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Structures of *N*-Methyl-4-piperidinyl Diphenyl Acetate Methyl Iodide (I) and Hyoscine Methyl Iodide (II)

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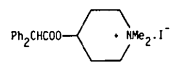
Abstract. (I): *N,N*-dimethyl-4-(diphenylacetoxy)piperidinium iodide, $C_{21}H_{26}NO_2^+.I^-$, $M_r = 451{\cdot}4$, monoclinic, $P2_1/c$, $a = 10{\cdot}106$ (4), $b = 22{\cdot}107$ (6), $c = 10{\cdot}090$ (3) Å, $\beta = 114{\cdot}11$ (2)°, $U = 2058$ (1) Å^3, $Z = 4$, $D_m = 1{\cdot}4$, $D_x = 1{\cdot}46$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 15{\cdot}5$ cm^{-1}, $F(000) = 912$, $T = 294$ K, $R(wR) = 0{\cdot}059(0{\cdot}063)$ for 3386 reflections. (II): 7-(3-hydroxy-1-oxo-2-phenylpropoxy)-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane bromide, $C_{18}H_{24}NO_4^+.I^-$, $M_r = 445{\cdot}3$, monoclinic, $P2_1$, $a = 12{\cdot}404$ (1), $b = 11{\cdot}033$ (1), $c = 6{\cdot}956$ (1) Å, $\beta = 95{\cdot}04$ (1)°, $U = 948{\cdot}3$ (2) Å^3, $Z = 2$, $D_m = 1{\cdot}6$, $D_x = 1{\cdot}56$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 16{\cdot}9$ cm^{-1}, $F(000) = 450$, $T = 294$ K, $R(wR) = 0{\cdot}022(0{\cdot}023)$ for 1713 reflections. These two structures, both 4-substituted *N,N*-dimethylpiperidines, are conformationally quite different and yet both block muscarinic acetylcholine receptors. A comparison of these two structures with other hyoscine and hyoscyamine derivatives is discussed with relevance to their biological activity.

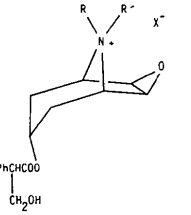
Introduction. Dale (1914) observed that the fall in blood pressure produced by low doses of acetylcholine was imitated by muscarine and the rise in blood pressure produced by much larger doses of acetylcholine was imitated by nicotine. These effects involve different receptors, muscarine-sensitive receptors in blood vessels and in the heart and nicotine-sensitive receptors in sympathetic ganglia and in the adrenal medulla. The muscarine-like effects are blocked by atropine [(±)-hyoscyamine] and the X-ray crystal structures of many atropine-like compounds have been studied (for a summary see Tollaneare, Moereels & Raymaekers, 1979). There is now reason to believe, however, that there is more than one class of 'muscarinic' receptor and the description M_1 has been given to those receptors (in sympathetic ganglia in the peripheral nervous system and in the cortex and other areas in the central nervous system) which have high affinity for the compound pirenzepine (review: Birdsall & Hulme, 1983). Other muscarinic receptors are classified as M_2 but there is evidence that these, too, may have to be subclassified, with muscarinic receptors in atria being different from those in gut and bronchial muscle.

This paper describes the crystal structure of 4-(diphenylacetoxy)-*N*-methylpiperidine methiodide (4DAMP methiodide), whose affinity for muscarinic receptors in guinea-pig ileum is about ten times that for muscarinic receptors in guinea-pig atria (Barlow, Berry, Glenton, Nikolaou & Soh, 1976; Barlow & Shepherd, 1985).

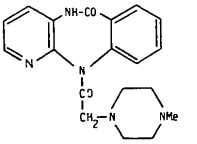
A study of (−)-hyoscine methiodide (scopolamine methiodide) has also been made. This compound shows some (but less) selectivity for receptors in ileum (Barlow & Kitchen, 1982) and we wished to compare its structure with (−)-hyoscyamine hydrobromide, which shows little selectivity, and whose structure has been examined by Küssather & Haase (1972). We also wished to compare it with (−)-hyoscine hydrobromide, studied by Pauling & Petcher (1969).



4DAMP methiodide (I)



R = R′ = Me, X = I: Hyoscine methiodide (II)
R = Me, R′ = *n*Bu, X = Br: Buscopan
R = H, no epoxide: Hyoscyamine



Pirenzepine

Experimental. Suitable crystals for diffraction studies grown from aqueous ethanol giving transparent needles, m.p. 480·5–482·2 K (I) and white opaque needles, m.p. 480·6–481·1 K (II). D_m by flotation. Crystals mounted on glass fibres, intensity data recorded (Nicolet *P*3*m*) using experimental parameters in Table 1. Structures solved by Patterson and Fourier methods using unique absorption-corrected intensities. All non-H atoms refined with anisotropic thermal parameters; H atoms constrained geometrically to ride on ligated atom;

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Table 1. *Additional crystal and experimental data for* (I) *and* (II)

	(I)	(II)
Temperature of data collection	294 K	294 K
Independent data	3932	1778
Data used in refinement	3386	1713
$I \geq n\sigma(I)$; n	3	3
$R(wR)$	0·059 (0·063)	0·022 (0·023)
Function minimized	$\sum w(F_o - \|F_c\|)^2$	$\sum w(F_o - \|F_c\|)^2$
Weighting scheme		
$w = [\sigma^2(F) + g(F^2)]^{-1}$; g	0·0015	0·0003
Scan type	ω:2θ	ω:2θ
Scan range: min., max. 2θ(°)	2·9, 55	2·9, 50
Refinement type	Block-cascade least squares	
Program system	*SHELXTL* (Sheldrick, 1981)	
Scattering factors and corrections for anomalous dispersion	*International Tables for X-ray Crystallography* (1974)	
Crystal size (mm)	0·45 × 0·25 × 0·4	0·4 × 0·3 × 0·25
Absorption correction		
number of grid points used	144	144
max., min. transmission coefficients	0·710, 0·506	0·685, 0·600
Range of hkl	008–11,21,8	$\bar{1}6,0,\bar{1}0$–16,15,0
Intensity variation of standards (%)	2·3	1·7
Frequency of standards	100	100
Unit-cell-determining reflections; 2θ range	15; 20 ≤ 2θ ≤ 30°	15; 20 ≤ 2θ ≤ 24°
Max. $\Delta\rho$, final difference Fourier map (e Å^{-3})	±2·0	±0·65
Max. Δ/σ (final)	0·03	0·06

hydroxyl atom (II) located from difference Fourier synthesis and refined.*

Discussion. Atomic coordinates are given in Table 2, bond lengths and interbond angles for (I) and (II) in Tables 3 and 4, respectively. Figs. 1 and 2 show the molecular geometries and crystallographic numbering scheme for (I) and (II), respectively.

The conformation of hyoscine methiodide is similar to those of hyoscine hydrobromide (Pauling & Petcher, 1969) and hyoscyamine hydrobromide (Küssather & Haase, 1972). This can be seen in Fig. 3(*a*) in which the atoms of the piperidine rings of (−)-(*s*)-hyoscine methiodide (II) and (−)-(*s*)-hyoscyamine are fitted by least squares. The intramolecular N···O interatomic distances of a number of hyoscine derivatives are compared in Table 5. The epoxide O atom is closer in hyoscine than in its methiodide but otherwise the distances are similar. Values for buscopan [*N*-butyl-hyoscine bromide: Leger, Gadret & Carpy (1978)] are appreciably different and this is illustrated in Fig. 3(*b*) where the piperidine rings of buscopan and hyoscine methiodide (II) are superimposed. Surprisingly, the tropic acid [$PhCH(CH_2OH)COO-$] in buscopan appears to have the *R* configuration.

The results do not suggest any obvious structural reason why (−)-hyoscine methiodide (II) has greater affinity for muscarinic receptors in ileum than for those in atria, whereas (±)-hyoscyamine (atropine) shows

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43496 (40 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Atomic coordinates* (×10^4) *and equivalent isotropic thermal parameters* (Å^2 ×10^3) *for 4DAMP methiodide* (I) *and hyoscine methiodide* (II)

	x	y	z	U*
(I)				
I	9237 (1)	−1034 (1)	7082 (1)	57 (1)
C(1)	8664 (6)	1908 (2)	5639 (7)	63 (2)
C(2)	8032 (5)	1314 (3)	5818 (7)	68 (2)
C(3)	9079 (5)	810 (2)	5994 (5)	59 (2)
N(4)	10525 (5)	908 (2)	7250 (4)	55 (2)
C(41)	10381 (7)	860 (3)	8679 (5)	66 (2)
C(42)	11538 (7)	438 (3)	7199 (7)	74 (3)
C(5)	11124 (5)	1518 (2)	7078 (6)	61 (2)
C(6)	10103 (6)	2029 (2)	6938 (6)	65 (2)
O(7)	7650 (4)	2376 (2)	5577 (4)	75 (2)
C(8)	7588 (5)	2876 (2)	4806 (5)	54 (2)
O(9)	8237 (5)	2935 (2)	4075 (4)	76 (2)
C(10)	6760 (4)	3370 (2)	5152 (4)	48 (2)
C(12)	4613 (4)	2679 (1)	4826 (3)	63 (2)
C(13)	3406	2549	5115	85 (3)
C(14)	3072	2916	6062	97 (4)
C(15)	3945	3412	6720	91 (3)
C(16)	5152	3542	6432	70 (3)
C(11)	5486	3176	5485	51 (2)
C(22)	5186 (4)	3751 (2)	2617 (4)	65 (2)
C(23)	4765	4207	1572	78 (3)
C(24)	5456	4768	1890	94 (3)
C(25)	6568	4873	3254	107 (4)
C(26)	6989	4416	4299	80 (3)
C(21)	6298	3855	3981	49 (2)
(II)				
I	6090 (1)	10112 (1)	7686 (1)	57 (1)
C(1)	3577 (3)	8971 (4)	219 (7)	59 (1)
C(2)	3101 (3)	10236 (6)	−263 (5)	59 (1)
C(3)	2648 (3)	10859 (4)	1473 (6)	59 (1)
C(4)	1818 (3)	10029 (8)	2182 (6)	69 (1)
C(5)	2358 (4)	9241 (6)	3582 (6)	72 (2)
C(6)	3555 (4)	9582 (4)	3756 (7)	54 (1)
C(7)	4113 (4)	8840 (4)	2269 (7)	64 (1)
O(1)	1621 (3)	10084 (8)	4202 (5)	95 (1)
N(1)	3552 (3)	10910 (3)	3126 (5)	50 (1)
C(21)	3301 (5)	11767 (5)	4733 (7)	77 (2)
C(22)	4624 (4)	11363 (4)	2561 (7)	63 (1)
O(2)	2723 (2)	8063 (3)	11 (4)	63 (1)
C(8)	2574 (3)	7473 (4)	−1676 (5)	51 (1)
O(3)	3103 (3)	7653 (4)	−3007 (4)	73 (1)
C(9)	1665 (3)	6574 (4)	−1603 (5)	52 (1)
C(10)	1440 (5)	5888 (5)	−3509 (7)	78 (2)
C(12)	353 (3)	6958 (3)	900 (4)	70 (2)
C(13)	−547	7540	1542	89 (2)
C(14)	−1140	8357	339	106 (3)
C(15)	−833	8592	−1507	104 (3)
C(16)	66	8010	−2149	75 (2)
C(11)	660	7193	−946	53 (1)
O(4)	2224 (4)	5031 (7)	−3800 (6)	110 (2)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 3. *Bond lengths* (Å) *and angles* (°) *for 4DAMP methiodide* (I)

C(1)–C(2)	1·504 (8)	C(1)–C(6)	1·532 (7)
C(1)–O(7)	1·439 (7)	C(2)–C(3)	1·496 (8)
C(3)–N(4)	1·508 (6)	N(4)–C(41)	1·511 (8)
N(4)–C(42)	1·473 (8)	N(4)–C(5)	1·516 (7)
C(5)–C(6)	1·497 (8)	O(7)–C(8)	1·339 (6)
C(8)–O(9)	1·178 (8)	C(8)–C(10)	1·501 (7)
C(10)–C(11)	1·519 (7)	C(10)–C(21)	1·520 (5)

C(2)–C(1)–C(6)	110·6 (4)	C(2)–C(1)–O(7)	107·7 (5)
C(6)–C(1)–O(7)	108·8 (4)	C(1)–C(2)–C(3)	110·5 (5)
C(2)–C(3)–N(4)	112·8 (4)	C(3)–N(4)–C(41)	110·7 (5)
C(3)–N(4)–C(42)	108·6 (4)	C(3)–N(4)–C(5)	109·1 (4)
C(41)–N(4)–C(5)	111·7 (4)	C(42)–N(4)–C(5)	107·9 (5)
N(4)–C(5)–C(6)	112·9 (5)	C(1)–C(6)–C(5)	109·0 (4)
C(1)–O(7)–C(8)	118·8 (5)	O(7)–C(8)–O(9)	123·3 (5)
O(7)–C(8)–C(10)	111·3 (5)	O(9)–C(8)–C(10)	124·9 (4)
C(8)–C(10)–C(11)	116·7 (4)	C(8)–C(10)–C(21)	110·8 (4)
C(10)–C(11)–C(12)	123·1 (2)	C(10)–C(11)–C(16)	116·8 (2)
C(10)–C(21)–C(22)	121·2 (2)	C(10)–C(21)–C(26)	118·8 (2)

little selectivity. The superposition of (−)-hyoscine methiodide (II) on 4DAMP methiodide (I) in Fig. 4(*a*), however, suggests that if the piperidine ring and charged N atoms fit the muscarinic receptor in the same way the benzene rings must fit quite differently.

Table 4. *Bond lengths* (Å) *and angles* (°) *for hyoscine methiodide* (II)

C(1)–C(2)	1·541 (8)	C(1)–C(7)	1·527 (6)
C(1)–O(2)	1·456 (5)	C(2)–C(3)	1·538 (6)
C(3)–C(4)	1·494 (8)	C(3)–N(1)	1·535 (6)
C(4)–C(5)	1·428 (8)	C(4)–O(1)	1·449 (5)
C(5)–C(6)	1·526 (7)	C(5)–O(1)	1·399 (8)
C(6)–C(7)	1·531 (7)	C(6)–N(1)	1·529 (6)
N(1)–C(21)	1·517 (7)	N(1)–C(22)	1·504 (6)
O(2)–C(8)	1·340 (5)	C(8)–O(3)	1·197 (5)
C(8)–C(9)	1·506 (6)	C(9)–C(10)	1·531 (6)
C(9)–C(11)	1·527 (6)	C(10)–O(4)	1·384 (9)
C(2)–C(1)–C(7)	114·6 (4)	C(2)–C(1)–O(2)	109·9 (3)
C(7)–C(1)–O(2)	106·4 (4)	C(1)–C(2)–C(3)	113·2 (4)
C(2)–C(3)–C(4)	107·2 (4)	C(2)–C(3)–N(1)	108·1 (3)
C(4)–C(3)–N(1)	104·7 (3)	C(3)–C(4)–C(5)	107·6 (4)
C(3)–C(4)–O(1)	118·3 (5)	C(5)–C(4)–O(1)	58·2 (4)
C(4)–C(5)–C(6)	107·4 (5)	C(4)–C(5)–O(1)	61·7 (4)
C(6)–C(5)–O(1)	118·0 (5)	C(5)–C(6)–C(7)	108·0 (4)
C(5)–C(6)–N(1)	103·7 (4)	C(7)–C(6)–N(1)	108·0 (4)
C(1)–C(7)–C(6)	113·2 (4)	C(4)–O(1)–C(5)	60·2 (4)
C(3)–N(1)–C(6)	99·4 (3)	C(3)–N(1)–C(21)	113·0 (4)
C(6)–N(1)–C(21)	112·4 (4)	C(3)–N(1)–C(22)	114·9 (3)
C(6)–N(1)–C(22)	114·4 (4)	C(1)–O(2)–C(8)	117·7 (3)
O(2)–C(8)–O(3)	123·6 (4)	O(2)–C(8)–C(9)	109·7 (3)
O(3)–C(8)–C(9)	126·7 (4)	C(8)–C(9)–C(10)	112·1 (4)
C(8)–C(9)–C(11)	110·4 (3)	C(10)–C(9)–C(11)	112·9 (4)
C(9)–C(10)–O(4)	112·8 (4)	C(9)–C(11)–C(12)	119·2 (2)
C(9)–C(11)–C(16)	120·8 (2)		

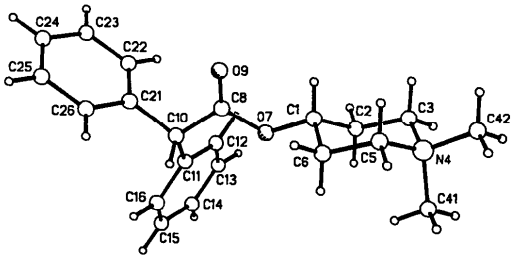

Fig. 1. Molecular structure of 4DAMP methiodide (I) and the atomic numbering scheme.

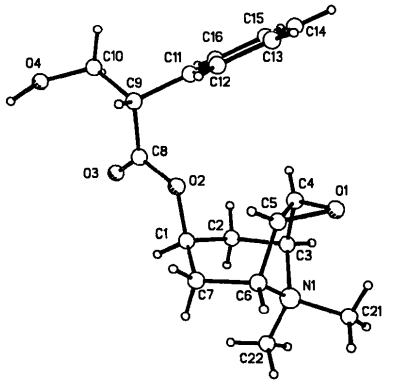

Fig. 2. Molecular structure of hyoscine methiodide (II) and the atomic numbering scheme.

(−)-Hyoscine methiodide has over 100 times the affinity of (+)-hyoscine methiodide for muscarinic receptors in ileum and just over ten times the affinity of 4DAMP methiodide. Perhaps 4DAMP methiodide fits in the form rotated through 180° about the C(1)···N axis of the piperidine ring. A comparison of 4DAMP methiodide with the M_1 receptor antagonist, pirenzepine (Trummlitz, Schmidt, Wagner & Luger, 1984) is made in Fig. 4(*b*) and shows how very different the geometries of the molecules are, even though there are structural similarities between the piperazine ring in pirenzepine and the piperidine ring of 4DAMP methiodide.

Table 5. N···O *interatomic distances* (Å)

	Ether	Carbonyl	Epoxide	Hydroxyl
(−)-Hyoscine methiodide (II)	3·901	5·568	2·790	8·161
(−)-Hyoscine hydrobromide (Pauling & Petcher, 1969)	3·88	5·41	2·47	8·04
(−)-Hyoscyamine hydrobromide (Küssather & Haase, 1972)	3·745	5·296	—	8·112
Hyoscine butylbromide (Leger, Gadret & Carpy, 1978)	3·339	4·688	2·706	5·866

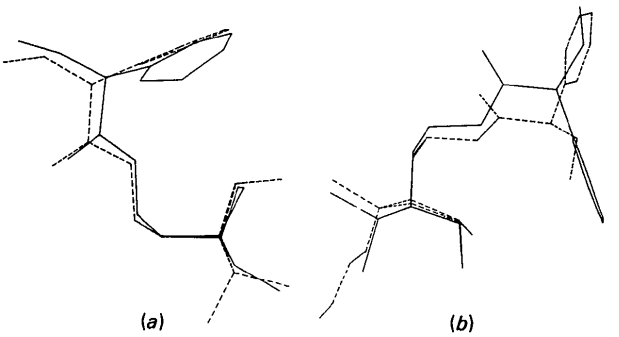

Fig. 3. Crystallographic fitting of the piperidine rings of (*a*) hyoscine methiodide [(II), dashed] and hyoscyamine (solid), (*b*) buscopan (dashed) and hyoscine methiodide [(II), solid].

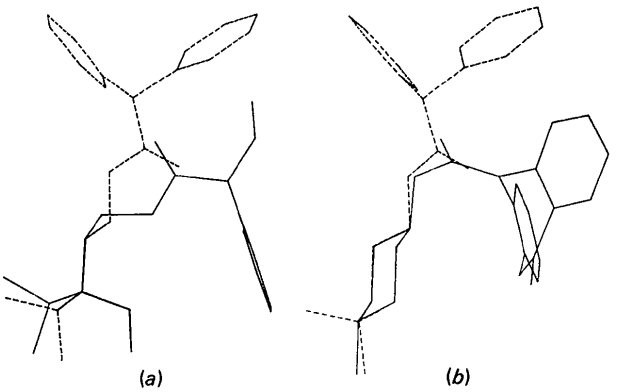

Fig. 4. Crystallographic fitting of: (*a*) the planar four-C-atom parts of the piperidine rings of 4DAMP methiodide [(I), dashed] and hyoscine methiodide [(II), solid]; (*b*) the piperidine rings of 4DAMP methiodide [(I), dashed] and pirenzepine (solid).

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Synthesis and Structure of 3-(4-Carbamoylphenyl)-1,3-dimethyltriazene 1-Oxide

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Abstract. $C_9H_{12}N_4O_2$, $M_r = 208{\cdot}22$, monoclinic, $P2_1/c$, $a = 9{\cdot}345$ (1), $b = 5{\cdot}059$ (1), $c = 21{\cdot}531$ (2) Å, $\beta = 95{\cdot}24$ (1)°, $V = 1013{\cdot}6$ Å^3, $Z = 4$, $D_x = 1{\cdot}364$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, μ(Cu $K\alpha$) = 7·955 cm^{-1}, $F(000) = 440$, $T = 298$ K, $R = 0{\cdot}063$ for 1112 significant reflections. The analysis confirms the *N*-oxide character of this compound. The triazene system is non-coplanar with the phenyl group, as a result of the relief of steric hindrance caused by the methyl group at N(1).

Introduction. Aryldialkyltriazenes have been examined extensively for possible antitumour activity in a continuing search for second-generation analogues of 5-(3,3-dimethyl-1-triazenyl)-1*H*-imidazole-4-carboxamide (DTIC; Wilman & Farmer, 1986). As a part of this study we have investigated different types of triazene *N*-oxide, including the title compound (I), in relation to both their structure and their antitumour activity (Wilman, 1985). The recent X-ray crystallographic analysis of 3-(4-carbamoylphenyl)-1-methyltriazene 1-oxide (II) (Kuroda & Wilman, 1985) has shown that, at least in the solid state, the *N*-oxide form is preferred to the *N*-hydroxyl.

The present study examines the geometry of the triazene analogue where *N*-methylation of (II) has forced the *N*-oxygenated substituent into the *N*-oxide form, since there is no longer a proton directly attached to an N atom (which instead now carries the methyl group).

Experimental. Compound (II) (Connors, Goddard, Merai, Ross & Wilman, 1976) was reacted successively in dimethylformamide with sodium hydride and iodomethane by the method of Miesel (1976) to give the title compound (CB 10-439) following chromatography on silica gel (Merck 7734) with ethyl acetate as eluant and crystallization from benzene; m.p. 478–480 K, 40% yield. Analysis calculated for $C_9H_{12}N_4O_2$: C, 51·9; H, 5·8; N, 26·9%. Found: C, 52·0; H, 5·9; N, 27·4%.

Colourless elongated crystals were readily obtained from ethanolic solution, although their tendency to twin caused difficulties in the selection of suitable single crystals. A crystal used for data collection had dimensions 0·04 × 0·05 × 0·04 mm. Cell dimensions from least-squares refinement of 25 θ values measured on an Enraf–Nonius CAD-4 diffractometer. Intensity measurements with ω–2θ scans, $1{\cdot}5 < \theta < 65{\cdot}0°$. $0 \le h \le 10$, $0 \le k \le 5$, $-25 \le l \le 25$, max. scan time 90 s. No significant change in three control reflections measured every 3600 s. 1881 unique reflections were measured, of which 1112 had $I > 2\sigma(I)$ and were used for refinement. Structure solved by *MULTAN*82 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982). Refined by a full-matrix

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