the anionic alkoxycopper(II) complex $[\{HOC(CF_3)_2O\}_4Cu]^{2-}$, four hydrogen bonds link the alcohol residues into a 16-membered ring (Hynes, Payne & Willis, 1990). In general, hydrogen bonding is stronger between a fluorinated alcohol and another

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