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# Structures of Colchicine Analogues. IV. An Aminodibromoallocolchicine, $C_{20}H_{22}Br_2N_2O_4$

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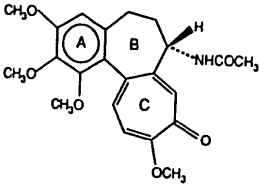
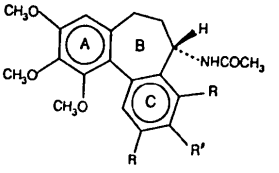
**Abstract.** *N*-(3-Amino-2,4-dibromo-6,7-dihydro-9,10,11-trimethoxy-5*H*-dibenzo[*a*,*c*]cycloheptен-5-yl)acetamide, $M_r = 514{\cdot}2$, monoclinic, $C2$, $a = 26{\cdot}331$ (2), $b = 9{\cdot}472$ (1), $c = 8{\cdot}311$ (1) Å, $\beta = 92{\cdot}50$ (1)°, $V = 2070{\cdot}9$ (2) Å$^3$, $Z = 4$, $D_x = 1{\cdot}649$ Mg m$^{-3}$, $\lambda$(Cu $K\alpha$) = 1·5418 Å, $\mu = 4{\cdot}88$ mm$^{-1}$, $F(000) = 1032$, $T = 290$ (1) K, final $R = 0{\cdot}032$ for 1642 observed data. The biaryl *A*/*C* ring system in this inactive colchicine analogue adopts an abnormal '*R*' configuration resulting from an inversion of the *B*-ring conformation typical of colchicinoids. This is due to steric interaction between the acetamido group and the bromine adjacent to it. Hydrogen bonds involving the acetamido groups link the molecules into infinite spirals along [010] in the crystal.

**Introduction.** Natural (7*S*)-colchicine (I), which has an '*S*'-biaryl configuration (helicity *M*),* is a potent antimitotic agent. It inhibits microtubule assembly in eukaryotic cells by binding to a single high-affinity site on the microtubule subunit tubulin (Dustin, 1984). Extensive studies of the structure–activity relationships of colchicinoids have been reported in an attempt to elucidate the structural prerequisites essential for antimitotic activity (Brossi, Yeh, Chrzanowska, Wolff, Hamel, Lin, Quin, Suffness & Silverton, 1988). An important aspect of these studies has been the determination of the solid-state conformations of many active analogues. Allocolchicine (II) is the first non-troponoid system of the colchicinoids studied to date (Mackay, Lacey & Burden, 1989). In (II), the *C* ring is chemically rearranged to a methyl benzoate moiety, a change which confers a significant enhancement in both biological activity and affinity for the colchicine site (Fitzgerald, 1976). In this study we report the X-ray structure of an aminodibromo derivative of allocolchicine, (III), an inactive analogue of colchicine. This is the first report of an X-ray structure of a colchicinoid in which the biaryl system adopts an abnormal '*R*' configuration resulting from an inversion of the *B*-ring conformation typical of colchicinoids.




(I)




(II) $R$ = H, $R'$ = $COOCH_3$
(III) $R$ = Br, $R'$ = $NH_2$

**Experimental.** (III) was synthesized from allocolchicine (II) in four steps by Curtis rearrangement of its carboxylic acid azide derivative in the presence of benzyl alcohol, hydrogenolysis of the resulting *O*-benzylurethane to the aniline derivative, followed by bromination. Crude (III) was purified by chromatography and recrystallized from dichloromethane/light petroleum ether. A tabular crystal (*ca* 0·11 × 0·38 × 0·59 mm) was aligned on a Rigaku-AFC diffractometer; cell parameters determined by least-squares refinement for 25 strong reflections ($50 < 2\theta < 80°$); Cu $K\alpha$ radiation (graphite-crystal monochromator, $\lambda = 1{\cdot}5418$ Å); $\omega$–$2\theta$ scan, scan rate 2° min$^{-1}$, scan range $(\Delta\omega)$ $(1{\cdot}2 + 0{\cdot}5\tan\theta)°$, 10 s stationary background counts; three standard reflections monitored every 50 reflections showed no significant variation; data to $2\theta_{max} = 130°$; 1682 unique data ($h$ − 30 to 30,

* Assignments of the *R* and *S* configurations and the helicity of the *A*/*C* biaryl systems have been made according to the chirality and helicity rules of Prelog & Helmchen (1982).

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$k$ 0 to 10, $l$ 0 to 9) of which 1642 [$I \geq 2\sigma(I)$] used for refinement; corrections for Lorentz and polarization effects and for absorption (Cromer & Liberman, 1970), transmission factors 0·140–0·593. Br-atom coordinates derived from vector map; sites of C, N, O and H atoms located by successive difference syntheses. To minimize the number of variables, methyl H atoms included at idealized positions (C—H 1·08 Å) and given a common isotropic temperature factor, $B = 15$ (2) Å$^2$; coordinates of other H atoms not refined. Full-matrix least-squares refinement with anisotropic temperature factors for non-H atoms and individual isotropic temperature factors for non-methyl H atoms converged at $R = 0{\cdot}032$, $wR = 0{\cdot}041$, $S = 4{\cdot}89$ (268 parameters varied); function minimized $\sum w(|F_o| - |F_c|)^2$ with weights $(\sigma^2|F_o| + 4{\cdot}7 \times 10^{-5}|F_o|^2)^{-1}$. Four low-order terms (201, 311, 312, 202) seriously affected by extinction omitted from final refinement. At convergence $(\Delta/\sigma)_{max} = 0{\cdot}10$ [$z$ coordinate of N(2)] and $(\Delta\rho)_{max}$, $(\Delta\rho)_{min} = 0{\cdot}55$, $-0{\cdot}47$ e Å$^{-3}$. Atomic scattering factors and anomalous-dispersion corrections from *International Tables for X-ray Crystallography* (1974, Vol. IV, pp. 99, 100, 149). Figures were prepared from the output of *ORTEP*II (Johnson, 1976). Major calculations were performed with *SHELX*76 (Sheldrick, 1976) on a VAX 11/780 computer.

Table 1. *Final atomic coordinates* (C, N, O × $10^4$, Br × $10^5$) *and equivalent isotropic temperature factors for the non-*H *atoms with e.s.d.'s in parentheses*

$B_{eq} = 8\pi^2 U_{eq} = (8\pi^2/3)\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$

| | $x$ | $y$ | $z$ | $B_{eq}$(Å$^2$) |
|---|---|---|---|---|
| Br(1) | 19493 (2) | 0 | 2126 (8) | 3·50 (1) |
| Br(2) | −45 (3) | 9380 (12) | 25545 (8) | 4·25 (2) |
| C(1) | 849 (2) | −3796 (9) | 5701 (7) | 3·0 (1) |
| C(2) | 835 (2) | −5096 (9) | 6436 (6) | 3·0 (1) |
| C(3) | 1047 (2) | −6289 (8) | 5717 (8) | 3·0 (1) |
| C(4) | 1226 (2) | −6140 (8) | 4165 (8) | 3·1 (1) |
| C(4a) | 1215 (2) | −4848 (9) | 3388 (6) | 2·6 (1) |
| C(5) | 1391 (2) | −4742 (8) | 1680 (6) | 3·1 (1) |
| C(6) | 1902 (2) | −3987 (9) | 1530 (7) | 3·3 (1) |
| C(7) | 1955 (2) | −2653 (8) | 2539 (7) | 2·9 (1) |
| C(7a) | 1462 (2) | −1785 (8) | 2465 (6) | 2·7 (1) |
| C(8) | 1413 (2) | −567 (7) | 1552 (6) | 2·6 (1) |
| C(9) | 984 (2) | 299 (7) | 1488 (7) | 2·8 (1) |
| C(10) | 586 (2) | −171 (8) | 2418 (6) | 2·9 (1) |
| C(12) | 609 (2) | −1417 (8) | 3269 (7) | 3·0 (1) |
| C(12a) | 1040 (2) | −2251 (8) | 3313 (6) | 2·6 (1) |
| C(12b) | 1039 (2) | −3635 (8) | 4141 (7) | 2·4 (1) |
| C(13) | 2311 (2) | −2043 (9) | 5234 (8) | 3·2 (1) |
| C(14) | 2473 (3) | −2620 (10) | 6862 (8) | 4·3 (1) |
| C(1*M*) | 922 (4) | −2245 (12) | 7926 (10) | 5·8 (2) |
| C(2*M*) | 66 (3) | −5105 (12) | 7796 (9) | 4·8 (2) |
| C(3*M*) | 1327 (3) | −8665 (10) | 5974 (9) | 4·7 (2) |
| O(1) | 658 (2) | −2636 (6) | 6457 (5) | 3·3 (1) |
| O(2) | 608 (2) | −5304 (6) | 7903 (4) | 3·8 (1) |
| O(3) | 1046 (2) | −7528 (6) | 6566 (6) | 4·0 (1) |
| O(13) | 2332 (2) | −767 (7) | 4921 (7) | 5·5 (1) |
| N(1) | 2124 (2) | −3001 (7) | 4197 (6) | 3·1 (1) |
| N(2) | 963 (2) | 1556 (7) | 632 (7) | 3·6 (1) |

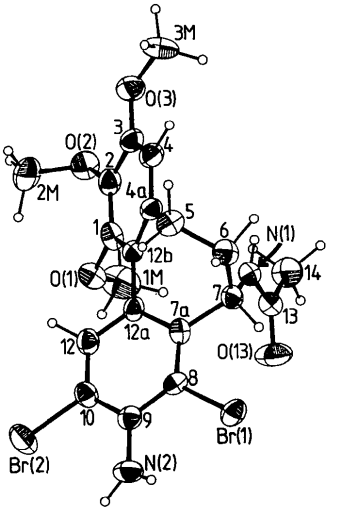


Fig. 1. A perspective view of the molecule with thermal ellipsoids scaled to 50% probability. The C symbol is omitted for carbon and the H atoms are denoted by spheres of arbitrary radius.

**Discussion.** Final atomic coordinates for the non-H atoms are given in Table 1.* The molecular conformation and the numbering scheme are illustrated in Fig. 1; bond lengths and valence angles are given in Table 2, and selected torsion angles in Table 3.

In contrast to colchicine (I) (Lessinger & Margulis, 1978*a*; Dumont, Brossi & Silverton, 1986), allocolchicine (II) (Mackay *et al.*, 1989) and other known colchicinoids, in which the *A*/*C* biaryl moiety adopts the '*S*' configuration, the '*R*' configuration is observed in (III) (Fig. 2). This no doubt results from an inversion of the *B* ring owing to steric interaction between the C(8) bromine substituent and the acetamido group, and thus causes the acetamido group in (III) to lie on the opposite side of the biaryl system relative to the other colchicinoids (see Table 3). As in (II), the phenyl ring *C*, which replaces the troponoid ring in colchicinoids, has caused a slight flattening of the *B* ring. This is reflected in the sum of the torsion angles of the *B* ring, 285° in both (I) and (III), compared with 305° in (II). Although the amino group at C(9) on the *C* ring lies in the ring plane the two bromine substituents at C(8) and C(10) lie significantly out of the plane and on opposite sides of it; for Br(1) the deviation is 0·15 (1) and for Br(2) 0·16 (1) Å. When the *A* rings of (II) and (III) are superimposed, the amino N atom at C(9) of (III) is essentially equidistant from the two O atoms of the ester function at C(9) of (II).

* Lists of structure amplitudes, anisotropic thermal parameters, H-atom coordinates and short intermolecular approaches have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54328 (22 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Bond lengths* (Å) *and valence angles* (°) *with e.s.d.'s in parentheses*

| | | | |
|---|---|---|---|
| Br(1)—C(8) | 1·913 (5) | C(7)—N(1) | 1·467 (8) |
| Br(2)—C(10) | 1·908 (6) | C(7a)—C(8) | 1·384 (9) |
| C(1)—C(2) | 1·376 (11) | C(7a)—C(12a) | 1·412 (8) |
| C(1)—C(12b) | 1·418 (8) | C(8)—C(9) | 1·395 (8) |
| C(1)—O(1) | 1·372 (9) | C(9)—C(10) | 1·402 (8) |
| C(2)—C(3) | 1·405 (10) | C(9)—N(2) | 1·387 (9) |
| C(2)—O(2) | 1·395 (7) | C(10)—C(12) | 1·376 (10) |
| C(3)—C(4) | 1·400 (9) | C(12)—C(12a) | 1·382 (9) |
| C(3)—O(3) | 1·369 (9) | C(12a)—C(12b) | 1·481 (10) |
| C(4)—C(4a) | 1·383 (11) | C(13)—C(14) | 1·504 (10) |
| C(4a)—C(5) | 1·516 (7) | C(13)—O(13) | 1·238 (11) |
| C(4a)—C(12b) | 1·397 (10) | C(13)—N(1) | 1·331 (9) |
| C(5)—C(6) | 1·534 (8) | C(1*M*)—O(1) | 1·427 (10) |
| C(6)—C(7) | 1·520 (11) | C(2*M*)—O(2) | 1·438 (10) |
| C(7)—C(7a) | 1·536 (9) | C(3*M*)—O(3) | 1·408 (10) |

| | | | |
|---|---|---|---|
| C(2)—C(1)—C(12b) | 121·3 (5) | Br(1)—C(8)—C(9) | 115·5 (4) |
| C(2)—C(1)—O(1) | 119·7 (5) | C(7a)—C(8)—C(9) | 124·5 (4) |
| C(12b)—C(1)—O(1) | 118·9 (5) | C(8)—C(9)—C(10) | 114·6 (4) |
| C(1)—C(2)—C(3) | 120·8 (5) | C(8)—C(9)—N(2) | 122·6 (4) |
| C(1)—C(2)—O(2) | 122·4 (5) | C(10)—C(9)—N(2) | 122·8 (4) |
| C(3)—C(2)—O(2) | 116·8 (5) | Br(2)—C(10)—C(9) | 118·8 (4) |
| C(2)—C(3)—C(4) | 117·8 (5) | Br(2)—C(10)—C(12) | 118·6 (4) |
| C(2)—C(3)—O(3) | 117·4 (5) | C(9)—C(10)—C(12) | 122·6 (5) |
| C(4)—C(3)—O(3) | 124·7 (5) | C(10)—C(12)—C(12a) | 121·4 (5) |
| C(3)—C(4)—C(4a) | 121·2 (5) | C(7a)—C(12a)—C(12) | 118·1 (4) |
| C(4)—C(4a)—C(5) | 119·7 (5) | C(7a)—C(12a)—C(12b) | 121·7 (5) |
| C(4)—C(4a)—C(12b) | 121·3 (5) | C(12)—C(12a)—C(12b) | 120·0 (5) |
| C(5)—C(4a)—C(12b) | 119·1 (5) | C(1)—C(12b)—C(4a) | 117·3 (5) |
| C(4a)—C(5)—C(6) | 114·3 (5) | C(1)—C(12b)—C(12a) | 121·9 (5) |
| C(5)—C(6)—C(7) | 113·7 (5) | C(4a)—C(12b)—C(12a) | 120·8 (5) |
| C(6)—C(7)—C(7a) | 111·5 (5) | C(14)—C(13)—O(13) | 122·0 (5) |
| C(6)—C(7)—N(1) | 110·4 (4) | C(14)—C(13)—N(1) | 114·7 (5) |
| C(7a)—C(7)—N(1) | 112·3 (4) | O(13)—C(13)—N(1) | 123·2 (5) |
| C(7)—C(7a)—C(8) | 121.8 (4) | C(1)—O(1)—C(1*M*) | 115·1 (5) |
| C(7)—C(7a)—C(12a) | 119·7 (5) | C(2)—O(2)—C(2*M*) | 112·9 (5) |
| C(8)—C(7a)—C(12a) | 118·5 (4) | C(3)—O(3)—C(3*M*) | 117·6 (5) |
| Br(1)—C(8)—C(7a) | 120·0 (4) | C(7)—N(1)—C(13) | 122·9 (5) |

Table 3. *Selected torsion angles* (°) *for* (III) *and related colchicinoids*

Values for the two independent molecules of colchicine (I) (Lessinger & Margulis, 1978*a*) and for allocolchicine (II) (Mackay *et al.*, 1989) are included for comparison.

| | (I) | | (II) | (III) |
|---|---|---|---|---|
| C(1*M*)—O(1)—C(1)—C(2) | −79 | −94 | −105 | 64·6 (9) |
| C(2*M*)—O(2)—C(2)—C(3) | −68 | −76 | −75 | −112·5 (7) |
| C(3*M*)—O(3)—C(3)—C(4) | −14 | 4 | −22 | 12·3 (10) |
| C(12b)—C(4a)—C(5)—C(6) | −73 | −70 | −74 | 72·6 (8) |
| C(4a)—C(5)—C(6)—C(7) | 43 | 42 | 42 | −43·7 (7) |
| C(5)—C(6)—C(7)—C(7a) | 48 | 49 | 44 | −41·5 (7) |
| C(6)—C(7)—C(7a)—C(12a) | −79 | −81 | −72 | 74·1 (7) |
| C(7)—C(7a)—C(12a)—C(12b) | 5 | 5 | −1 | −6·5 (6) |
| C(7a)—C(12a)—C(12b)—C(4a) | 53 | 53 | 50 | −44·6 (9) |
| C(12a)—C(12b)—C(4a)—C(5) | −4 | −5 | 3 | −2·1 (9) |
| C(7a)—C(7)—N(1)—C(13) | −88 | −86 | −100 | −70·7 (8) |
| C(7)—N(1)—C(13)—O(13) | 6 | 6 | −3 | 4·2 (11) |
| C(7)—N(1)—C(13)—C(14) | −178 | −176 | 179 | −178·7 (6) |
| C(12)—C(12a)—C(12b)—C(1) | 54 | 52 | 49 | −47·1 (9) |

As in other solid-state conformations of colchicinoids containing three methoxy substituents on the *A* ring, those at C(1) and C(2) are nearly orthogonal to the ring whilst that at C(3) lies close to the ring plane (*cf.* the first three torsion angles in Table 3). In (III) the methoxy groups at C(1) and C(2) point in the opposite direction. This is different from their orientation in both (I) and (II) in which they point in the same direction. However, in a number of the colchicinoids these two methoxy groups also point in opposite directions, *e.g.* in colchiceine (Silverton, 1979; Mackay, Morrison & Gulbis, 1985) and in one of the independent molecules of isocolchicine (Lessinger & Margulis, 1978*b*). The flexibility of these groups (which is due to the free rotation about the O—$CH_3$ bonds) allows their different orientations in the crystals; the observed orientations most likely arise from packing forces.

The aminodibromo analogue (III) was tested as an inhibitor of tubulin polymerization and [$^3$H]-colchicine binding to ovine tubulin and found to be inactive (E. Lacey, P. Burden & T. R. Watson, unpublished results). The lack of activity of (III) is consistent with the model of colchicine biaryl conformations required for antitubulin activity proposed by Brossi *et al.* (1988). In this model it is proposed that binding to tubulin requires the *A*/*C* rings of colchicinoids to adopt an '*S*'-biaryl configuration which results in the acetamido group lying above the *A*-ring plane as viewed in (I). The equilibrium between so-called '*S*' and '*R*' configurations is controlled by interaction between the methoxyl group at C(1) in the *A* ring and the hydrogen at C(12) in the *C* ring. For all colchicinoids reported as active, the equilibrium favours an '*S*' configuration (Brossi *et al.*, 1988) (Fig. 2*a*).

In the crystal, molecules are linked into infinite spirals along the [010] direction by hydrogen bonds, with N(1)···O(13)($\frac{1}{2}-x$, $-\frac{1}{2}+y$, $1-z$) 3·060 (9) Å. All other contacts are normal, the shortest being the Br(2)···O(3)($-x$, $y$, $1-z$) distance of 3·197 (5) Å.

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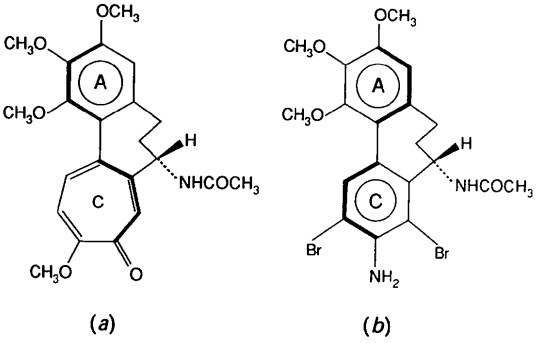


Fig. 2. (*a*) The '*S*'-biaryl configuration (helicity *M*) of natural (7*S*)-colchicine (I). (*b*) The abnormal '*R*'-biaryl configuration (helicity *P*) of (7*S*)-dibromoallocolchicine (III). These assignments have been made according to the chirality and helicity rules of Prelog & Helmchen (1982).

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# Structure of Ronidazole

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**Abstract.** (1-Methyl-5-nitro-2-imidazolyl)methyl carbamate, $C_6H_8N_4O_4$, $M_r = 200{\cdot}15$, monoclinic, $P2_1/a$, $a = 10{\cdot}336\ (5)$, $b = 7{\cdot}964\ (4)$, $c = 10{\cdot}549\ (5)$ Å, $\beta = 103{\cdot}90\ (2)°$, $V = 842{\cdot}9\ (7)$ Å$^3$, $Z = 4$, $D_m = 1{\cdot}57$, $D_x = 1{\cdot}577$ Mg m$^{-3}$, $\lambda$(Cu $K\alpha$) = 1·54178 Å, $\mu = 1{\cdot}114$ mm$^{-1}$, $F(000) = 416$, $T = 293$ K, final $R = 0{\cdot}041$ for 1288 unique [$F \geq 6\sigma(F)$] reflections. The molecules are stacked in planes parallel to the *b* axis. These molecular layers are built up by three hydrogen bonds. A fourth hydrogen bond connects these layers perpendicularly. Substituent effects on the imidazole ring angles are discussed.

**Introduction.** Nitroimidazoles are generally known as antiprotozoic and antibiotic drugs (Edwards, 1981). The investigation of ronidazole is part of an extensive structure–activity study including conformational analysis on room-temperature data as well as charge-density analysis on high-resolution data sets.

**Experimental.** Colourless crystals were obtained from a 1:1 $CHCl_3$/1,4-dioxane mixture and were used for density measurements by flotation in *n*-heptane/$CCl_4$. A prismatic crystal with approximate dimensions of 0·7 × 0·6 × 0·3 mm was mounted on a Stoe STADI-4 four-circle diffractometer with graphite-monochromated (reflection 200) Cu $K\alpha$ radiation. The space group, $P2_1/a$, was determined from observed symmetry and systematic absences. Cell dimensions were obtained by least-squares refinement of accurately determined $2\theta$ values of 24 reflections with $14 \leq 2\theta \leq 50°$. X-ray intensities were collected in the $\omega/2\theta$ scan mode up to maximum $(\sin\theta)/\lambda = 0{\cdot}588$ Å$^{-1}$ ($2\theta_{max} = 130°$) and for $0 \leq h \leq 12$, $-9 \leq k \leq 0$, $-12 \leq l \leq 12$. Intensities of three standard reflections (202, 211, 112), monitored every hour of radiation, showed no decrease in intensity. A total of 1609 reflections were measured. Symmetry-related reflections were averaged to give 1400 unique reflections of which 1288 with $F \geq 6\sigma(F)$ were used for refinement. $R_{int}$ on $F$ for observed reflections is 0·012. Data reduction with a locally adapted Stoe & Co. (1985) *REDU*4 program. Lorentz and polarization corrections were applied. Absorption corrections were performed by the method of North, Phillips & Mathews (1968) based on the observed absorption of seven reflections (200, $3\bar{1}0$, $4\bar{1}\bar{1}$, $5\bar{1}\bar{1}$, $6\bar{1}\bar{1}$, $7\bar{1}\bar{1}$, $8\bar{1}\bar{2}$) as a function of $\varphi$. The transmission factor varied between 0·81 and 1·00. Structure factors were calculated with scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Table 2.2B) and contracted hydrogen form factors from Stewart, Davidson & Simpson (1965). Anomalous-dispersion corrections were performed for all non-H atoms (Ibers & Hamilton, 1964). The structure was solved by direct methods using *MULTAN*11/82 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982) which revealed the positions of all non-H atoms. Full-matrix least-squares refinements were performed on $F$, first iso-

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