

Around the twofold axes there are quadrangles of O atoms with short O...O distances (Fig. 2) which have been assumed to represent hydrogen bonds and are given by dashed lines in Figs. 3 and 4. Fig. 3 depicts the connection of the molecules by hydrogen bonds in the *ac* plane, whereas Fig. 4 illustrates the way in which the hydrogen-bonding system is extended in the (**a + b**) and (**a - b**) directions, so that a three-dimensional network is formed. Fig. 2 shows that the shortest O...O distance occurs between atoms of type O(1) around which the largest deviations from tetrahedral angular values are observed. The hydrogen-bonding system is hardly affected by the disorder of  $\beta$ , as the O atoms of the superimposed molecules nearly coincide (Fig. 1). Because of the disorder the deformation density of  $\alpha$  could not be determined accurately.

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### (1*S*,3*R*,4*S*)-1-Methyl-3-(4-methoxyphenoxy-methyl)-4-phenylpiperidinium Chloride (FG4963): a Selective Inhibitor of Serotonin Uptake

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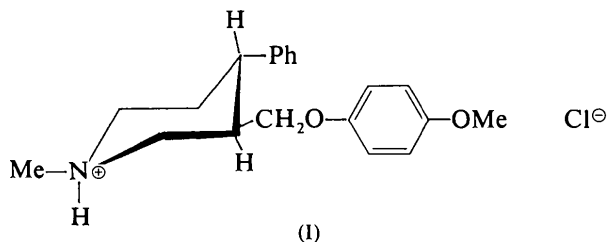
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**Abstract.**  $C_{20}H_{26}NO_2^+ \cdot Cl^-$ ,  $M_r = 347.89$ , orthorhombic,  $P2_12_12_1$ ,  $a = 6.004$  (4),  $b = 11.398$  (10),  $c = 28.587$  (17) Å,  $U = 1956$  Å<sup>3</sup>,  $Z = 4$ ,  $D_x = 1.180$  Mg m<sup>-3</sup>,  $\mu(Cu K\alpha) = 1.7$  mm<sup>-1</sup>. The structure was refined to  $R = 0.041$  for 2520 unique reflexions. Absolute configurations at N(1) and C(4) are *S*, and at C(3) *R*.  $Cl^-$  is hydrogen bonded to the positively charged N atom.

**Introduction.** The tricyclic antidepressants such as imipramine (Post, Kennard & Horn, 1975) and chlorimipramine (Post & Horn, 1977) inhibit the neuronal uptake of the biogenic amines noradrenaline (NA) and serotonin (5-hydroxytryptamine, 5-HT); this property may be related to their clinical mode of action (Horn,

1976). There is currently interest in developing more selective inhibitors of biogenic amine uptake in the hope of learning more about the neurochemical mechanisms involved in depressive states. A recently developed drug which has a more selective effect on 5-HT than on NA uptake is (3*R*,4*S*)-1-methyl-3-(4-methoxyphenoxy-methyl)-4-piperidine hydrochloride (I), which has the trivial name FG4963 (Lassen, Petersen, Kjellberg & Olsson, 1975). We report here the structure of this compound.



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A crystal in the form of a tapering needle, 0.8 × 0.15 × 0.07 mm, was used for data collection. 3651 reflexions (including a full set of Friedel opposites) were measured in the range 3° < 2θ < 116°, on a Syntex P2<sub>1</sub> diffractometer with monochromated Cu Kα radiation. Cell dimensions were obtained by a least-squares procedure from 15 strong reflexions. Systematic absences, *h*00, *h* odd; 0*k*0, *k* odd; and 00*l*, *l* odd, indicated space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>. After application of Lp corrections, averaging equivalent reflexions gave 2521 which were unique with *F* > 4σ(*F*).

Table 1. Atom coordinates (× 10<sup>4</sup>)Overall isotropic temperature factor for H atoms: 0.088 (2) Å<sup>2</sup>.

	<i>x</i>	<i>y</i>	<i>z</i>
Cl(1)	8457 (1)	10827 (1)	7549 (1)
N(1)	5489 (3)	8674 (2)	7539 (1)
C(11)	5230 (6)	8355 (3)	7040 (1)
C(2)	6541 (4)	7698 (2)	7805 (1)
C(3)	6938 (3)	8051 (2)	8312 (1)
C(4)	4683 (4)	8369 (2)	8543 (1)
C(5)	3598 (4)	9349 (2)	8257 (1)
C(6)	3292 (4)	9004 (2)	7750 (1)
C(31)	8194 (4)	7077 (2)	8562 (1)
O(32)	6738 (3)	6090 (1)	8600 (1)
C(21)	7634 (4)	5118 (2)	8820 (1)
C(22)	9682 (5)	4658 (2)	8703 (1)
C(23)	10433 (5)	3647 (2)	8924 (1)
C(24)	9142 (4)	3101 (2)	9250 (1)
C(25)	7092 (4)	3565 (2)	9372 (1)
C(26)	6357 (4)	4583 (2)	9157 (1)
O(33)	9765 (4)	2095 (2)	9489 (1)
C(34)	11672 (6)	1488 (3)	9324 (1)
C(41)	4912 (4)	8692 (2)	9055 (1)
C(42)	6339 (5)	9581 (2)	9209 (1)
C(43)	6503 (5)	9844 (2)	9680 (1)
C(44)	5269 (5)	9260 (2)	10008 (1)
C(45)	3848 (5)	8384 (3)	9860 (1)
C(46)	3662 (4)	8103 (2)	9390 (1)
H(11)	6570	9430	7559
H(111)	4707	9118	6845
H(112)	3986	7675	7008
H(113)	6796	8040	6903
H(21)	5457	6942	7795
H(22)	8117	7479	7644
H(31)	7969	8825	8336
H(41)	3624	7604	8540
H(51)	4642	10119	8273
H(52)	1988	9546	8406
H(61)	2596	9735	7560
H(62)	2171	8265	7730
H(311)	8690	7368	8906
H(312)	9655	6839	8363
H(221)	10698	5081	8440
H(231)	12049	3293	8838
H(251)	6074	3137	9632
H(261)	4772	4958	9255
H(341)	11922	692	9522
H(342)	13099	2055	9367
H(343)	11470	1275	8958
H(421)	7321	10065	8958
H(431)	7632	10527	9791
H(441)	5404	9479	10374
H(451)	2867	7910	10114
H(461)	2530	7418	9282

The structure was solved by multiresolution tangent refinement with *SHELX*. A starting set of eight reflexions was chosen from a convergence map; this provided 2<sup>7</sup> phase permutations. The best *E* map (calculated from 299 *E* > 1.2) showed all non-H

Table 2. Bond lengths (Å) and angles (°)

C(11)—N(1)	1.481 (4)	C(2)—N(1)	1.488 (4)
C(2)—C(3)	1.525 (5)	C(3)—C(4)	1.548 (5)
C(3)—C(31)	1.519 (5)	C(4)—C(5)	1.529 (5)
C(4)—C(41)	1.516 (5)	C(5)—C(6)	1.512 (5)
C(6)—N(1)	1.499 (4)	C(31)—O(32)	1.429 (4)
C(21)—O(32)	1.382 (4)	C(21)—C(22)	1.377 (5)
C(21)—C(26)	1.375 (4)	C(22)—C(23)	1.390 (5)
C(23)—C(24)	1.363 (5)	C(24)—C(25)	1.384 (5)
C(24)—O(33)	1.386 (4)	C(25)—C(26)	1.385 (5)
C(34)—O(33)	1.418 (5)	C(41)—C(42)	1.397 (5)
C(41)—C(46)	1.389 (4)	C(42)—C(43)	1.383 (5)
C(43)—C(44)	1.369 (5)	C(44)—C(45)	1.380 (5)
C(45)—C(46)	1.387 (4)		
C(11)—N(1)—C(2)	110.6 (3)	C(11)—N(1)—C(6)	111.0 (3)
C(2)—N(1)—C(6)	110.8 (3)	N(1)—C(2)—C(3)	110.8 (3)
C(2)—C(3)—C(4)	109.3 (3)	C(2)—C(3)—C(31)	109.3 (3)
C(4)—C(3)—C(31)	113.9 (3)	C(3)—C(4)—C(5)	108.5 (3)
C(3)—C(4)—C(41)	112.9 (3)	C(5)—C(4)—C(41)	112.2 (3)
C(4)—C(5)—C(6)	111.9 (3)	N(1)—C(6)—C(5)	110.1 (3)
C(3)—C(31)—O(32)	107.9 (3)	C(31)—O(32)—C(21)	115.3 (3)
O(32)—C(21)—C(22)	122.8 (3)	O(32)—C(21)—C(26)	117.2 (3)
C(22)—C(21)—C(26)	119.9 (3)	C(21)—C(22)—C(23)	119.6 (3)
C(22)—C(23)—C(24)	120.4 (4)	C(23)—C(24)—C(25)	120.2 (3)
C(23)—C(24)—O(33)	124.2 (3)	C(25)—C(24)—O(33)	115.6 (3)
C(24)—C(25)—C(26)	119.5 (3)	C(21)—C(26)—C(25)	120.3 (3)
C(24)—O(33)—C(34)	117.2 (3)	C(4)—C(41)—C(42)	122.3 (3)
C(4)—C(41)—C(46)	119.9 (3)	C(42)—C(41)—C(46)	117.7 (3)
C(41)—C(42)—C(43)	120.5 (3)	C(42)—C(43)—C(44)	121.5 (4)
C(43)—C(44)—C(45)	118.5 (3)	C(44)—C(45)—C(46)	120.9 (3)
C(41)—C(46)—C(45)	120.9 (3)		

Table 3. Selected torsion angles (°)

Sign convention as defined by Klync &amp; Prelog (1960).

C(11)—N(1)—C(2)—C(3)	176.6 (3)
C(6)—N(1)—C(2)—C(3)	-59.9 (3)
C(11)—N(1)—C(6)—C(5)	-178.9 (3)
C(2)—N(1)—C(6)—C(5)	57.7 (3)
N(1)—C(2)—C(3)—C(4)	59.6 (3)
N(1)—C(2)—C(3)—C(31)	-175.1 (3)
C(2)—C(3)—C(4)—C(5)	-57.1 (3)
C(2)—C(3)—C(4)—C(41)	178.0 (3)
C(31)—C(3)—C(4)—C(5)	-179.7 (3)
C(31)—C(3)—C(4)—C(41)	55.4 (3)
C(2)—C(3)—C(31)—O(32)	-68.3 (3)
C(4)—C(3)—C(31)—O(32)	54.3 (3)
C(3)—C(4)—C(5)—C(6)	56.9 (3)
C(41)—C(4)—C(5)—C(6)	-177.8 (3)
C(3)—C(4)—C(41)—C(42)	55.6 (4)
C(3)—C(4)—C(41)—C(46)	-125.0 (3)
C(5)—C(4)—C(41)—C(42)	-67.3 (4)
C(5)—C(4)—C(41)—C(46)	112.1 (3)
C(4)—C(5)—C(6)—N(1)	-57.2 (3)
C(3)—C(31)—O(32)—C(21)	179.9 (3)
C(31)—O(32)—C(21)—C(22)	-49.1 (4)
C(31)—O(32)—C(21)—C(26)	133.1 (3)
C(23)—C(24)—O(33)—C(34)	-11.7 (5)
C(25)—C(24)—O(33)—C(34)	170.1 (3)

atoms. Isotropic and anisotropic refinement (to  $R$  0.14 and 0.08 respectively), followed by a difference synthesis, revealed all H atoms. These were employed in all further refinements with  $X-H$  ( $X = C, N$ ) and  $\angle H-C-H$  fixed at 1.08 Å and 109.5°. The absolute configuration was established when one enantiomorph refined to an  $R$  factor 1% lower than the other.

In the final stages, an overall isotropic temperature factor was employed for the H atoms, and one reflexion clearly in error was omitted. The final  $R' = \sum w^{1/2} \Delta / \sum w^{1/2} |F_o|$  was 0.046, with a corresponding  $R$  of 0.041. The weighting scheme was  $w = 1/[\sigma^2(F) + gF^2]$ , where  $g$  refined to 0.00069; this gave mean  $w\Delta^2$  varying only slightly with  $\sin \theta$  or  $|F_o|$ . Slow refinement of the rigid methyl groups may indicate some rotational disorder, but there were no significant peaks in the methyl regions of a final difference synthesis (largest peak 0.4 e Å<sup>-3</sup>, associated with the Cl atom).

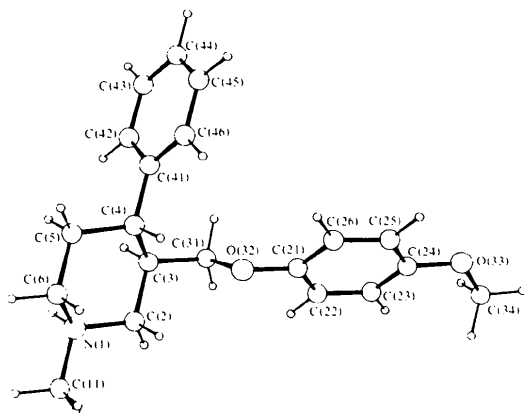


Fig. 1. Perspective view of the cation of FG4963, showing the atom numbering. H atoms are numbered such that H( $mn$ ) is the  $n$ th H on  $X$  ( $m$ ) ( $X = C$  or  $N$ ).

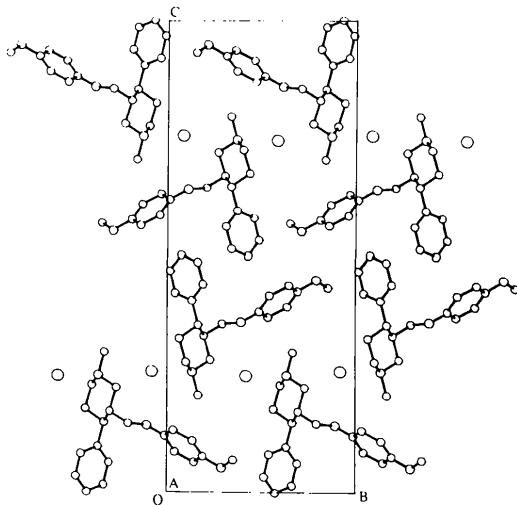


Fig. 2. Packing diagram projected down  $a$ ; H atoms have been omitted for clarity.

Final atomic coordinates are given in Table 1, bond lengths and angles and torsion angles in Tables 2 and 3. Diagrams of the structure are given in Figs. 1 and 2.\*

**Discussion.** Unlike the classical tricyclic antidepressants, FG4963 has a selective action on biogenic amine uptake, *viz* it selectively inhibits 5-HT uptake (Lassen *et al.*, 1975). Despite this selectivity, it has the same disadvantage as imipramine and chlorimipramine as regards discussion of conformation-activity relationships; it is a flexible molecule, and thus one cannot be sure that the crystal structure will correspond to the preferred conformation at the biological receptor. We have however determined various non-bonded distances (Table 4) that may be of significance when they can be compared with similar parameters in other more rigid molecules with the same pharmacological activity, such as Org. 6582 (Jones, Kennard & Horn, 1979). Results from several more compounds are needed before a meaningful comparison can be made. MO calculations on FG4963 may also be useful, to assess the energy of its various possible conformations.

Absolute configurations at N(1) and C(4) are  $S$ , and at C(3)  $R$ , consistent with the previously known relative stereochemistry at C(3) and C(4). Only one of the two possible isomers formed on protonating N(1) has crystallized.

The Cl<sup>-</sup> ion is hydrogen bonded to the positively charged N atom, with H(11)⋯Cl(1) 1.96, N(1)⋯Cl(1) 3.03 Å. There are no other unusually short non-bonded distances.

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\* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34340 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 4. Selected non-bonded distances (Å)

E.s.d.'s are not greater than 0.01 Å.

N(1) to centroids of aromatic rings:	5.72 [C(41) <i>et seq.</i> ]
	6.96 [C(21) <i>et seq.</i> ]
N(1) to planes of aromatic rings:	0.16 [C(41) <i>et seq.</i> ]
	0.94 [C(21) <i>et seq.</i> ]
N(1)⋯O(33)	9.69
N(1)⋯C(34)	10.33

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**(2*S*,4*R*)-4-Ethoxy-2-phthalimido- $\gamma$ -butyrolactone**

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**Abstract.** C<sub>14</sub>H<sub>13</sub>NO<sub>5</sub>, orthorhombic,  $P2_12_12_1$ ,  $a = 11.940$  (3),  $b = 15.725$  (3),  $c = 7.018$  (3) Å,  $Z = 4$ ,  $V = 1317.68$  Å<sup>3</sup>,  $D_c = 1.135$  Mg m<sup>-3</sup>. The structure has been refined to  $R = 0.071$  for 431 reflexions and 120 parameters. The molecular conformation may be described in terms of three planes: the phthalimido group, the lactone ring and the ethoxy side chain. The phthalimido and ethoxy planes make angles of 86.5 and 57.0° respectively with the main plane of the  $\gamma$ -butyrolactone ring. The almost planar  $\gamma$ -butyrolactone ring has substituents in positions 2 and 4 which are *trans* to each other, thus indicating that in this case the generally less stable *trans* isomer is preferred.

**Introduction.** In the continuation of our work on the stereochemistry of 2,4-disubstituted  $\gamma$ -butyrolactones (Sikirica & Vicković, 1977) we have undertaken the crystal structure analysis of the title compound.

The compound was prepared by cyclization of (2*S*)-3-formyl-2-phthalimidopropionic acid (Deljac, 1978) and recrystallized from ethanol as prismatic crystals.

The cell parameters were determined and refined from diffractometer data. The space group is  $P2_12_12_1$  with four molecules in the unit cell. The intensities were collected, at room temperature, on a Philips PW 1100/10 four-circle diffractometer (Cu  $K\alpha$  radiation,  $\lambda = 1.5418$  Å) using the  $\theta$ - $2\theta$  scanning technique:  $9.3^\circ \leq 2\theta \leq 133.4^\circ$ ; only 431 independent reflexions were measured, the option of skipping the measurement of 'weak' reflexions having been used.

An attempt to solve the structure by means of the *MULTAN* procedure (Declercq, Hull, Germain, Les-

singer, Main & Woolfson, 1976), using the measured reflexions only, was unsuccessful. The observed amplitudes were then completed by introducing the unobserved reflexions, within  $\sin \theta/\lambda = 0.6$  Å<sup>-1</sup> (66.9% of the total), with statistically evaluated amplitudes (Vicković & Viterbo, 1979) and the solution was straightforward. With 199  $E$ 's ( $E_{\min} = 1.24$ ) and 2000  $\sum_2$  relationships, 32 sets of phases were generated. The  $E$  map computed with the set having the best figures of merit revealed all 20 non-hydrogen atoms. The isotropic refinement was carried out by full-matrix least squares, using the *CRYLSQ* program of the XRAY 72 system (Stewart, Kruger, Ammon, Dickinson & Hall, 1972). Following the suggestion of Hamilton (1955), the statistically evaluated reflexions were also used in the refinement, being treated as 'less-thans'. The H atoms were located in a difference map computed in the final stages of the refinement. Their positions, but not their thermal parameters, were allowed to vary in the subsequent refinement. The final discrepancy factor was  $R = 0.071$ . The weighting function  $w = 1/\sigma^2(|F_o|)$  was used, where  $\sigma^2(|F_o|)$  is the square of the standard deviation of the observed structure factor.\*

The atomic coordinates and isotropic thermal parameters as obtained from the final refinement are given in Table 1.

\* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34376 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.