Synthesis and P-388 Antitumor Properties of the Four Diastereomeric 1-Hydroxy-3,4-diaminocyclohexane-Cl_2Pt^{II} Complexes[1]

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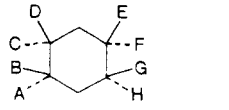
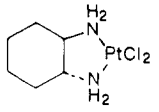
Synthesis and antileukemic activity in vivo of the four diastereomeric 1-hydroxy-3,4-diaminocyclohexane-Cl_2Pt^{II} complexes (Cl_2Pt^{II}-**3a-d**) are described. Respective bis(phenylmethyl) (1α,2α,4β)-, (1α,2α,4α)-, (1α,2β,4β)-, and (1α,2β,4α)-(4-hydroxy-1,2-cyclohexanediyl)bis(carbamates) (**5a**, **5b**, **7a**, **7b**) were prepared by hydroboration–oxidation of the bis(carbobenzoxyamino) derivatives (**4**, **5**) of *cis*- and *trans*-4,5-diaminocyclohexene. The relative stereochemistry of intermediates **5a** and **5b** was established by correlation with the alcohol obtained by $NaBH_4$ reduction of bis(phenylmethyl) (1α,2α,3α,4α)-(3,4-epoxy-1,2-cyclohexanediyl)bis(carbamate) (**8**), the all-cis stereochemistry of which was unambiguously determined by X-ray crystallographic analysis. In the P-388 murine leukemia model these monohydroxycyclohexanediamine-Pt^{II} complexes were more effective than the Pt^{II} complexes of the related diol diamines **1a-e** but were less active than the cisplatin positive control.

A previous report[2] from these laboratories detailed stereocontrolled syntheses and antineoplastic activity in a P-388 tumor model of the diastereomeric 1,2-dihydroxy-4,5-diaminocyclohexane-Cl_2Pt^{II} complexes of **1a-e**. These compounds were among the first organoplatinum agents designed to explore the utility of hydroxyl-substituted diaminocyclohexane-Pt^{II} complexes[3] in an effort to improve upon the physical and biological properties of the prototypical compound in this series, 1,2-diaminocyclohexane (DACH)-Cl_2Pt^{II} (**2**).[4,5]

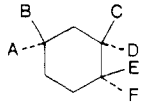
Most of these diol diamine complexes as well as their acetate esters proved to be water insoluble and consequently (likely owing to poor diffusion[2]) displayed only modest antineoplastic activity in the P-388 system. An analysis of the unit cell packing of **1b** indicated a very tight and extensive network of both intra- and intermolecular hydrogen bonding involving water. Possibly this factor was the primary cause of the limited aqueous solubility of these species. Pt^{II} complexes of monohydroxy derivatives **3a-d** were constructed to further assess hydroxyl group substitution on attenuation of physical and biological properties of organoplatinum drugs.





1 (undesignated letters = H)
a: B = D = OH; E = G = NH_2
b: A = C = OH; E = G = NH_2
c: B = C = OH; E = G = NH_2
d: B = D = OH; F = G = NH_2
e: B = C = OH; F = G = NH_2

2

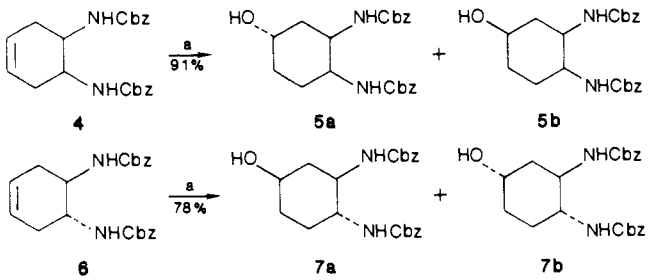


3 (undesignated letters) = H)
a: A = OH; C = E = NH_2
b: B = OH; C = E = NH_2
c: A = OH; E = D = NH_2
d: B = OH; E = D = NH_2

Chemistry

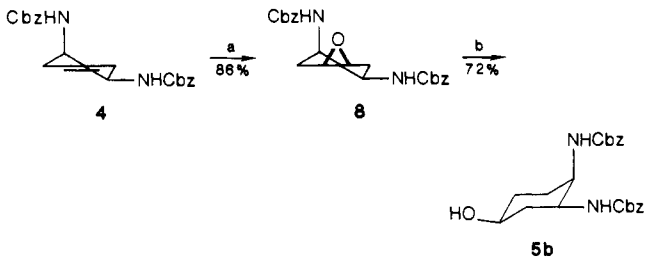
The respective bis(carbobenzoxyamino)cyclohexanols **5a,b** and **7a,b**, which served as stable sources of the easily air-oxidizable free diamines, were conveniently prepared in 91 and 78% yields, respectively, from the corresponding alkenes[2] *cis*-**4** and *trans*-**6** by hydroboration with excess B_2H_6 followed by alkaline peroxide oxidation (Scheme I) and separation by flash chromatography. By this procedure *trans*-**6** afforded **7a,b** in a ratio of 1.4:1.0. The modest level of stereocontrol observed during conversion of *cis*-**4**

Scheme I[a]



[a] a = excess B_2H_6, THF, 6 h at 0 °C, $NaOH/H_2O_2$ at −20 °C, 3 h at room temperature.

Scheme II[a]



[a] a = MCPBA, CH_2Cl_2, room temperature;[2] b = $NaBH_4$, *t*-BuOH–MeOH, reflux.

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(1) A preliminary account of this work was presented to the Division of Medicinal Chemistry, 191st National Meeting of the American Chemical Society, New York, NY. Rotella, D. P.; Witiak, D. T.; MEDI-65, 1986. This article was abstracted in part from a Ph.D. dissertation (1985) presented by D.P.R. to the Ohio State University. Present address for D.P.R. is Department of Pharmacognosy, School of Pharmacy, University of Mississippi, University, MS 38677.
(2) Witiak, D. T.; Rotella, D. P.; Filppi, J. A.; Gallucci, J. C. *J. Med. Chem.* **1987**, *30*, 1327–1336.
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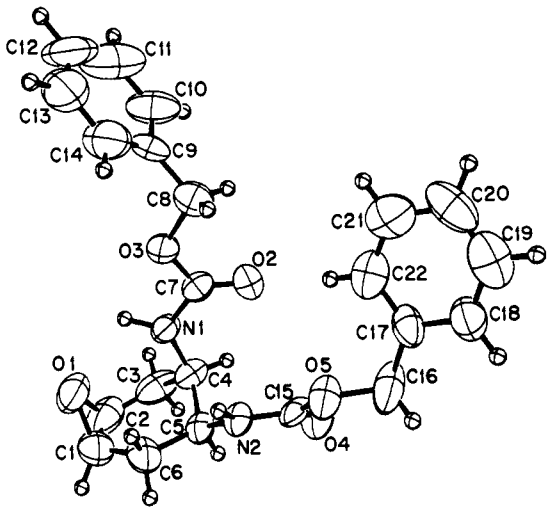
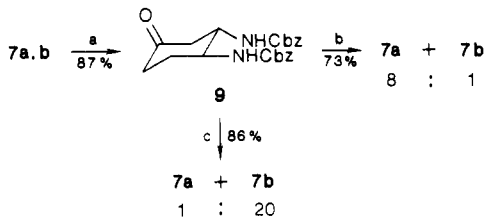


Figure 1. The ORTEP drawing for oxirane 8 was generated with 50% probability thermal ellipsoids for the non-hydrogen atoms. The hydrogen atoms are drawn with an artificial radius.

Scheme III[a]



[a] a = Jones reagent, Me_2CO; b = $NaBH_4$, EtOH, −20 °C; c = K-Selectride, THF, −78 °C.

to **5a,b** (3:1, respectively) could not be significantly improved by use of the sterically more demanding reagent disiamylborane.

NMR (500 MHz) analysis of cyclohexanols **5a,b** was not useful for making diastereomeric assignments since in a variety of solvents ($CDCl_3$, Me_2CO-d_6, or DMSO-d_6) the H-1 and H-4 proton resonance signals were observed as complex overlapping multiplets. However, oxirane 8,[2] produced free of isomeric products in 86% yield by peracid oxidation of cyclohexene **4**, underwent stereospecific reduction[6] affording cyclohexanol **5b** in 72% yield (Scheme II). The syn relationship of the oxirane ring to the *cis*-bis(CbzNH) functions in 8 was established by X-ray crystallographic analysis (Figure 1), and trans diaxial hydride ring cleavage was expected to produce the all-cis diastereomer **5b**, which was identical in all respects with the minor diastereomer obtained by the action of diborane on **4**. Delivery of the oxygen atom in 8 syn to the protected amino groups clearly implicates a Henbest-type of stereoelectronic participation[7,8] by the pseudoaxial carbamate function in **4** during epoxidation. In the absence of stereoelectronic participation, anti delivery of oxygen owing only to steric considerations would be anticipated.[9]

The relative stereochemical assignments for the epimeric trans diamino alcohols **7a,b** were supported by analysis of their respective 500-MHz ^1H NMR spectra in $CDCl_3$ solution. Thus, the axial hydrogen α to the hydroxyl group in **7a** was observed as a multiplet centered at δ 3.72 whereas the corresponding equatorial proton resonance signal multiplet in **7b** was observed further downfield (δ 4.16). Additionally, reduction of ketone **9**, prepared by oxidation of the **7a,b** mixture, with the stereochemically complimentary[10] hydride reagents K-Selectride and sodium borohydride (Scheme III) confirmed these assignments. Treatment of **9** with $NaBH_4$ in EtOH at −20 °C gave a carbinol mixture (8:1) with **7a** predominating, but reaction of **9** with K-Selectride in THF at −78 °C furnished almost exclusively the epimeric axial cyclohexanol **7b**.

Platination (K_2PtCl_4, H_2O)[4] of diamino alcohols **3a–d** following catalytic hydrogenolysis (10% Pd–C, MeOH) of the respective urethane derivatives (**5a,b**, **7a,b**) afforded Cl_2Pt^{II}-**3a** (37%), Cl_2Pt^{II}-**3b** (37%), Cl_2Pt^{II}-**3c**·$0.5H_2O$ (65%), and Cl_2Pt^{II}-**3d**·$1.0H_2O$ (49%) isolated as sparingly water-soluble yellow crystals. Trans, but not cis, diamino complexes formed hydrates.

Table I. Comparative Evaluation of Pt^{II} Complexes in P-388-Infected CDF_1 Mice[a]

compound	dose, mg/kg	MST	% T/C[b]
cisplatin	6	24.5	249
	3	18.5	188
	1.5	15.5	158
Cl_2Pt^{II}-**3a**	80	4.2	42
	40	8.5	86
	20	16.5	168
	10	15.2	154
Cl_2Pt^{II}-**3b**	80	13.5	137
	40	18.0	183
	20	15.0	153
	10	13.8	141
Cl_2Pt^{II}-**3c**	80	2.2	22
	40	3.2	32
	20	3.3	34
	10	15.8	161
Cl_2Pt^{II}-**3d**	80	2.2	22
	40	5.0	51
	20	14.5	147
	10	16.5	168

[a] P-388 tumor cells (1×10^6 cells/animal) were implanted into the peritoneal cavity of CDF_1 recipient, test mice. Drug was reconstituted in 0.3% Klucel and injected on a day 1 ip schedule. Animals were observed daily for at least 30 days and survival times were calculated as a percent treated/control (T/C). % T/C = median survival time in days (MST) of treated groups divided by MST of negative control groups × 100. [b] Toxic % T/C ≤ 85, active % T/C ≥ 120.

Biological Results and Discussion

Antineoplastic evaluation (Table I) of complexes Cl_2Pt^{II}-**3a–d** in the P-388 murine leukemia model was carried out as previously described[2] with cisplatin as a positive control. At 10 mg/kg Pt^{II} complexes of all four diastereomers were active exhibiting percent T/C values of 141–168, but none of the experimental drugs were more efficacious than cisplatin. At higher concentrations (40–80 mg/kg) only Cl_2Pt^{II}-**3b** was not toxic to the host animal. Previously we observed[2] Cl_2Pt^{II} complexes of cyclohexanediol trans diamines **1d,e** to be more toxic than cis diamine complexes of **1a–c** to the host animals, and in these studies Cl_2Pt^{II} complexes of cyclohexanol trans diamines also were most toxic to the recipient mice. The enhanced potency of mono- vs bishydroxylated species cannot easily be explained in terms of relative hydroxyl configuration, but may reflect subtle differences in crys-

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talline structure, thereby influencing drug dissolution, solubility properties, and bioavailability.

Experimental Section

Melting points were determined in open capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were recorded with a Beckman Model 4230 spectrophotometer. Nuclear magnetic resonance spectra were recorded with either a Bruker HX-90E or a 500-MHz spectrometer. TMS ($CDCl_3$) was used as internal standard. Chemical shifts are reported on the δ scale with peak multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets. THF was freshly distilled from sodium/benzophenone ketyl. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Bis(phenylmethyl) (1α,2α,4β)-(4-Hydroxy-1,2-cyclohexanediyl)bis(carbamate) (5a) and Bis(phenylmethyl) (1α,2α,4α)-(4-Hydroxy-1,2-cyclohexanediyl)bis(carbamate) (5b). Cis olefin 4 (1.5 g, 3.95 mmol) was dissolved in 50 mL of dry THF under argon and cooled in an ice bath. Diborane (1 M in THF, 12 mL, 12 mmol) was added dropwise by syringe. After 6 h at 0 °C, the reaction was cooled to −20 °C (ice–salt bath). NaOH (12 mL of a 6 N solution) and 30% H_2O_2 (8 mL) were added cautiously. The reaction was allowed to warm to room temperature over 3 h. The aqueous layer was saturated with K_2CO_3, separated from the organic layer, and extracted with 4 × 25 mL of Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford a thick oil which was purified by flash chromatography (Et_2O/Me_2CO, 20:1) to afford 0.35 g of **5b** and 1.07 g of **5a** for a total yield of 91%. Both compounds were obtained as clear oils which solidified after treatment with Et_2O/hexane. For **5b**: mp 82–86 °C, IR (KBr) 3460 (sh), 3380, 3340, 1695, 1685, 1265, 1070, and 1040 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 7.34 (s, 10 H, aromatic), 6.27 (s, 1 H, NH), 5.41 (s, 1 H, NH), 5.08 (s, 4 H, benzylic), 4.00–4.10 (m, 2 H), 3.66–3.72 (m, 1 H), 1.60–1.92 (m, 6 H, methylene). Anal. ($C_{22}H_{26}N_2O_5$) C, H, N. For **5a**: mp 163–164 °C; IR (KBr) 3460 (sh), 3320, 1725, 1700, 1675, 1270, 1245, and 1015 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 7.34 (s, 10 H, aromatic), 5.09 (br s, 6 H, 2 NH and benzylic), 4.15–4.20 (m, 1 H, H_4), 3.85–3.91 (m, 2 H, H_1 and H_2), 1.4–2.1 (m, 6 H, methylene). Anal. ($C_{22}H_{26}N_2O_5$) C, H, N.

Synthesis of 5b by $NaBH_4$ Reduction of Epoxide 8. Epoxide 8[2] (100 mg, 0.26 mmol) was dissolved in 4 mL of *t*-BuOH. $NaBH_4$ (39 mg, 1.05 mmol) was added, and the reaction was heated to reflux. MeOH (0.8 mL) was added in 0.2-mL portions every 15 min for 1 h. After 4 h, the mixture was cooled and concentrated in vacuo. The residue was partitioned between 25 mL of EtOAc and 5 mL of H_2O and washed with 2 × 10 mL of brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to afford a clear oil which was purified by flash chromatography as described above to afford 72 mg (72%) of alcohol **5b**.

Bis(phenylmethyl) (1α,2β,4α)-(4-Hydroxy-1,2-cyclohexanediyl)bis(carbamate) (7b) and Bis(phenylmethyl) (1α,2β,4β)-(4-Hydroxy-1,2-cyclohexanediyl)bis(carbamate) (7a). Trans olefin **6** (1.5 g, 3.95 mmol) was treated as described for *cis*-4. Flash chromatography of the mixture (Et_2O/Me_2CO, 25:1) afforded 0.52 g of **7b** and 0.71 g of **7a** for a total yield of 78%. For **7b**: mp 142–143 °C; IR (KBr) 3390, 3280, 1695, 1270, 1120, and 990 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 7.30 (s, 10 H, aromatic), 5.30 (d, 1 H, NH, J = 7.6 Hz), 5.14 (d, 1 H, NH, J = 7.5 Hz), 5.00–5.12 (m, 4 H, benzylic), 4.13–4.18 (m, 1 H, H_4), 3.84–3.92 (m, 1 H, H_2), 3.40–3.50 (m, 1 H, H_1), 2.19 (deceptively simple d, 1 H, H_{3e}, J = 13 Hz), 1.70–1.90 (m, 3 H, H_{5e}, H_{6e}, and H_{6a}), 1.53 (deceptively simple t, 1 H, H_{5a}, J = 12 Hz), 1.42 (deceptively simple t, 1 H, H_{3a}, J = 12.6 Hz). Anal. ($C_{22}H_{26}N_2O_5$) C, H, N. For **7a**: mp 184–185 °C; IR (KBr) 3320, 1680, 1280, 1070, and 1020 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 7.32 (s, 10 H, aromatic), 5.00–5.18 (m, 6 H, 2NH and benzylic), 3.68–3.76 (m, 1 H, H_4), 3.45–3.52 (m, 1 H, H_2), 3.36–3.45 (m, 1 H, H_1), 2.3 (deceptively simple d, 1 H, H_{3e}, J = 10 Hz), 2.07 (deceptively simple dd, 1 H, H_{6e}, J = 2 and 8 Hz), 1.98 (deceptively simple d, 1 H, H_{5e}, J = 9 Hz), 1.2–1.4 (m, 3 H, H_{5a}, H_{3a}, and H_{6a}). Anal. ($C_{22}H_{26}N_2O_5$) C, H, N.

Bis(phenylmethyl) (1α,2β)-(4-Oxo-1,2-cyclohexanediyl)bis(carbamate) (9). Alcohol mixture **7a** and **7b** (100 mg, 0.25 mmol) was dissolved in 5 mL of Me_2CO and cooled in an ice bath. Jones reagent (0.3 mL of a 2.5 M solution) was added dropwise. After 2 h at 0 °C, *i*-PrOH was added, and the inorganic salts were filtered and washed with Me_2CO. The blue-green filtrate was concentrated in vacuo, and the residue was partitioned between EtOAc (25 mL) and H_2O (10 mL). The organic layer was washed with H_2O (10 mL) and brine (2 × 10 mL) and dried (Na_2SO_4). EtOAc was removed (in vacuo) to afford 87 mg (87%) of a white powder (CCl_4): mp 135–136 °C; IR (KBr) 3320, 1725, 1685, 1280, 1240, and 1020 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 5 H, aromatic), 7.30 (s, 5 H, aromatic), 5.28 (d, 2 H, NH, J = 6.1 Hz), 5.00–5.10 (m, 4 H, benzylic), 3.75–3.90 (m, 2 H, H_1 and H_2), 2.76 (dd, 1 H, H_{3e}, J = 3.8 and 14.3 Hz), 2.45–2.55 (m, 2 H, H_{5e} and H_{5a}), 2.34 (deceptively simple t, 1 H, H_{3a}, J = 12.2 Hz), 2.20–2.30 (deceptively simple d, 1 H, H_{6e}, J = 7.6 Hz), 1.50–1.60 (m, 1 H, H_{6a}). Anal. ($C_{22}H_{24}N_2O_5$) C, H, N.

$NaBH_4$ and K-Selectride Reduction of Ketone 9 To Yield 7a,b. For $NaBH_4$ reduction, ketone **9** (100 mg, 0.26 mmol) was dissolved in 5 mL of absolute EtOH and cooled to −20 °C (dry ice/CCl_4). $NaBH_4$ (13 mg, 0.34 mmol) was added in three portions over 30 min. After 1 h at −20 °C, the reaction was concentrated to dryness. The residue was dissolved in 10 mL of EtOAc and washed with 2 × 5 mL each of H_2O and brine and dried (Na_2SO_4). The mixture was purified by flash chromatography as described above to afford 68 mg of **7a** and 7 mg of **7b** for a total yield of 72%. For K-Selectride reduction, ketone **9** (100 mg, 0.26 mmol) was dissolved in 5 mL of dry THF under argon and cooled to −78 °C. K-Selectride (0.3 mL of a 1 M solution in THF) was added dropwise by syringe. After 30 min at −78 °C, excess hydride was quenched by addition of 20 mL of Et_2O saturated with H_2O. The solution was concentrated in vacuo and the residue dissolved in 25 mL of Et_2O and washed with 2 × 5 mL each of H_2O and brine. The organic layer was dried (Na_2SO_4) and concentrated to an oil which was purified as described above, affording 82 mg of **7b** and 4 mg of **7a** for a total yield of 86%.

(*SP*-4,2-(1α,2α,4β))-Dichloro(4-hydroxy-1,2-cyclohexanediamine-*N*,*N*')platinum (Cl_2Pt^{II}-3a). Cyclohexanol **5a** (300 mg, 0.76 mmol) was added to a suspension of 60 mg of 10% Pd–C in 15 mL of MeOH. The Parr bottle was alternatively evacuated (water aspirator) and refilled five times to 20 psi with H_2 gas. The suspension was shaken at room temperature for 2 h under 20 psi H_2. The catalyst was removed by filtration and the filtrate concentrated in vacuo to afford a clear oil. Distilled deionized H_2O (15 mL) was added followed by K_2PtCl_4 (312 mg, 0.76 mmol). The flask was swirled to dissolve the salt, stoppered, covered with foil, and allowed to stand at room temperature for 24 h. The canary yellow precipitate was filtered and washed with 5% HCl solution, Me_2CO, and Et_2O, affording 112 mg (37%) of a yellow powder. Anal. ($C_6H_{14}N_2OPtCl_2$) C, H, N, Pt, Cl.

(*SP*-4,2-(1α,2α,4α))-Dichloro(4-hydroxy-1,2-cyclohexanediamine-*N*,*N*')platinum (Cl_2Pt^{II}-3b). Cyclohexanol **5b** (125 mg, 0.314 mmol) was treated as described previously. After 24 h the greenish yellow crystals were recrystallized from H_2O to afford 46 mg (37%) of similarly colored crystals of Cl_2Pt^{II}-**3b**. Anal. ($C_6H_{14}N_2OPtCl_2$) C, H, N, Pt, Cl.

(*SP*-4,2-(1α,2β,4β))-Dichloro(4-hydroxy-1,2-cyclohexanediamine-*N*,*N*')platinum (Cl_2Pt^{II}-3c). Cyclohexanol **7a** (100 mg, 0.25 mmol) was treated as described previously. The precipitate was collected and recrystallized from H_2O, affording 65 mg (65%) of Cl_2Pt^{II}-**3c** as bright yellow needles. Anal. ($C_6H_{14}N_2OPtCl_2 \cdot 0.5H_2O$) C, H, N, Pt; Cl: calcd, 17.50; found, 16.98.

(*SP*-4,2-(1α,2β,4α))-Dichloro(4-hydroxy-1,2-cyclohexanediamine-*N*,*N*')platinum (Cl_2Pt^{II}-3d). Cyclohexanol **7b** (200 mg, 0.50 mmol) was treated as described previously, affording 99 mg (48%) of Cl_2Pt^{II}-**3d** as yellow-green needles. Anal. ($C_6H_{14}N_2OPtCl_2 \cdot 1.0H_2O$): C, H, N, Pt, Cl.

X-ray Crystallographic Analysis of Oxirane 8. Crystals of oxirane **8** from Et_2O are clear and colorless. The data collection crystal was cut from a clump of crystals, and preliminary examination of its diffraction pattern on a Syntex (Nicolet) $P\bar{1}$ diffractometer indicated an orthorhombic crystal system with systematic absences $h00$, $h = 2n + 1$, $0k0$, $k = 2n + 1$, and 001, $l = 2n + 1$. The space group is uniquely determined as $P2_12_12_1$. The unit cell constants a = 9.278 (1) Å, b = 10.391 (1) Å, and c = 21.214 (1) Å were determined at ambient temperature by the least-squares fit of the diffractometer setting angles for 25 reflections

Table II. Crystallographic Details for Oxirane 8

formula	$C_{22}H_{24}N_2O_5$
formula wt	396.45
space group	$P2_12_12_1$
a, Å	9.278 (1)
b, Å	10.391 (1)
c, Å	21.214 (1)
volume, Å^3	2045
Z	4
density (calcd), g/cm^3	1.29
crystal size	0.17 mm × 0.31 mm × 0.34 mm
radiation	Mo Kα with graphite monochromator
linear abs coeff, cm^{-1}	0.86
temperature	19 °C
2θ limits	4 to 46°
scan speed	2.0 to 24.0 deg/min in 2θ
background time/scan time	0.5
scan range	$(K\alpha_1 - 1.0)°$ to $(K\alpha_2 + 1.0)°$
data collected	$+h,+k,+l$
unique data	1665
unique data, with $F_o > 0.5\sigma(F_o^2)$	1321
final number of variables	262
$R(F)^a$	0.079
$R_w(F)^b$	0.044
error in observation of unit weight, e	1.34
R(on F for $F_o^2 > 3\sigma(F_o^2)$)	0.043

$^a R(F) = \sum||F_o| - |F_c||/\sum|F_o|$. $^b R_w(F) = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$ with $w = 1/\sigma^2(F_o)$.

in the 2θ range 16 to 25° with Mo Kα radiation ($\lambda(K\bar{\alpha}) = 0.71069$ Å).

Intensities were measured by the θ–2θ scan technique out to a maximum 2θ value of 46°. The data set was such that only 807 intensities out of a total of 1665 satisfy the condition $F_o^2 > 3\sigma(F_o^2)$. Corrections for Lorentz and polarization effects were made, and the data was put onto an absolute scale by means of a Wilson plot.[11] Six standard reflections were measured after every 100 reflections during data collection and indicated no problem with crystal decomposition.

The structure was solved by the direct methods package MITHRIL,[12] with all of the atoms, except for one phenyl ring carbon atom, located at this point. The missing atom was found by standard Fourier methods. The SHELX-76 package[13] was used for all full-matrix least-squares refinements. The hydrogen atoms bonded to carbon atoms were included in the model as fixed contributions in calculated positions: C–H = 0.98 Å with $B_H = B_{Ceq} + 1.0$ Å^2. The two hydrogen atoms bonded to the nitrogen atoms were located on a difference electron density map and also included in the model as fixed contributions. The final refinement cycle resulted in agreement indices of $R = 0.079$ and $R_w = 0.044$ (based on F) for the 1321 unique intensities with $F_o^2 > 0.5\sigma(F_o^2)$ and 262 variables (anisotropic non-hydrogen atoms and hydrogen atoms fixed). The final difference electron density map is featureless, with maximum and minimum peaks of 0.24 and −0.25 e/Å^3. Scattering factors used were those provided by SHELX-76.[14] Further crystallographic details appear in Table II. Final positional parameters (Table III), bond lengths (Table IV), bond angles (Table V), deviations from least-squares planes (Table VI), selected torsion angles (Table VII), anisotropic thermal parameters (Table VIII), calculated hydrogen atom positions (Table IX), and observed and calculated structure factor amplitudes (Table X) are provided in the supplementary material.

Figure 1 shows the labeling scheme used for this structure. The amino groups occupy axial and equatorial positions and so are cis with respect to each other and they are also cis with respect to the epoxide ring. This molecule can exist as a pair of conformational enantiomers. Since the space group is $P2_12_12_1$, only one of these conformational enantiomers is present in the crystal structure reported here.

The conformation of the cyclohexane ring is best described as a distorted half-chair; atoms C3, C2, C1, and C6 lie approximately in one plane and atoms C4 and C5 are disposed on opposite sides of this plane by unequal amounts. This is more accurately described in the listing for some least-squares planes in Table VI (supplementary material). The angle between the epoxide ring and the least-squares plane through atoms C3, C2, C1, and C6 is 77°. The bond lengths within the epoxide ring vary from the expected lengths as summarized by Allen.[15] This compilation of X-ray studies of structures containing oxirane rings gives an average range for C–O bond lengths of 1.444–1.451 Å and an average range for the C–C bond length of 1.464–1.468 Å. The C2–O1 bond length for this structure is surprisingly short at 1.408 (10) Å, although it is not significantly different from the C1–O1 bond length at 1.439 (9) Å. The C1–C2 bond, 1.401 (11) Å, is also very short. It is interesting to note that the oxygen atom of the epoxide is involved in an intramolecular hydrogen bonding interaction with the axial nitrogen atom, N1. The equatorial nitrogen atom, N2, is intermolecularly hydrogen bonded to O4. Tables IV and V (supplementary material) contain the relevant distances and angles.

The conformations about the nitrogen atoms are very close to trigonal planar. In addition, the chain of atoms between the cyclohexane ring and one of the phenyl rings, C4–N1–C7–O3–C8, is close to planarity, as is the other chain, composed of atoms C5–N2–C15–O5–C16. Torsion angles for these chains are listed in Table VII (supplementary material). The N1–C4 and N2–C5 distances are as expected for an aliphatic amine–carbon bond length.

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Supplementary Material Available: Tables III–IX giving final positional parameters, bond lengths, bond angles, deviations from least-squares planes, selected torsion angles, anisotropic thermal parameters, and calculated hydrogen atom positions (7 pages); Table X giving observed and calculated structure factor amplitudes (5 pages). Ordering information is given on any current masthead page.

(11) The programs used for data reduction are from the CRYM crystallographic computing package: Duchamp, D. J.; Trus, B. L.; Westphal, B. J. (1964), California Institute of Technology, Pasadena, CA and modified by G. G. Christoph at The Ohio State University, Columbus, OH.
(12) Gilmore, C. J. *MITHRIL. A Computer Program for the Automatic Solution of Crystal Structures from X-ray Data*; University of Glasgow, Glasgow, Scotland, 1983.
(13) Sheldrick, G. M. *SHELX-76. Program for Crystal Structure Determination*; University Chemical Laboratory, Cambridge, England, 1976.
(14) Scattering factors are from *International Tables for X-ray Crystallography*; The Kynoch Press: Birmingham, England, 1974; Vol. IV, p 99.
(15) Allen, F. H. *Tetrahedron* **1982**, *38*, 2843–2853.