# Crystal and Molecular Structures of
## cis-1-Phenyl-3-piperidinocyclohexan-1-ol Hydrochloride

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Mr = 295.84, triclinic, Pl, a = 6.786(1), b = 7.658(1), c = 8.561(1) Å, $\alpha$ = 108.17(1), $\beta$ = 97.94(1), $\gamma$ = 103.32(2)°, V = 400.6 Å$^3$, Z = 1, $D_m$ = 1.23, $D_x$ = 1.226 Mgm$^{-3}$, $\lambda$(Cu K$\alpha$) = 1.5418 Å, $\mu$ = 20.81 cm$^{-1}$, F(000) = 160. The structure has been solved by direct and Fourier methods and refined by a least-squares procedure to the final R = 0.043 for 1182 observed reflections ($|F_o| > 3\sigma(F_o)$). cis-1-Phenyl-3-piperidinocyclo-hexan-1-ol possessing 1,3-diaxial positions between the piperidine and hydroxyl groups is converted to the isomer with 1,3-diequatorial positions in its hydrochloride. The hydrogen bond is formed between the chloride anion and the protonated nitrogen atom of piperidine instead of the intramolecular hydrogen bond in the free cis-base between the oxygen and nitrogen atoms.

## Introduction.

In the search for synthetic analgetics of high potency and low toxicity, many piperidine derivatives have been synthesized [1]. Some of them have potent activities similar to morphine but addiction or other side effects could not be removed. Recently, it has been reported that cis-Ia and trans-1-phenyl-3-piperidinocyclohexan-1-ol (Ib) were synthesized and the analgetic activity was examined according to the hot plate and tail clip test in mice [1,2]. The preparation of Ia, Ib and the hydrochloride II is shown in Scheme. With regard to the pharmacological results of Ia and Ib, it has been shown that the trans isomer Ib possesses small but significant analgetic activity, but the cis isomer Ia is totally inactive even at 100 mg/kg dose level [2]. According to the analgetic receptor consideration by Beckett [3], the cis isomer appears to be a better fit on the analgetic receptor.

In this paper, the X-ray analysis of the hydrochloride II of the cis isomer Ia was undertaken in order to elucidate its three dimensional structure and get some information about the analgetic receptor for piperidine derivatives.

### Scheme
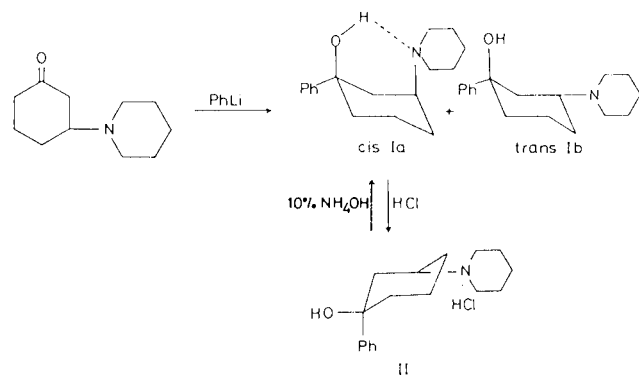


## EXPERIMENTAL

cis-Ia and trans-1-Phenyl-3-piperidinocyclohexan-1-ol (Ib) were prepared by Greenhill [2]. The cis isomer Ia was recrystallized from n-pentane, colorless prisms, mp 72-73° (260-261° for the hydrochloride); ir (potassium bromide): $\nu$ max 3150 cm$^{-1}$; nmr (deuteriochloroform): $\delta$ 1.30-2.60 (19H, m, ring methylene), 7.10-7.60 (5H, m, aromatic H); ms: m/z 259 (M$^+$), 216, 124, 105, 98, 77; high resolution ms: Found 259.1932, Calcd. for C$_{17}$H$_{25}$NO (M$^+$) 259.1934.

The trans isomer Ib was recrystallized from ethyl acetate, colorless prisms, mp 107-108° (253-254° for the hydrochloride); ir (potassium bromide): $\nu$ max 3400, 3230 cm$^{-1}$; nmr (deuteriochloroform): $\delta$ 1.10-3.00 (19H, m, ring methylene), 7.10-7.60 (5H, m, aromatic H); ms: m/z 259 (M$^+$), 216, 124, 105, 98, 77; high resolution ms: Found 259.1994, Calcd. for C$_{17}$H$_{25}$NO (M$^+$) 259.1934.

The cis isomer Ia was recovered when the hydrochloride II was basified with 10% ammonium hydroxide and extracted with ethyl ether as shown in the Scheme.

A crystal of the title compound, C$_{17}$H$_{26}$ClNO (fw 295.84), having dimensions 0.20 x 0.30 x 0.35 mm was selected for investigation. Preliminary examination of crystals shows the triclinic space group Pl. Unit cell dimensions, obtained by least-squares refinement using Bragg angles (Cu K$\alpha$, $\lambda$ = 1.5418 Å) of 25 reflections (50° < 2$\theta$ < 60°) are: a = 6.786(1), b = 7.658(1), c = 8.561(1) Å, $\alpha$ = 108.17(1), $\beta$ = 97.94(1), $\gamma$ = 103.32(2)°, Z = 1, volume = 400.6 Å$^3$, Dx = 1.226 gcm$^{-3}$, $\mu$ = 20.81 cm$^{-1}$. Intensity data were collected at room temperature on a Rigaku AFC diffractometer using Cu K$\alpha$ radiation filtered by Nikel by the $\theta$-2$\theta$ scan mode. The scan rate was 4° min$^{-1}$ in $\theta$, and the scan range in $\theta$ was varied by 1.2° + 0.15° tan$\theta$. Backgrounds were counted for 5s at both ends of the scan with an off set of 50% of the scan range from the calculated position of the K$\alpha$ peak. A total of 1382 unique reflections were measured in the range 1° < 2$\theta$ < 120°; 1182 reflections had intensities greater than 3$\sigma$ (I). The intensities of four standard reflections, measured after every 56 reflections, showed no significant variation during data collection. Lorlentz and polarization corrections were applied, but no absorption corrections were made. Standard deviations in the intensities, $\sigma$ (I), and in the structure amplitudes, $\sigma$ (Fo), were derived directly from counting statistics. The structure was solved by direct methods using MULTAN [4] to calculate phases for the 200 $|Eo|$ values greater than 1.81. The E-map obtained from the phase set with the largest combined figure of merit (2.00) revealed all non-hydrogen atoms except for an oxygen of hydroxyl group. The subsequent difference map readily gave the remaining carbon atom. The 1182 reflections (Fo > 3$\sigma$(Fo)) were used for the full-matrix least-squared refinement of

the structure, in which the function minimized was $\Sigma w(|Fo|-|Fc|)^2$ where $w = 1/\sigma^2$ (Fo). The initial refinement of non-hydrogen atoms using individual isotropic temperature factors resulted in a conventional R = $(\Sigma\|Fo|-|Fc\|)/\Sigma|Fo|$ of 0.125. Alternate Fourier maps and least-squares cycles yielded the coordinates of all hydrogen atoms. Refinement of non-hydrogen atoms with anisotropic temperature factors and hydrogen atoms with isotropic temperature factors was terminated at a conventional R of 0.042 and a weighted Rw of 0.043 (Rw = $(\Sigma w(|Fo|-|Fc|)^2/\Sigma w|Fo|^2)^{1/2}$). The hydrogen atoms refined normally with thermal parameters which ranged from 3.2 to 4.5 Å$^2$. The final

atomic positional parameters are given in Table I. The atomic scattering factors for O, N and C were those of Cromer and Weber [6]; for H, the scattering factors of Stewart, Davidson, and Simpson [7] were used.
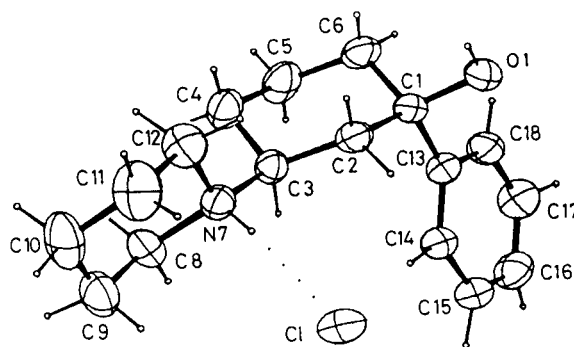


Figure 1.    ORTEP drawing of the Title Compound. Thermal ellipsoids are drawn at the 50% probability level.

Table I

Final Positional and Thermal Parameters of Non-hydrogen and Hydrogen atoms with Estimated Standard Deviations

| Atom | x | y | z | $B_{eq}/B_{iso}$ |
|---|---|---|---|---|
| CL | 0.0000 | 0.0000 | 0.0000 | 3.99 |
| C1 | −0.6661(8) | −0.0870(8) | −0.3352(7) | 2.94 |
| C2 | −0.5521(8) | −0.1396(8) | −0.1969(7) | 2.86 |
| C3 | −0.5003(8) | −0.3273(7) | −0.2643(7) | 2.81 |
| C4 | −0.6930(9) | −0.4955(9) | −0.3638(8) | 3.90 |
| C5 | −0.8043(9) | −0.4459(9) | −0.5030(8) | 4.44 |
| C6 | −0.8590(8) | −0.2604(9) | −0.4372(8) | 3.87 |
| N7 | −0.3716(7) | −0.3621(6) | −0.1239(6) | 2.94 |
| C8 | −0.2741(9) | −0.5187(9) | −0.1912(8) | 3.85 |
| C9 | −0.1199(9) | −0.5304(9) | −0.0497(9) | 5.10 |
| C10 | −0.2295(9) | −0.5638(9) | 0.0877(9) | 5.54 |
| C11 | −0.3322(9) | −0.4109(9) | 0.1514(9) | 5.56 |
| C12 | −0.4865(9) | −0.4004(9) | 0.0063(8) | 4.07 |
| C13 | −0.5305(8) | −0.0296(2) | −0.4508(7) | 2.97 |
| C14 | −0.3144(8) | 0.0099(8) | −0.4121(7) | 3.33 |
| C15 | −0.1961(8) | 0.0748(9) | −0.5154(8) | 3.62 |
| C16 | −0.2896(9) | 0.1032(9) | −0.6549(8) | 4.02 |
| C17 | −0.5043(9) | 0.0655(9) | −0.6946(8) | 4.12 |
| C18 | −0.6231(8) | 0.0011(8) | −0.5923(7) | 3.28 |
| O1 | −0.7292(6) | 0.0789(6) | −0.2599(5) | 3.60 |
| HO1 | −0.784(8) | 0.061(7) | −0.184(7) | 3.99 |
| H2A | −0.429(8) | −0.017(7) | −0.119(7) | 3.74 |
| H2B | −0.634(7) | −0.144(7) | −0.120(6) | 3.15 |
| H3 | −0.398(8) | −0.327(7) | −0.351(6) | 3.49 |
| H4A | −0.658(8) | −0.631(7) | −0.425(6) | 3.43 |
| H4B | −0.776(8) | −0.502(8) | −0.279(6) | 3.54 |
| H5A | −0.726(8) | −0.456(7) | −0.592(6) | 3.55 |
| H5B | −0.916(8) | −0.549(7) | −0.564(6) | 3.57 |
| H6A | −0.938(8) | −0.232(7) | −0.526(6) | 3.59 |
| H6B | −0.940(8) | −0.255(7) | −0.351(6) | 3.59 |
| HN7 | −0.277(7) | −0.258(7) | −0.069(6) | 3.09 |
| H8A | −0.385(8) | −0.653(8) | −0.259(7) | 3.99 |
| H8B | −0.205(7) | −0.496(7) | −0.277(6) | 3.60 |
| H9A | −0.083(8) | −0.659(8) | −0.115(7) | 4.47 |
| H9B | −0.014(8) | −0.410(7) | −0.004(7) | 3.90 |
| H10A | −0.122(8) | −0.562(7) | 0.180(6) | 3.66 |
| H10B | −0.340(8) | −0.706(8) | 0.024(7) | 4.48 |
| H11A | −0.406(8) | −0.418(8) | 0.232(6) | 3.96 |
| H11B | −0.245(8) | −0.291(8) | 0.219(7) | 4.19 |
| H12A | −0.602(8) | −0.546(7) | −0.061(6) | 3.57 |
| H12B | −0.534(8) | −0.278(7) | 0.059(6) | 3.39 |
| H14 | −0.233(7) | 0.000(7) | −0.297(6) | 3.29 |
| H15 | −0.046(7) | 0.090(7) | −0.493(6) | 3.28 |
| H16 | −0.208(8) | 0.112(7) | −0.748(7) | 4.11 |
| H17 | −0.575(8) | 0.106(7) | −0.804(7) | 3.86 |
| H18 | −0.765(8) | −0.015(7) | −0.613(7) | 4.16 |

$B_{eq}$ is isotropic equivalent of the anisotropic thermal parameters (Hamilton, 1959).
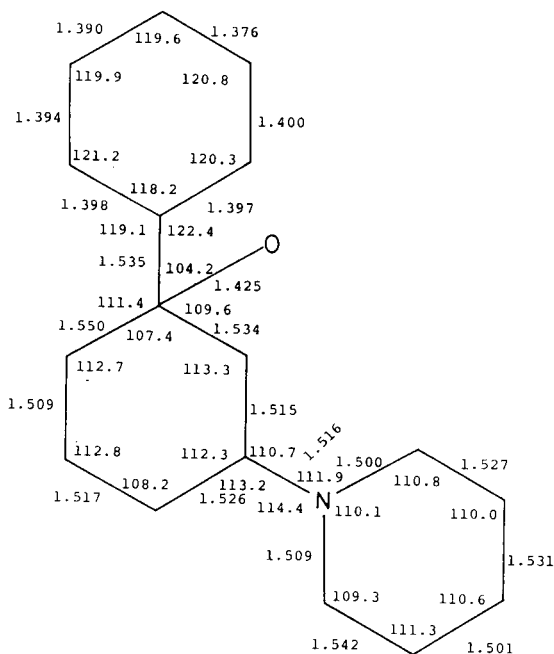


Figure 2.    Bond Lengths (Å) and Angles (°). Standard deviations ranged between 0.006 and 0.009, and 0.4 and 0.6, respectively.
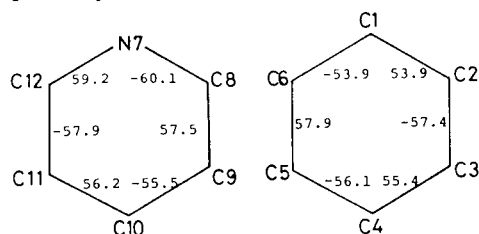


Figure 3.    Torsion Angles of Piperidine and Cyclohexane Rings.
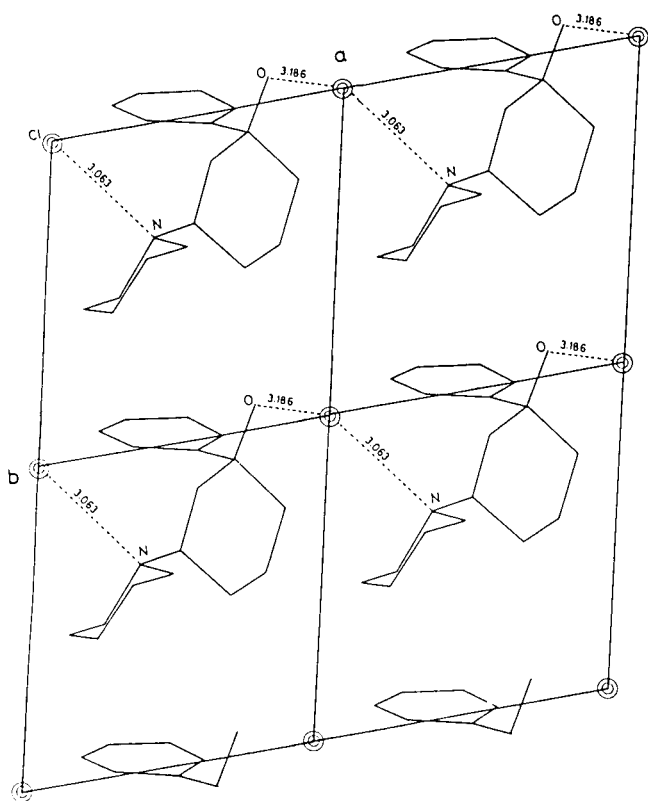
Figure 4.   Projection of the Structure Down (001).

Discussion.

The molecular geometry and the respective atom labeling are presented in the ORTEP [8] drawing of Figure 1. The bond lengths and angles are schematically shown in

Figure 2. The C-C bonds of piperidine and cyclohexane rings have the average values of 1.525 and 1.525 Å, respectively, while the C-N bond of piperidine ring has an average value of 1.505 Å. The mean bond length and angle of the phenyl group are normal values of 1.393 Å and 120.0°, respectively. Both piperidine and cyclohexane rings have the chair conformation, which are best understood in terms of torsion angles described in Figure 3. The characteristic feature of this structure is that the *cis* relation of piperidine ring to hydroxyl group in the free base interconverts to the *trans* relation in its hydrochloride. The packing of the molecules is illustrated in Figure 4. A hydrogen bond (3.186 Å) is found between the hydrogen group and the chloride anion which occupies the origin in the unit cell. Another hydrogen bond (3.063 Å) is formed between the chloride anion and protonated nitrogen atom of piperidine which forms zigzag chains along the a-axis. Other interatomic contacts correspond to the van der Waals interactions. The shortest inter-molecular distance is 3.440 Å, while the others are almost all within 3.70 Å.

## REFERENCES AND NOTES

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