

The Absolute Configuration of Rimiterol, a Sympathomimetic Bronchodilator. The Crystal Structure of (*R, R*)-Ethoxy-(3,4-dihydroxyphenyl)(2-piperidiny)methane Hydrochloride

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The absolute configurations of the benzylic and 2-piperidiny centres of (+)-rimiterol have been established as (*S*) and (*R*), respectively. These assignments are based on the crystal structure determination of (*R, R*)-(-)-ethoxy(3,4-dihydroxyphenyl)(2-piperidiny)methane hydrochloride which had been prepared by reacting (+)-rimiterol with EtOH in the presence of HCl. Spin-spin coupling constants observed in the ¹H NMR spectra of (+)-rimiterol and the ethoxy compound revealed that inversion of configuration had occurred at the benzylic centre.

Racemic rimiterol hydrobromide [(±)-1·HBr; (±)-*erythro*-3,4-dihydroxyphenyl(2-piperidiny)methanol hydrobromide], introduced in 1970 as a selective β₂-adrenergic stimulant with negligible β₁-adrenergic effects, is a beneficial drug in the treatment of reversible bronchospasm in asthmatic patients.^{1–4}

Optical resolution and assignment of the absolute stereochemistry of rimiterol constitute the subject of the present report.

Results and discussion

The relative stereochemistry of the four stereoisomers of rimiterol has been inferred² from ¹H NMR data. Previous ¹H NMR studies^{5–9} of diastereomeric 1,2-amino alcohols, –CH_a(OH)–CH_b(NR₂)–, e.g. the ephedrine isomers, C₆H₅–CH(OH)–CH(CH₃)–NHCH₃,⁵ have invariably revealed that the vicinal spin-spin interaction between the H_a and H_b protons is significantly weaker in the *erythro* series than in the *threo* series; e.g. $J_{ab} = 4.0$ Hz and $J_{ab} = 8.2$ Hz, respectively, for *erythro*- and *threo*-ephedrine.⁵

In the *threo* series, intramolecular hydrogen bonding stabilizes a staggered conformation in which the dihedral angle between the C–H_a and C–H_b bonds is of the order 150–160°, implying a large coupling constant^{5,10} [cf. Fig. 1; (*R, R*)-(-)-2]. The *erythro* series is devoid of hydrogen bonding stabilization, and two of the staggered rotamers have dihedral angles in the range 80–90° between the C–H_a and C–H_b bonds. Thus, the value of J_{ab} , which reflects the weighted average of all conformations, is consistently found to be smaller in the *erythro* series^{5–9} [cf. Fig. 1; (*S, R*)-(+)-1·HBr].

The vicinal coupling constant, J_{ab} , for (±)-rimiterol hydrobromide [(±)-1·HBr] is 4.5 Hz as compared to 8.5 Hz for the diastereomeric racemate.² Consequently, (±)-rimiterol has been assigned² the *erythro* configuration [(*S, R*)-1 and (*R, S*)-1].

Our method for establishing the absolute configuration of the rimiterol enantiomers has been optical resolution followed by synthesis of a crystalline, heavy atom-containing derivative suitable for X-ray diffraction analysis.

Optical resolution. Resolution of racemic rimate-

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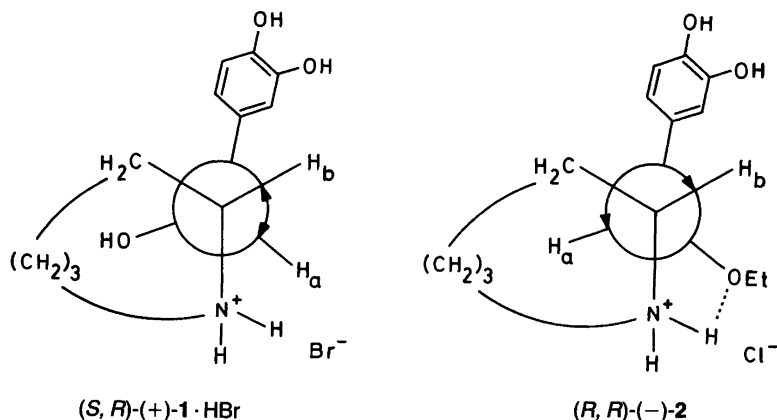


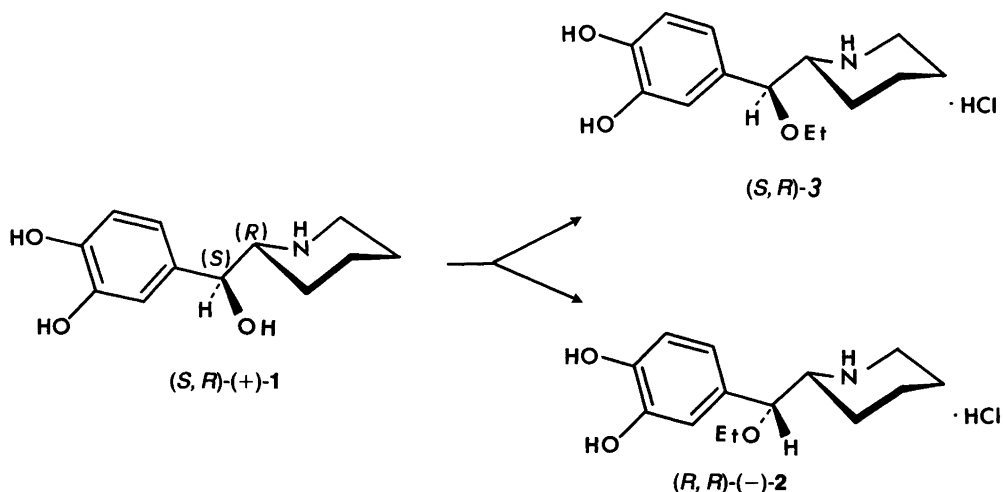
Fig. 1. Newman projections of (S, R)-(+)-1 · HBr and (R, R)-(-)-2 indicating dihedral angles between the C-H_a and C-H_b bonds in preferred conformations.

rol was accomplished by fractional crystallization of diastereomeric tartrates.¹¹ Thus, (+)-rimiterol was obtained when (R, R)-(+)-tartaric acid was utilized as resolving agent.

Crystalline derivative for X-ray analysis. *p*-Hydroxy-substituted 2-alkylamino-1-phenylethanol derivatives are known to racemize in acidic aqueous solution or to react smoothly with nucleophiles under acidic conditions;¹²⁻¹⁴ e.g., corresponding *p*-hydroxybenzyl methyl ethers are formed in excellent yields on treatment with MeOH containing HCl.¹² The presence of the

p-hydroxy group has been shown to be a prerequisite for these reactions; formation of a quinoidal intermediate by protonation of the benzylic OH group, loss of water and subsequent proton abstraction from the *p*-OH group has been postulated.¹²

On reaction with EtOH in the presence of HCl, (+)-rimiterol furnished the corresponding *threo* [(R, R)-(-)-2] and *erythro* [(S, R)-3] ethyl ether hydrochlorides in the ratio 5:1 (see Scheme 1). ¹H NMR and ¹³C NMR data, and the elemental composition (only the *threo* isomer was isolated in the pure state) established the struc-



Scheme 1. Reaction of (S, R)-(+)-rimiterol [(S, R)-(+)-1] with EtOH in the presence of HCl.

tures of the epimeric ethyl ethers. Their relative stereochemistry was deduced from the vicinal spin-spin coupling constants observed for the doublets ascribed to the benzylic protons: $J_{ab} = 3.7$ Hz and 9.5 Hz, respectively, for the *erythro* and *threo* isomers (cf. Fig. 1). The *threo* ethyl ether **2**, possessing either (*R,R*) or (*S,S*) configuration, crystallized from the product mixture as prisms which were analyzed by X-ray diffraction.

Crystal structure. A schematic drawing of the ethyl ether **2** is given in Fig. 2 and a stereoscopic view¹⁵ of the molecule is shown in Fig. 3, which reveals the absolute configuration of **2** as (*R,R*)-ethoxy(3,4-dihydroxyphenyl)(2-piperidinyl)methane hydrochloride. Since the synthesis of **2** implied inversion of configuration at the benzylic centre (*vide supra*), (+)-rimiterol is assigned the (*S,R*)-configuration [(*S,R*)-(+)-**1**; cf. Scheme 1].

Bond lengths and angles in the molecule (**2**) are all normal. The torsion angle H(16)–C(1)–C(10)–H(17) is 180°. The intramolecular distance O(1)···H(15) is 2.27(3) Å. There are a few short intermolecular distances in the crystal structure: Cl(1)···O(2) = 3.050(2) Å, Cl(1)···O(5) [$-x, \frac{1}{2} + y, \frac{1}{2} - z$] = 3.123(3) Å, Cl(1)···O(5) [$\frac{1}{2} - x, -y, \frac{1}{2} + z$] = 3.165(3) Å, O(3)···O(5) = 2.642(4) Å, and N(1)···O(4) [$-x + 1, \frac{1}{2} + y, \frac{1}{2} - z$] = 2.825(4) Å.

Experimental

Melting points were recorded on a Reichert melt-

ing point apparatus and are uncorrected. Optical rotations were recorded on a Carl Zeiss or a Perkin-Elmer 241 instrument. ¹H NMR and ¹³C NMR spectra at 270 MHz and 68 MHz, respectively, were recorded on a Jeol JNM GX 270 instrument. TMS or the central solvent peak (¹³C) of CD₃OD (δ 49.04) were used as internal references. Elemental analyses were performed by Novo Microanalytical Laboratory, Bagsværd, Denmark.

Optical resolution of (\pm)-rimiterol [(\pm)-1**]. (+)-Rimiterol (*R,R*)-(+)-tartrate. (\pm)-Rimiterol hydrobromide [(\pm)-3,4-dihydroxyphenyl(2-piperidinyl)methanol hydrobromide ((\pm)-**1** HBr)] was resolved essentially as described¹¹ by Riker Research Laboratory. To a solution of (\pm)-rimiterol hydrobromide (20.5 g; 67.4 mmol) in water (200 ml) was added 25% aqueous NH₃ (35 ml) to pH ca. 9.5. The mixture was stirred for 1 h at room temperature. A crystalline precipitate was collected by filtration, washed with water (80 ml) and propanone (40 ml), and dried, furnishing (\pm)-rimiterol base (14.4 g; 96%). (*R,R*)-(+)-Tartaric acid (10.1 g; 67.3 mmol) and MeOH (170 ml) was added to the base and the mixture heated to reflux temperature. Some insoluble material was removed by filtering the hot solution through Celite. The volume was reduced to about 50 ml and the solution left at ambient temperature overnight. The crystalline precipitate (ca. 19 g) was recrystallized five times from MeOH (40 ml was used each time) at 5°C, furnishing (+)-rimi-**

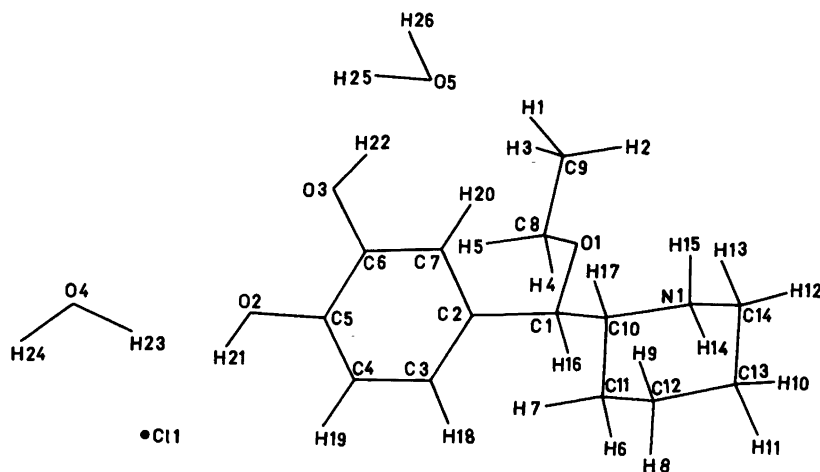


Fig. 2. Schematic drawing of (*R,R*)-ethoxy(3,4-dihydroxyphenyl)(2-piperidinyl)methane hydrochloride dihydrate [(*R,R*)-(-)-**2**] showing the numbering of atoms.

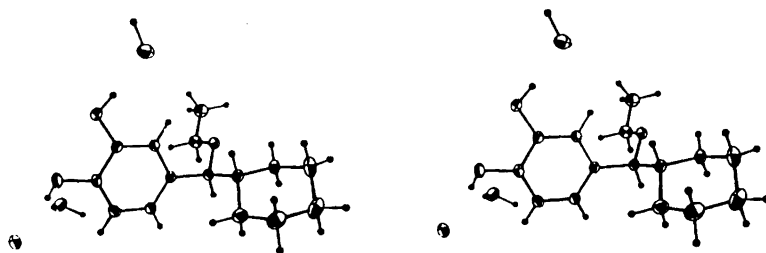


Fig. 3. Stereoscopic view¹⁵ of *(R,R)*-ethoxy(3,4-dihydroxyphenyl)(2-piperidinyl)methane hydrochloride dihydrate [(*R,R*)-(-)-2].

terol *(R,R)*-(+)-tartrate (4.43 g; 37 %). M.p. 106°C (decomp.); lit.¹¹ m.p. 105°C (decomp.); $[\alpha]_D^{20} +17.01^\circ$ (*c* 11.6; water); lit.¹¹ for the enantiomeric salt: $[\alpha]_D^{24} -17.1^\circ$ (*c* 1; water).

(S,R)-(+)-Rimiterol base [(*S,R*)-(+)-1]. To a solution of (+)-rimiterol *(R,R)*-(+)-tartrate (4.31 g; 11.5 mmol) in water (30 ml) was added 25 % aqueous NH₃ (3 ml) to pH ca. 9.5. The precipitate was isolated by filtration, washed successively with water and propanone, and dried, giving *(S,R)*-(+)-rimiterol [(*S,R*)-(+)-1] as a white powder (2.27 g; 88 %). M.p. 199–201°C (decomp.); lit.¹¹ m.p. 201°C (decomp.); $[\alpha]_D^{21} +13.5^\circ$, $[\alpha]_{578}^{21} +14.2^\circ$, $[\alpha]_{546}^{21} +15.9^\circ$, $[\alpha]_{436}^{21} +24.7^\circ$ (*c* 1.8; DMSO); ¹H NMR (CD₃OD): δ 1.2–1.65 (4H, m), 1.75–2.0 (2H, m), 2.4–2.7 (2H, m), 2.9–3.0 (1H, m), 4.24 (1H, d, *J* 7.3 Hz), 6.6–6.8 (3H, m); ¹³C NMR (CD₃OD): δ 25.2, 26.5, 28.7, 47.6, 63.4, 77.7, 114.9, 116.2, 119.3, 134.5, 146.5, 146.9; the NMR spectra were virtually identical with those of (±)-1.

(R,R)-Ethoxy(3,4-dihydroxyphenyl)(2-piperidinyl)methane hydrochloride [(*R,R*)-(-)-2]. 2.2 M HCl in dry EtOH (4 ml) was added to *(S,R)*-(+)-rimiterol [(*S,R*)-(+)-1; 296 mg; 1.33 mmol]. The solution was heated at 78°C for 5 min and then quickly cooled to room temperature. An aliquot (ca. 20 μl) was withdrawn, dissolved in D₂O and examined by ¹H NMR. The reaction was monitored by comparing the integral of the signal for the three aromatic protons at δ 6.8–7.0 with those for the benzylic protons, which appeared as doublets at δ 4.24 (*J* 9.2 Hz; *threo*) and δ 4.49 (*J* 4.4 Hz; *erythro*). When the reaction mixture had been heated for another two periods of 5 min a ratio close to 3:1 was found between the integral of the aromatic proton signal and the sum of the

integrals of the signals for the benzylic protons. A ratio of ca. 5:1 was measured between the integrals of the benzylic proton signals at δ 4.24 and δ 4.49, respectively. The reaction was then terminated by removal of excess HCl-EtOH *in vacuo*. The remaining colourless oil was redissolved in EtOH (10 ml) which was subsequently evaporated under reduced pressure. Colourless crystals (249 mg; 65 %) were obtained at room temperature from EtOH (2 ml) – diethyl ether (4 ml). Recrystallization from a mixture of MeOH and diethyl ether, and subsequently from water (181 mg in 2 ml; initially ambient temperature, then 5°C) furnished large prisms (139 mg) which, after drying *in vacuo*, appeared to be hygroscopic (weight increased on exposure to air). M.p. 159°C (bubbles appeared on the surface of the crystals at ca. 105°C); $[\alpha]_D^{20} -64.0^\circ$, $[\alpha]_{578}^{20} -66.8^\circ$, $[\alpha]_{546}^{20} -76.9^\circ$, $[\alpha]_{436}^{20} -128.1^\circ$, $[\alpha]_{365}^{20} -198.9^\circ$ (*c* 1.3; MeOH; the weight of the sample was recorded immediately after drying *in vacuo* to constant weight). ¹H NMR (D₂O): δ 1.15 (3H, t, *J* 6.96 Hz), 1.3–1.95 (6H, m), 2.99 (1H, doublet of t, *J* 2.93 and 12.82 Hz), 3.2–3.34 (1H, m), 3.36–3.5 (3H, m), 4.24 (1H, d, *J* 9.16 Hz), 6.84 (1H, doublet of d, *J* 2 and 8.1 Hz), 6.91 (1H, d, *J* 2 Hz), 6.96 (1H, d, *J* 8.1 Hz); proton decoupling experiments revealed mutual spin-spin coupling between the protons giving rise to signals at δ 2.99 and δ 4.24, respectively. ¹³C NMR (CD₃OD): δ 15.3 (q), 22.7 (t), 23.5 (t), 26.5 (t), 45.8 (t), 62.3 (d), 64.9 (t), 83.0 (d), 115.3 (d), 116.5 (d), 120.6 (d), 129.5 (s), 146.9 (s), 147.2 (s). Anal. C₁₄H₂₂ClNO₃ · 2H₂O: C, H, N.

(S,R)-Ethoxy(3,4-dihydroxyphenyl)(2-piperidinyl)methane hydrochloride [(*S,R*)-3]. The *(S,R)* ethyl ether **3** was not isolated as a pure compound. The mother liquors obtained on crystalli-

Table 1. Positional parameters and equivalent or isotropic temperature factors (\AA^2). The values are multiplied by 10^4 . $U_{\text{eq}} = (U_{11} \times U_{22} \times U_{33})^{1/3}$.

Atom	x	y	z	U_{eq} or U_{iso}
Cl(1)	-408.8(7)	-1519.4(7)	5067.9(4)	594(4)
O(1)	6830(2)	-46(1)	2178(1)	442(9)
O(2)	563(2)	180(2)	3730(1)	512(11)
O(3)	1460(2)	1000(2)	2316(1)	500(11)
O(4)	1423(3)	-3463(4)	3971(2)	812(18)
O(5)	2586(3)	2158(4)	1066(2)	770(21)
N(1)	8557(2)	1642(2)	2759(2)	461(12)
C(1)	6546(2)	255(2)	3021(1)	403(12)
C(2)	4960(2)	173(2)	3222(1)	383(11)
C(3)	4477(3)	-287(2)	3950(2)	459(13)
C(4)	3016(3)	-300(2)	4141(2)	467(14)
C(5)	2026(2)	152(2)	3591(2)	408(12)
C(6)	2501(2)	605(2)	2844(1)	402(12)
C(7)	3952(2)	616(2)	2661(2)	398(12)
C(8)	6597(4)	-1264(3)	2002(2)	565(17)
C(9)	6779(5)	-1442(4)	1102(2)	716(22)
C(10)	7065(2)	1524(2)	3106(1)	427(12)
C(11)	7045(4)	1949(3)	3994(2)	636(19)
C(12)	7618(5)	3201(3)	4074(3)	746(24)
C(13)	9111(4)	3291(3)	3714(3)	752(25)
C(14)	9103(4)	2883(3)	2830(3)	644(21)
H(1)	6608(42)	-2296(37)	948(24)	948(121)
H(2)	7727(58)	-921(46)	916(32)	1441(186)
H(3)	5905(50)	-1030(45)	846(28)	1230(175)
H(4)	7119(48)	-1785(40)	2361(27)	1249(162)
H(5)	5583(33)	-1564(26)	2225(18)	623(81)
H(6)	7582(45)	1387(35)	4303(22)	832(124)
H(7)	5994(41)	1915(32)	4227(23)	861(123)
H(8)	7662(38)	3439(30)	4664(22)	798(104)
H(9)	6981(41)	3827(35)	3777(24)	871(119)
H(10)	9487(40)	4198(32)	3715(22)	897(114)
H(11)	9967(49)	2674(39)	4105(27)	1254(150)
H(12)	9976(42)	2893(30)	2574(23)	753(105)
H(13)	8427(34)	3291(28)	2457(19)	665(91)
H(14)	9203(42)	1153(35)	3032(23)	853(125)
H(15)	8509(36)	1409(30)	2217(21)	652(95)
H(16)	7200(29)	-331(25)	3385(16)	530(74)
H(17)	6413(27)	2031(20)	2745(15)	360(59)
H(18)	5126(35)	-651(27)	4299(18)	610(89)
H(19)	2681(30)	-603(23)	4630(16)	481(73)
H(20)	4314(28)	831(22)	2109(17)	442(69)
H(21)	385(38)	-218(31)	4083(20)	654(107)
H(22)	1901(35)	1279(28)	1901(19)	614(92)
H(23)	2535(57)	-3465(43)	4132(29)	1230(164)
H(24)	1078(132)	-2992(128)	4076(84)	1780(802)
H(25)	1858(53)	2655(42)	704(28)	1253(157)
H(26)	2908(67)	1639(49)	931(37)	1976(286)

zation of (*R, R*)-(-)-2 consisted of approximately 1:1 mixtures of (*R, R*)-(-)-2 and (*S, R*)-3. The ¹H NMR spectra (CD₃OD) of these mixtures revealed one-proton doublets at δ 4.21 (*J* 9.5 Hz; *threo*) and δ 4.59 (*J* 3.7 Hz; *erythro*) ascribed to the benzylic protons of (*R, R*)-(-)-2 and (*S, R*)-3, respectively. ¹³C NMR spectra (CD₃OD) revealed two sets of lines of which the following are assigned to (*S, R*)-3: δ 15.3 (q, coinciding with the methyl signal for (*R, R*)-(-)-2; two signals appeared at δ 16.93 and δ 16.98 when D₂O was used as solvent), 23.1 (t ?), 23.4 (t ?), 23.8 (t ?), 46.5 (t), 62.7 (d), 65.9 (t), 81.2 (d), 114.9 (d), 116.6 (d), 119.6 (d), 128.8 (s), 146.6 (s), 146.7 (s).

Crystal data. (*R, R*)-Ethoxy (3,4-dihydroxyphenyl) (2-piperidinyl)methane hydrochloride dihydrate, C₁₄H₂₆NO₅Cl, *M* = 323.82. Orthorhombic space group *P* 2₁2₁2₁. *a* = 9.265(1), *b* = 11.362(1), *c* = 16.312(2) Å, *Z* = 4, *D_m* = 1.26 g cm⁻³, *D_x* = 1.252 g cm⁻³, μ (CuKα) = 21.5 cm⁻¹. Cell dimensions were found from least-squares refinement of the 2θ values of 25 reflections.

Data collection. A crystal of size 0.4×0.3×0.2 mm was used for all data collection. Unit cell dimensions and intensity data were measured at room temperature (20°C) on a CAD 4 diffractometer using graphite-monochromated (CuKα radiation (λ = 1.5418 Å). The intensities of 1955 independent Friedel pairs within θ = 76.5° were

Table 2. Ratios of calculated and observed structure factors for selected Bijvoet pairs most affected by anomalous dispersion. (+) and (-) denote (*hkl*) and (*h̄k̄l̄*), respectively.

<i>h</i>	<i>k</i>	<i>l</i>	<i>F_o</i> (+)/ <i>F_o</i> (-)	<i>F_c</i> (+)/ <i>F_c</i> (-)
4	5	1	0.78	0.80
9	3	2	1.47	1.48
9	6	3	1.32	1.25
9	7	4	1.33	1.31
5	2	7	0.73	0.72
4	6	9	1.81	2.31
9	4	10	0.67	0.64
2	2	11	0.76	0.70
4	2	14	1.57	1.40
7	3	14	1.59	1.80
2	3	16	0.63	0.66
4	5	16	1.49	1.66

measured using a ω - 2θ scan (Δω° = 0.60 + 0.14 tan θ). After sorting and merging, 3166 unique reflections with *I* > 2σ(*I*) were used for the structure determination. Corrections were

Table 3. Selected bond distances (Å) and bond angles (°) for non-hydrogen atoms. Standard deviations in parentheses.

Distance			
O(1)	-C(1)		1.422(3)
O(1)	-C(8)		1.431(3)
O(2)	-C(5)		1.375(3)
O(3)	-C(6)		1.369(3)
N(1)	-C(10)		1.500(3)
N(1)	-C(14)		1.502(4)
C(1)	-C(2)		1.513(3)
C(1)	-C(10)		1.528(4)
C(2)	-C(3)		1.372(3)
C(2)	-C(7)		1.402(3)
C(3)	-C(4)		1.389(3)
C(4)	-C(5)		1.382(3)
C(5)	-C(6)		1.393(3)
C(6)	-C(7)		1.377(3)
C(8)	-C(9)		1.491(4)
C(10)	-C(11)		1.528(4)
C(11)	-C(12)		1.524(5)
C(12)	-C(13)		1.506(6)
C(13)	-C(14)		1.515(6)
Angle			
C(1)	-O(1)	-C(8)	113.4(2)
C(10)	-N(1)	-C(14)	111.4(2)
O(1)	-C(1)	-C(2)	112.6(2)
C(2)	-C(1)	-C(10)	109.9(2)
O(1)	-C(1)	-C(10)	105.4(2)
C(3)	-C(2)	-C(7)	119.0(2)
C(3)	-C(2)	-C(1)	122.6(2)
C(7)	-C(2)	-C(1)	118.4(2)
C(2)	-C(3)	-C(4)	121.0(2)
C(3)	-C(4)	-C(5)	119.9(2)
O(2)	-C(5)	-C(4)	123.8(2)
O(2)	-C(5)	-C(6)	116.6(2)
C(4)	-C(5)	-C(6)	119.7(2)
O(3)	-C(6)	-C(7)	123.2(2)
O(3)	-C(6)	-C(5)	116.7(2)
C(5)	-C(6)	-C(7)	120.1(2)
C(6)	-C(7)	-C(2)	120.4(2)
O(1)	-C(8)	-C(9)	108.2(3)
N(1)	-C(10)	-C(11)	109.9(2)
N(1)	-C(10)	-C(1)	109.6(2)
C(1)	-C(10)	-C(11)	113.1(2)
C(10)	-C(11)	-C(12)	111.9(3)
C(11)	-C(12)	-C(13)	110.5(3)
C(12)	-C(13)	-C(14)	110.2(3)
N(1)	-C(14)	-C(13)	111.3(3)

made for Lorentz and polarization effects and also for absorption, using an empirical method.¹⁶

Structure solution and refinements. The structure was partly solved using the MULTAN program system¹⁷ and averaged intensities. Successive Fourier syntheses revealed the remaining non-hydrogen atoms. Hydrogen atoms for which positions could be calculated were then included, and the positional and thermal (anisotropic) parameters for the non-hydrogen atoms were refined by full-matrix least-squares refinement. The positional and thermal (isotropic) parameters for the hydrogen atoms were kept constant at this stage of the refinement. Anomalous dispersion corrections for Cl were included in the last stages of refinement and without averaging the intensities. By using anomalous scattering factors for Cl with $+f'' = 0.702$,¹⁸ the refinement converged to an *R*-factor of 0.080. On changing the sign of the f'' term the refinement converged to an *R* of 0.065. On the basis of this, signs were changed for the *y*-coordinates and anisotropic temperature factors U_{12} and U_{23} . The remaining hydrogen atoms were then located from subsequent difference maps, and all the positional and thermal parameters were finally refined simultaneously to an *R*-factor of 0.040. At the end of the refinement the average shift/error ratio was 0.48 and the maximum electron density in the final difference map was $0.40 \text{ e} \cdot \text{\AA}^{-3}$. The weights used were $w = 1/\sigma^2(F)$ and the final $R_w = 0.048$. Lists of observed and calculated structure factors and anisotropic temperature parameters may be obtained from one of the authors (L.K.H.) on request.

The final positional parameters and U_{eq}/U_{iso} values corresponding to the correct absolute configuration are given in Table 1. Ratios of calculated and observed structure factors for selected Bijvoet pairs most affected by anomalous dispersion are given in Table 2. Selected bond distances and bond angles are given in Table 3. Scattering factors were taken from Ref. 19. All calculations were performed on the VAX 8600 computer at the University of Tromsø. With the exception of MULTAN, the computer programs used are included in the Oxford CRYSTALS package.²⁰

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