References

BAKER, M. S. & WILLIAMS, D. E. (1977). *Acta Cryst.* B33, 2325–2326.

BYSTROEM, K. (1983). *J. Comput. Chem.* **4**, 308–312.

CANNON, J. R., RASTON, C. L., TOIA, R. F. & WHITE, A. H. (1980). *Aust. J. Chem.* **33**, 2229–2236.

HOESCH, L. & WEBER, H. P. (1977). *Helv. Chim. Acta*, **60**, 3015-3019.

KRIGBAUM, W. R. & BARBER, P. G. (1971). *Acta Cryst.* B27, 1884–1891.

KRIGBAUM, W. R., CHATAIN, Y. & BARBER, P. G. (1970). *Acta Cryst.* B26, 97–102.

MAIN, P. (1982). *MULTAN*82. Department of Physics, Univ. of York, England.

MAVERICK, A. W., MAVERICK, E. F. & OLSEN, H. (1980). *Helv. Chim. Acta*, **63**, 1304–1307.

NELSON, V., SERIANZ, A. & KOVACIC, P. (1976). *J. Org. Chem.* **41**, 1751–1754.

OBER, C. K., JIN, J.-I. & LENZ, R. W. (1984). *Advances in Polymer Science.* 59. *Liquid Crystal Polymers* I, edited by M. GORDON. Berlin: Springer Verlag.

PATAI, S. (1975). Editor. *The Chemistry of the Hydrazo, Azo and Azoxy Groups*, Parts 1 and 2. New York: John Wiley.

YANDOVSKII, V. N., GIDASPOV, B. V. & TSELINSKII, I. V. (1981). *Russ. Chem. Rev.* **50**, 164–179.

Acta Cryst. (1988). C**44**, 489–495

Structure of 21-Acetoxy-11(*R*)-rifamycinol S. The Role of the One- and Two-Phase Semi-invariants in Multisolution Phasing Methods

BY S. CERRINI AND D. LAMBA

Istituto di Strutturistica Chimica 'G. Giacomello' CNR CP n. 10 – 00016 *Monterotondo Stazione, Roma, Italy*

AND M. C. BURLA, G. POLIDORI AND A. NUNZI

Dipartimento Scienze della Terra, Università di Perugia, Piazza Università, 06100 *Perugia, Italy*

(*Received* 29 *April* 1987; *accepted* 18 *September* 1987)

Abstract. $C_{39}H_{49}NO_{13}.CH_3OH.H_2O$, $M_r = 789{\cdot}87$, monoclinic, $P2_1$, $Z = 2$, $F(000) = 844$, Mo $K\alpha$ radiation, $\lambda = 0{\cdot}71069$ Å, room temperature; $a = 11{\cdot}860$ (4), $b = 9{\cdot}140$ (3), $c = 20{\cdot}423$ (4) Å, $\beta = 90{\cdot}72$ (2)°, $U = 2213$ (1) Å^3, $D_x = 1{\cdot}18$ Mg m^{-3}, μ(Mo $K\alpha$) = 0·099 mm^{-1}, $R = 0{\cdot}071$, $wR = 0{\cdot}099$ for 4043 observed reflections. The structure was solved by direct methods, using one-phase and two-phase semi-invariants in an active way. An *a posteriori* examination of the convergence/divergence map showed that conventional direct methods failed because of the role played by aberrant triplet relationships in the very early stages of the phase-extension procedure. The conformational stability of the ansa-bridge, as observed in many active rifamycin derivatives, is unaffected in this new derivative by the acetylation at O(10) and the reduction at C(11). Nevertheless the acetylation at O(10) does prevent biological activity.

Introduction. Rifamycins are a class of natural and semi-synthetic antibiotics very active on Gram-positive bacteria and mycobacteria; they act as inhibitors of the bacterial enzyme DNA-dependent RNA polymerase (Hartmann, Honikel, Knusel & Nuesch, 1967; Umezawa, Mizuno, Yamazaki & Nitta, 1968).

Many active derivatives of the natural compounds have been studied in the solid state: rifamycin B *p*-iodoanilide (RIFB) (Brufani, Cerrini, Fedeli & Vaciago, 1974), rifampicin (RIFMP) (Gadret, Goursolle, Leger & Colleter, 1975), 3-methoxycarbonyl-rifamycin S (RIFCM) (Cellai, Cerrini, Segre, Brufani, Fedeli & Vaciago, 1982*a*), rifamycin SV (RIFSV) (Arora, 1983), rifamycin S (RIFAS) (Arora, 1985), and rifamycinol (RIFOLS) (Cellai, Cerrini, Lamba, Brizzi & Brufani, 1987).

Structure–activity relationships based on structural investigations (Brufani, Cerrini, Fedeli & Vaciago, 1974; Brufani, Cellai, Cerrini, Fedeli & Vaciago, 1978) suggested the basic three-dimensional requirements for biological activity. They are: (i) the presence at the chromophoric nucleus of two oxygenated functions at C(1) and C(8), the former either in the quinone form (rifamycin S) or as free hydroxyl (rifamycin SV), the latter as free hydroxyl; (ii) the presence at the ansa-chain of two free hydroxyl groups at C(21) and C(23); (iii) the conformation of the ansa-chain being such that the spatial arrangement of the oxygenated functions is suitable for hydrogen-bond interactions.

Recently, ^{1}H NMR studies have been carried out, both in water and organic solvents, on many 3-substituted rifamycin S and SV derivatives (Cellai, Cerrini, Segre, Brufani, Fedeli & Vaciago, 1982*b*). It transpires that the oxygen atoms O(1), O(2), O(9) and O(10) show the same spatial arrangement that has been found in the solid state irrespective of the oxidation state of the chromophoric nucleus.

0108-2701/88/030489-07$03.00

Among the rifamycin derivatives, two inactive semi-synthetic compounds, rifamycin S iminomethyl ether (Arora, 1981) and cyclized rifamycin SV (Arora, 1984), have been studied in the solid state. The molecular structures show that the chemical modifications that they have undergone produce remarkable conformational changes and destroy the above-mentioned three-dimensional requirements responsible for the biological activity.

Starting from rifamycin S, other derivatives have been prepared (Brizzi, Brufani, Cellai & Segre, 1983; Brufani, Cecchini, Cellai, Federici, Guiso & Segre, 1985; Brufani, Cellai, Cozzella, Federici, Guiso & Segre, 1985) which have asymmetric carbon atoms with different chirality and different acetylation patterns on the chromophoric rings as well as on the ansa-chain.

One of these new compounds is the 21-acetoxy-11(*R*)-rifamycinol S (ARIFOLS) prepared according to standard rifamycin-chemistry procedures (Brufani, Cecchini, Cellai, Federici, Guiso & Segre, 1985) (see Fig. 1). This compound is an inactive derivative owing to the presence of the acetoxy group at C(21) of the ansa-chain. Similarly, 21-*O*-acetyl derivatives of rifamycin S and of rifampicin lack any microbial activity (Brufani, 1977; Maggi, Vigevani, Gallo & Pasqualucci, 1968).

The crystal structure of ARIFOLS has been undertaken in order to assign the absolute configuration of the new asymmetric carbon atom C(11) and to investigate whether the reduction at C(11) and the acetylation at O(10) would result in a conformation of the ansa-chain different from that of the active compounds.

Experimental. Well shaped prismatic red crystals of ARIFOLS were grown from an aqueous–methanolic solution. The preliminary cell dimensions and the space group $P2_1$ were derived from Weissenberg photographs. A crystal (0·8 × 0·5 × 0·5 mm) was selected for the data collection and set on a Nicolet *P*3 diffractometer equipped with Mo $K\alpha$ radiation and graphite monochromator. Intensity data were collected, the experimental conditions being: $2\theta < 57°$, ω-scan mode, scan range 1·0°, scan rate 0·5–29·3° min^{-1} (depending on the reflection intensity), background count time half of the scan time. Accurate unit-cell parameters were determined by least-squares fit of the setting angles of 15 selected reflections with $30 < 2\theta < 40°$. Three control reflections, monitored every hundred, showed a very smooth variation of intensity during the data collection, superimposed on the fluctuations (maximum 5%) of the current values.

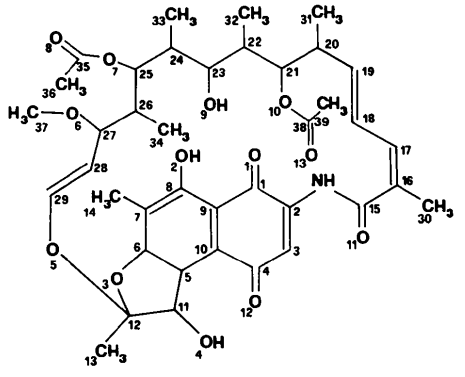


Fig. 1. Structural formula of 21-acetoxy-11(*R*)-rifamycinol S, showing the numbering scheme.

Intensity data were corrected for the average change in the intensity of the reference reflections. Lorentz and polarization corrections were applied but no absorption or extinction corrections were made. Of the 5429 unique reflections measured, 4043 with $I > 2\sigma(I)$ were used for the structure elucidation. $R_{int} = 5{\cdot}5\%$.

The structure was solved by direct methods. No meaningful structural models were obtained using the *MULTAN*80 package (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). Several attempts on the evaluation of the *E* values were made by providing structural information as randomly positioned and randomly oriented molecular fragments. The *E*-synthesis maps corresponding to the highest figures of merit showed a characteristic 'chicken-wire' distribution of the peaks. Karle recycling procedures, starting with many of the molecular fragments picked up by the program, failed to develop in the correct model.

The structure was eventually solved using the semi-invariant representation package (*SIR*) (Cascarano, Giacovazzo, Burla, Nunzi, Polidori, Camalli, Spagna & Viterbo, 1985), providing seven permutable phases, four one-phase semi-invariants (SS1) as known phases in the starting set, and 491 *E*'s > 1·60. After the phase expansion by tangent formula the sets were ranked according to a combined figure of merit CFOM, calculated with the conventional ABSFOM and RESID values and with SS1FOM (one-phase semi-invariants), SS2FOM (two-phase semi-invariants) and NQUEST (negative quartets) defined as follows:

$$\text{SS1FOM} = \sum_i G_i \cos^1 \Phi_i / \sum |G_i|$$

$$\text{SS2FOM} = \sum_i G_i \cos^2 \Phi_i / \sum |G_i|$$

$$\text{NQUEST} = \sum_i G_i \cos^4 \Phi_i / \sum |G_i|$$

where G_i and ${}^n\Phi_i$ are respectively the arguments and the estimated phases of the relationship of order *n*.

The *E* synthesis calculated with the phase set having the best CFOM unambiguously revealed 22 peaks corresponding to the naphthoquinone moiety of the molecule. The remaining atoms were localized by Karle-recycling and weighted-Fourier procedures.

An *a posteriori* examination of the divergence map revealed the important role played by SS1 in the

Table 1. *Solution conditions*

h	*k*	*l*	*E*	$\Phi(^\circ)$
Origin definition				
−1	0	7	3·19	0
−3	1	1	2·97	45
−5	0	12	2·54	0
One-phase semi-invariants (SS1)				
6	0	20	2·11	180
8	0	12	1·93	0
−2	0	14	1·68	0
8	0	14	1·62	180
Permuted phases				
−7	0	19	3·80	
−2	0	1	2·71	
−3	0	1	2·59	
−8	1	19	2·50	
−9	2	20	2·47	
−6	2	19	2·38	
4	4	14	2·31	
Two-phase semi-invariants (SS2)				
−8	1	19	2·50	(*a*)
−4	1	17	2·34	
−6	1	18	3·77	(*b*)
0	1	8	2·27	
−2	2	16	2·56	(*c*)
−2	2	24	2·23	
−1	2	16	2·57	(*d*)
−9	2	20	2·47	

Table 2. *Comparison of the phase generation pathway*

SIR						*MULTAN*80					
*N**	*h*	*k*	*l*	*E*	$\Delta\overline{\cos}\Phi$	*N**	*h*	*k*	*l*	*E*	$\Delta\overline{\cos}\Phi$
(1)	−5	0	8	3·30	0·05	(1)	−5	0	18	3·30	0·05
(2)	−6	0	19	4·06	0·08	(6)	−6	1	18	3·77	0·07
(3)	−4	0	18	2·14	0·13	(8)	−3	2	17	2·49	0·36
(4)	−3	0	18	3·36	0·07	(9)	−4	2	2	1·71	0·09
(5)	−3	2	1	2·00	0·18	(10)	−4	1	17	2·34	0·03
(6)	−6	1	18	3·77	0·07	(11)	−1	2	16	2·57	0·12
(7)	2	1	0	1·68	0·13	(2)	−6	0	19	4·06	0·08
(8)	−3	2	17	2·49	0·36	(4)	−3	0	18	3·36	0·13
(9)	−4	2	2	1·71	0·09	(5)	−3	2	1	2·00	0·18
(10)	−4	1	17	2·34	0·03	(30)	−3	1	17	1·75	0·12
(11)	−1	2	16	2·57	0·12	(27)	−5	1	18	1·68	0·44
(12)	−8	4	4	2·65	0·11	(19)	−8	0	19	2·42	0·15
(13)	−10	4	5	2·23	0·16	(31)	−2	1	1	1·82	0·13
(14)	3	4	14	2·27	0·11	(29)	−4	1	2	1·91	0·03
(15)	2	5	14	2·22	0·26	(18)	−7	2	3	2·40	0·16
(16)	6	4	13	2·25	0·16	(3)	−4	0	18	2·14	0·13
(17)	−11	4	5	1·97	0·16	(7)	2	1	0	1·68	0·13
(18)	−7	2	3	2·40	0·16	(38)	−6	2	2	1·97	0·16
(19)	−8	0	19	2·42	0·15	(39)	1	2	16	1·92	0·30
(20)	1	2	15	1·95	0·55	(46)	−1	2	17	2·14	0·22
(21)	−1	6	16	2·39	0·12	(110)	1	0	6	1·99	1·75†
(22)	−6	6	3	1·87	0·17	(113)	−5	1	11	2·02	0·56
(23)	1	6	15	1·86	0·22	(114)	−1	2	17	2·43	1·09†
(24)	7	2	12	2·07	0·18	(111)	−2	0	24	2·75	1·01†
(25)	−11	3	5	2·46	0·09	(69)	−1	0	17	1·81	0·28

* Sequential number in the divergence map of the *SIR* package.
† Negative triplets involved.

starting set definition and by two-phase semi-invariants (SS2) in the phase-extension procedure (see Table 1).

Of the four SS2's used in the convergence and divergence steps, two relationships contributed in the very early stage of the phase development. In Table 2 are listed the first 25 reflections appearing in the divergence and convergence map, as determined by *SIR* and *MULTAN*80 packages.

As Table 2 shows, the mean error

$$\Delta\cos\Phi = \langle\,|\cos\Phi_{\rm est} - \cos\Phi_{\rm real}|\,\rangle$$

of the relationships contributing to the phase determination is lower in *SIR*. The phases of the reflections $\bar{4}$,1,17 and $\bar{1}$,2,16 were determined (in the case of the *SIR* package) also by means of the contribution of the SS2's (*a*) and (*d*) respectively. The phase of the reflection 1,2,15 was determined also by the contribution of the SS1 8,0,12.

The failure of the phase expansion in the case of *MULTAN*80 can be attributed to the negative triplets contributing to the phase estimation of reflections 106, $\bar{1}$,2,17 and $\bar{2}$,0,24. It is worthy of note that in the first cycle of the tangent formula, reflections 106 and $\bar{1}$,2,17 are both determined only by two negative triplets.

The crystal structure was then refined isotropically and anisotropically by block-diagonal (9 × 9) least-squares methods; the H atoms of ARIFOLS and of the water and methanol molecules were found by difference-Fourier syntheses using only data with $(\sin\theta)/\lambda < 0{\cdot}5$ Å^{-1}. In the later refinement, isotropic temperature factors were chosen for water and methanol and the parameters of the H atoms were fixed with *B* values equal to those of the carrier atoms.

The final *R* value is 0·071 ($wR = 0{\cdot}099$), minimizing the function $\sum w|\Delta F|^2$, with $w = (16{\cdot}26 + |F_o| + 0{\cdot}0024|F_o|^2)^{-1}$. At convergence the shift-to-e.s.d. ratios were less than 0·33, $S = 0{\cdot}607$. In the final difference Fourier synthesis significant residual peaks [$\rho > 3\sigma(\rho)$, $\sigma(\rho) = 0{\cdot}09$ e Å^{-3}] were found near the water and methanol positions. The high thermal parameters associated with O(14) (water), O(15) and C(40) (methanol) indicate a certain disorder of these molecules in the crystal which in turn is responsible for the relatively high *R* value at the end of the refinement.

The atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974). Calculations for the structure solution were performed on a UNIVAC 1110 with *MULTAN*80 and on an IBM 3033 with *SIR*; a Data General Eclipse MV8000 II with the Crystal Analysis Operating System package (*SIR–CAOS*) (Camalli, Capitani, Cascarano, Cerrini, Giacovazzo & Spagna, 1986) was used for all the other crystallographic calculations.

Discussion. The fractional atomic coordinates and $B_{\rm eq}$ values of the non-hydrogen atoms are listed in Table 3; bond lengths and valence angles for the non-hydrogen atoms are reported in Table 4.* The mean distances for

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters and selected intermolecular distances have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44385 (28 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

the C–H, O–H and N–H bonds are 0·97 (10), 1·02 (3) and 0·90 (3) Å respectively, and the related average values of the valence angles, involving the C(sp^3), C(sp^2), N and O as carrier atoms, are 109 (6), 118 (5), 116 (6) and 114 (10)° respectively.

No measurements of the anomalous-dispersion effect have been made; the molecular structure of ARIFOLS with its absolute configuration (Leitich, Oppolzer & Prelog, 1964) is shown in Fig. 2. The *R* configuration can be assigned to the new asymmetric centre at C(11) following the reducing reaction.

The ten atoms of the naphthoquinone nucleus are coplanar, within ±0·05 Å; C(11) and O(3) also lie on this plane, as do the other substituents of the naphthoquinone moiety, within the same limits. The C(12) and O(4) atoms are out of the plane, on the same side of the ansa-bridge, with distances of 0·367 (14) and 0·940 (14) Å respectively.

The endocyclic torsion angles of the hydrofuran ring are 2·5 (6), 11·3 (6), −19·7 (5), 20·0 (5) and −14·0 (6)° along the bond sequence C(11)–C(5)–

Table 3. *Fractional atomic coordinates and equivalent isotropic temperature factors for the non-hydrogen atoms with e.s.d.'s in parentheses*

$$B_{eq} = 8\pi^2(U_1^2U_2^2U_3^2)^{1/3}.$$

	x	*y*	*z*	B_{eq}(Å²)
O(1)	0·5368 (3)	−0·1488 (4)	0·8557 (2)	4·1 (1)
O(2)	0·5314 (5)	−0·2624 (5)	0·7428 (2)	6·3 (2)
O(3)	0·3423 (3)	0·0026 (5)	0·5752 (2)	4·7 (2)
O(4)	0·3063 (4)	0·3524 (5)	0·6467 (2)	4·0 (2)
O(5)	0·3912 (3)	0·2359 (5)	0·5385 (2)	4·8 (2)
O(6)	0·7241 (4)	0·1857 (6)	0·5981 (2)	5·4 (2)
O(7)	0·8799 (3)	0·4578 (5)	0·6602 (2)	4·5 (2)
O(8)	1·0065 (4)	0·2801 (7)	0·6450 (3)	7·6 (3)
O(9)	0·9612 (3)	0·2042 (5)	0·7825 (2)	4·8 (2)
O(10)	0·8868 (3)	0·1457 (4)	0·9110 (2)	3·9 (1)
O(11)	0·4198 (4)	0·2473 (5)	0·9962 (2)	5·4 (2)
O(12)	0·2935 (4)	0·3104 (6)	0·7771 (2)	6·2 (2)
O(13)	0·7158 (3)	0·1212 (5)	0·8610 (2)	5·1 (2)
O(14)	0·0841 (15)	0·3978 (28)	0·3508 (9)	24·4 (7)
O(15)	0·1824 (14)	0·6762 (30)	0·7501 (10)	24·8 (7)
N(1)	0·4828 (4)	0·0419 (5)	0·9453 (2)	3·4 (2)
C(1)	0·4786 (4)	−0·0469 (5)	0·8357 (2)	3·2 (2)
C(2)	0·4417 (4)	0·0679 (6)	0·8826 (2)	3·2 (2)
C(3)	0·3774 (4)	0·1810 (7)	0·8630 (2)	3·9 (2)
C(4)	0·3448 (4)	0·2004 (7)	0·7938 (2)	4·0 (2)
C(5)	0·3467 (4)	0·0949 (6)	0·6798 (2)	3·5 (2)
C(6)	0·3765 (4)	−0·0208 (7)	0·6386 (2)	4·0 (2)
C(7)	0·4356 (5)	−0·1404 (8)	0·6567 (2)	4·9 (3)
C(8)	0·4694 (5)	−0·1484 (7)	0·7230 (2)	4·2 (2)
C(9)	0·4411 (4)	−0·0348 (6)	0·7675 (2)	3·3 (2)
C(10)	0·3763 (4)	0·0863 (6)	0·7458 (2)	3·3 (2)
C(11)	0·2814 (4)	0·2052 (7)	0·6400 (2)	4·2 (2)
C(12)	0·3057 (4)	0·1549 (7)	0·5688 (2)	4·2 (2)
C(13)	0·2032 (6)	0·1583 (10)	0·5230 (3)	5·8 (3)
C(14)	0·4654 (8)	−0·2641 (10)	0·6108 (3)	7·8 (4)
C(15)	0·4734 (4)	0·1351 (6)	0·9984 (2)	3·5 (2)
C(16)	0·5350 (4)	0·0862 (6)	1·0586 (2)	3·3 (2)
C(17)	0·6423 (5)	0·1231 (7)	1·0677 (2)	3·0 (2)
C(18)	0·7089 (5)	0·2053 (8)	1·0218 (2)	4·4 (2)
C(19)	0·8144 (5)	0·2473 (8)	1·0338 (3)	4·9 (3)
C(20)	0·8882 (5)	0·3390 (8)	0·9892 (3)	4·7 (2)
C(21)	0·8739 (4)	0·3022 (6)	0·9161 (2)	3·7 (2)
C(22)	0·9621 (4)	0·3788 (7)	0·8729 (3)	4·0 (2)
C(23)	0·9427 (4)	0·3537 (7)	0·7979 (3)	4·1 (2)
C(24)	0·8256 (4)	0·4024 (6)	0·7715 (2)	3·7 (2)
C(25)	0·8105 (4)	0·3633 (6)	0·6995 (2)	3·7 (2)
C(26)	0·6890 (4)	0·3822 (7)	0·6735 (2)	3·0 (2)
C(27)	0·6818 (5)	0·3284 (8)	0·6011 (2)	4·6 (2)
C(28)	0·5613 (5)	0·3369 (8)	0·5725 (2)	4·9 (3)
C(29)	0·4981 (4)	0·2261 (7)	0·5661 (2)	4·3 (2)
C(30)	0·4627 (5)	0·0085 (7)	1·1080 (2)	4·6 (2)
C(31)	0·8700 (8)	0·4992 (10)	1·0026 (4)	7·5 (4)
C(32)	1·0834 (5)	0·3377 (10)	0·8917 (3)	5·0 (3)
C(33)	0·8045 (5)	0·5628 (7)	0·7853 (3)	4·0 (3)
C(34)	0·6049 (5)	0·3014 (11)	0·7147 (3)	5·9 (3)
C(35)	0·9746 (4)	0·4012 (9)	0·6334 (3)	4·9 (3)
C(36)	1·0302 (6)	0·5030 (13)	0·5888 (4)	7·8 (5)
C(37)	0·7668 (8)	0·1464 (15)	0·5353 (4)	8·0 (5)
C(38)	0·8021 (5)	0·0684 (7)	0·8832 (3)	4·4 (2)
C(39)	0·8243 (8)	−0·0897 (9)	0·8851 (5)	7·6 (4)
C(40)	0·1324 (16)	0·8024 (26)	0·7838 (9)	16·1 (6)

Table 4. *Bond lengths* (Å) *and valence angles* (°) *with e.s.d.'s in parentheses*

O(1)–C(1)	1·227 (6)	C(6)–C(7)	1·348 (9)
O(2)–C(8)	1·335 (8)	C(7)–C(8)	1·410 (7)
O(3)–C(6)	1·368 (6)	C(7)–C(14)	1·513 (10)
O(3)–C(12)	1·464 (8)	C(8)–C(9)	1·422 (7)
O(4)–C(11)	1·384 (8)	C(9)–C(10)	1·416 (7)
O(5)–C(12)	1·405 (7)	C(11)–C(12)	1·557 (7)
O(5)–C(29)	1·384 (6)	C(12)–C(13)	1·524 (8)
O(6)–C(27)	1·398 (9)	C(15)–C(16)	1·492 (6)
O(6)–C(37)	1·432 (10)	C(16)–C(17)	1·328 (7)
O(7)–C(25)	1·444 (6)	C(16)–C(30)	1·508 (7)
O(7)–C(35)	1·358 (7)	C(17)–C(18)	1·443 (8)
O(8)–C(35)	1·192 (11)	C(18)–C(19)	1·329 (8)
O(9)–C(23)	1·420 (8)	C(19)–C(20)	1·522 (9)
O(10)–C(21)	1·443 (7)	C(20)–C(21)	1·537 (7)
O(10)–C(38)	1·347 (7)	C(20)–C(31)	1·505 (12)
O(11)–C(15)	1·207 (7)	C(21)–C(22)	1·544 (7)
O(12)–C(4)	1·220 (8)	C(22)–C(23)	1·564 (8)
O(13)–C(38)	1·215 (7)	C(22)–C(32)	1·531 (8)
N(1)–C(2)	1·385 (5)	C(23)–C(24)	1·549 (7)
N(1)–C(15)	1·384 (6)	C(24)–C(25)	1·521 (7)
C(1)–C(2)	1·489 (7)	C(24)–C(33)	1·515 (9)
C(1)–C(9)	1·462 (6)	C(25)–C(26)	1·539 (7)
C(2)–C(3)	1·343 (8)	C(26)–C(27)	1·558 (7)
C(3)–C(4)	1·471 (6)	C(26)–C(34)	1·507 (9)
C(4)–C(10)	1·483 (7)	C(27)–C(28)	1·540 (8)
C(5)–C(6)	1·399 (8)	C(28)–C(29)	1·265 (9)
C(5)–C(10)	1·390 (6)	C(35)–C(36)	1·465 (12)
C(5)–C(11)	1·503 (8)	C(38)–C(39)	1·470 (10)
		O(15)–C(40)	1·47 (3)

C(6)–O(3)–C(12)	108·5 (4)	C(11)–C(12)–C(13)	114·3 (5)
C(12)–O(5)–C(29)	116·8 (4)	O(11)–C(15)–N(1)	122·8 (4)
C(27)–O(6)–C(37)	113·8 (6)	O(11)–C(15)–C(16)	122·5 (4)
C(25)–O(7)–C(35)	118·5 (5)	N(1)–C(15)–C(16)	114·7 (4)
C(21)–O(10)–C(38)	118·1 (4)	C(15)–C(16)–C(17)	119·8 (4)
C(2)–N(1)–C(15)	126·0 (4)	C(15)–C(16)–C(30)	114·6 (4)
O(1)–C(1)–C(2)	119·3 (4)	C(17)–C(16)–C(30)	125·3 (4)
O(1)–C(1)–C(9)	122·5 (4)	C(16)–C(17)–C(18)	125·0 (5)
C(2)–C(1)–C(9)	118·1 (4)	C(17)–C(18)–C(19)	123·6 (5)
N(1)–C(2)–C(1)	111·7 (4)	C(18)–C(19)–C(20)	126·7 (5)
N(1)–C(2)–C(3)	126·9 (4)	C(19)–C(20)–C(21)	113·8 (5)
C(1)–C(2)–C(3)	121·3 (4)	C(19)–C(20)–C(31)	110·0 (6)
C(2)–C(3)–C(4)	121·5 (5)	C(21)–C(20)–C(31)	112·0 (6)
O(12)–C(4)–C(3)	119·4 (5)	O(10)–C(21)–C(20)	106·0 (4)
O(12)–C(4)–C(10)	121·6 (4)	O(10)–C(21)–C(22)	109·6 (4)
C(3)–C(4)–C(10)	119·0 (5)	C(20)–C(21)–C(22)	112·8 (4)
C(6)–C(5)–C(10)	118·5 (5)	C(21)–C(22)–C(23)	113·7 (4)
C(6)–C(5)–C(11)	108·3 (4)	C(21)–C(22)–C(32)	112·7 (5)
C(10)–C(5)–C(11)	133·1 (5)	C(23)–C(22)–C(32)	109·6 (5)
O(3)–C(6)–C(5)	112·2 (5)	O(9)–C(23)–C(22)	109·7 (5)
O(3)–C(6)–C(7)	122·2 (5)	O(9)–C(23)–C(24)	109·8 (4)
C(5)–C(6)–C(7)	125·6 (5)	C(22)–C(23)–C(24)	114·7 (4)
C(6)–C(7)–C(8)	116·5 (5)	C(23)–C(24)–C(25)	111·3 (4)
C(6)–C(7)–C(14)	124·2 (5)	C(23)–C(24)–C(33)	111·3 (5)
C(8)–C(7)–C(14)	119·3 (6)	C(25)–C(24)–C(33)	113·0 (5)
O(2)–C(8)–C(7)	118·7 (5)	O(7)–C(25)–C(24)	109·7 (4)
O(2)–C(8)–C(9)	120·6 (4)	O(7)–C(25)–C(26)	106·2 (4)
C(7)–C(8)–C(9)	120·6 (5)	C(24)–C(25)–C(26)	114·0 (4)
C(1)–C(9)–C(8)	118·9 (5)	C(25)–C(26)–C(27)	109·4 (4)
C(1)–C(9)–C(10)	121·0 (4)	C(25)–C(26)–C(34)	112·1 (4)
C(8)–C(9)–C(10)	120·1 (4)	C(27)–C(26)–C(34)	110·3 (5)
C(4)–C(10)–C(5)	122·6 (5)	O(7)–C(27)–C(26)	108·7 (5)
C(4)–C(10)–C(9)	118·9 (4)	O(6)–C(27)–C(28)	111·2 (5)
C(5)–C(10)–C(9)	118·5 (4)	C(26)–C(27)–C(28)	112·5 (4)
O(4)–C(11)–C(5)	119·4 (4)	C(27)–C(28)–C(29)	123·0 (6)
O(4)–C(11)–C(12)	109·7 (4)	O(5)–C(29)–C(28)	121·9 (6)
C(5)–C(11)–C(12)	101·9 (5)	O(7)–C(35)–O(8)	122·4 (6)
O(3)–C(12)–O(5)	109·0 (4)	O(7)–C(35)–C(36)	112·9 (7)
O(3)–C(12)–C(11)	104·7 (4)	O(8)–C(35)–C(36)	124·7 (6)
O(5)–C(12)–C(11)	113·5 (5)	O(10)–C(38)–O(13)	124·7 (6)
O(3)–C(12)–C(13)	107·9 (5)	O(10)–C(38)–C(39)	111·8 (6)
O(5)–C(12)–C(13)	107·1 (4)	O(13)–C(38)–C(39)	123·4 (6)

C(6)–O(3)–C(12). The ring assumes an envelope conformation with C(12) in the flap position. A pseudosymmetry plane C_s passes through C(12) and the mid-point of the C(5)–C(6) bond, the asymmetry parameter (Duax, Weeks & Rohrer, 1976) being $\Delta C_s = 1{\cdot}9\ (7)°$.

The spatial relationships found in ARIFOLS for the ansa-bridge with respect to the naphthoquinone rings are very similar to those observed in RIFB, RIFMP, RIFCM, RIFSV, RIFAS and RIFOLS.

Indeed, the best plane passing through the 17-membered ansa-chain and that passing through the ten atoms of the chromophoric rings make an angle of 96·1 (1)°. The corresponding angles for RIFB, RIFMP, RIFCM, RIFSV, RIFAS and for the two independent molecules of RIFOLS are 98, 109, 97, 105, 114, 89 and 87° respectively. The bonds C(21)–O(10) and C(23)–O(9) are nearly perpendicular to the ansa-bridge plane and almost parallel to the naphthoquinone nucleus.

The distances between the oxygen atoms O(1), O(2), O(9) and O(10) are the following: O(1)···O(2) 2·529 (5), O(1)···O(9) 6·179 (6), O(1)···O(10) 5·063 (5), O(2)···O(9) 6·687 (7), O(2)···O(10) 6·566 (6) and O(9)···O(10) 2·831 (5) Å. They are very close to those found in active compounds.

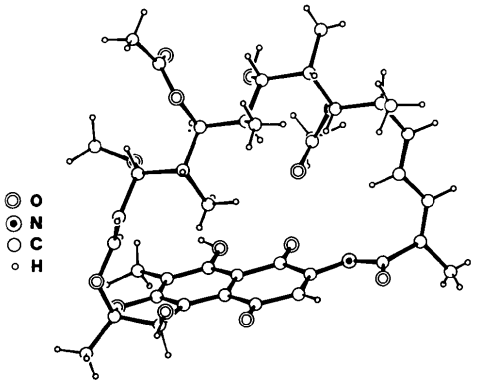


Fig. 2. A perspective view of the molecular structure.

As shown in Fig. 2, the central part of the ansa-bridge, spanning from C(20) to C(27), lies almost parallel to the naphthoquinone moiety, at a mean distance of 5·6 Å above it. The plane of the acetoxy group at C(21) is nearly perpendicular to the ansa-bridge plane and gives no short-contact interaction with the other neighbouring atoms of the ansa-chain. Distances of 3·257 (6) and 3·241 (6) Å have been found for O(13) from O(1) and C(1) of the chromophoric nucleus. All the substituents of the ansa-chain are oriented at the outside of the bridge with the exception of the methyl group C(34) which points towards the chromophoric rings, at a distance of 3·41 (5) Å from this plane.

A comparison of the torsion angles of the RIFB, RIFMP, RIFCM, RIFSV, RIFAS and RIFOLS derivatives, describing the conformation of the ansa-bridge, is reported in Table 5.

To discuss the conformation of the ansa-bridge of ARIFOLS with respect to the other rifamycins, the dihedral angles defining the orientation of the amide and the ethylenic –HC(28)=C(29)H groups and those along the sequence C(16)=C(17)–C(18)=C(19)–C(20)–C(21)–C(22)–C(23)–C(24)–C(25)–C(26)–C(27) are of interest. The double bonds C(16)=C(17), C(18)=C(19) and C(28)=C(29) have *Z*, *E* and *E* configuration respectively; the C(17)–C(18) bond is in *trans* conformation and the remaining dihedral angles are such that their substituents are arranged in a staggered conformation.

The maximum dispersion of 50° occurs around the C(19)–C(20) bond which, indeed, is in the region of maximum bending of the ansa-skeleton.

The most significant differences in the conformation of the ansa-chain are localized near the junctions of the

Table 5. *Torsion angles* (°) *with e.s.d.'s in parentheses along the skeleton of the ansa-chain of several related rifamycins*

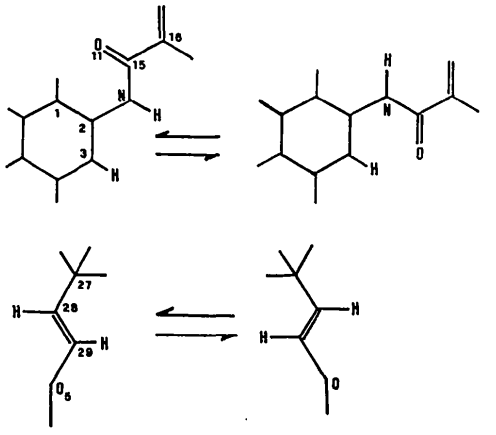
	ARIFOLS	RIFB	RIFMP	RIFCM	RIFSV	RIFAS	RIFOLS*		$\bar{\tau}$°	$\Delta\tau$°†
C(1)–C(2)–N(1)–C(15)	173·1 (4)	−32	−55	−141	167	166	179	168	‡	‡
C(2)–N(1)–C(15)–C(16)	−174·4 (4)	180	179	177	−171	−163	−177	−178	−176 (6)	20
N(1)–C(15)–C(16)–C(17)	87·9 (6)	−43	−31	63	119	133	97	118	‡	‡
C(15)–C(16)–C(17)–C(18)	−2·3 (9)	5	4	2	−3	−4	−5	−11	−2 (5)	16
C(16)–C(17)–C(18)–C(19)	176·2 (6)	168	155	169	−173	−174	−180	−174	176 (11)	32
C(17)–C(18)–C(19)–C(20)	−177·4 (6)	−175	−165	−179	−179	176	−179	180	−177 (5)	19
C(18)–C(19)–C(20)–C(21)	−38·6 (10)	−11	−19	−30	−52	−61	−40	−40	−36 (16)	50
C(19)–C(20)–C(21)–C(22)	−171·2 (5)	170	169	180	176	−177	−178	180	178 (7)	20
C(20)–C(21)–C(22)–C(23)	−175·0 (5)	−179	−176	−178	−175	−170	−174	−177	−175 (3)	9
C(21)–C(22)–C(23)–C(24)	57·3 (7)	53	62	57	62	65	56	60	59 (4)	12
C(22)–C(23)–C(24)–C(25)	−175·6 (5)	174	165	−174	180	−168	−177	−176	−179 (8)	27
C(23)–C(24)–C(25)–C(26)	169·2 (5)	155	159	169	176	172	165	166	166 (7)	21
C(24)–C(25)–C(26)–C(27)	−175·9 (5)	174	153	180	174	−165	−169	−174	180 (13)	42
C(25)–C(26)–C(27)–C(28)	177·3 (5)	−170	−171	180	−179	−165	−169	−169	−173 (6)	15
C(26)–C(27)–C(28)–C(29)	−102·6 (7)	117	118	−110	−101	−114	−113	−111	‡	‡
C(27)–C(28)–C(29)–O(5)	−178·1 (4)	−168	−175	−176	−179	−180	−177	−175	−176 (4)	12
C(28)–C(29)–O(5)–C(12)	−138·4 (6)	49	65	−127	−118	−135	−134	−135	‡	‡
C(29)–O(5)–C(12)–O(3)	−52·5 (3)	−79	−78	−52	−58	−65	−51	54	−61 (11)	28

* Two molecules in the asymmetric unit.
† Maximum variation range.
‡ See text.

bridge with the naphthoquinone rings. In fact, quite different values are observed for the torsion angles C(1)–C(2)–N(1)–C(15) and N(1)–C(15)–C(16)=C(17) defining the orientation of the *trans* amide group, and for the torsion angles C(26)–C(27)–C(28)=C(29) and C(28)=C(29)–O(5)–C(12) defining the orientation of the ethylenic group with respect to the rest of the molecule. While the orientation (defined as above) of the rigid amide group is spread over the whole 0–360° range (see Table 5), the inclination of the –HC(28)=C(29)H– plane is restricted within two narrow intervals. They are C(28)=C(29)–O(5)–C(12) = −131 (7)° [and the related C(26)–C(27)–C(28)=C(29)=−109 (5)°] or =57(8)° [and the related 118(1)°]. The two alternative arrangements correspond to the complete overturning of the ethylenic group with respect to the rest of the molecule.

As previously pointed out (Cellai, Cerrini, Segre, Brufani, Fedeli & Vaciago, 1982*b*), these groups are the only fragments with conformational variability along the ansa-chain of rifamycins. The amide and the ethylenic groups can be rotated as a whole around the lines C(2)···C(16) and C(27)···O(5) respectively, by means of a cooperative variation of the torsion angles around the bonds C(2)–N(1) and C(15)–C(16) for the former, and around C(27)–C(28) and C(29)–O(5) for the latter.

This conformational freedom gives rise to the following type of local conformers:



There is no correlation between them, and they do not produce any significant change in the overall shape of the molecules. This can be inferred by the similar inclination of the ansa-bridge with respect to the naphthoquinone nucleus in all the above quoted compounds, as well as by the similarity of the relative positions of the oxygenated functions O(1), O(2), O(9) and O(10).

In ARIFOLS, the best plane passing through C(27), C(28), C(29) and O(5) is nearly perpendicular to that of the ansa-bridge. The orientation of the ethylenic group –HC(28)=C(29)H– corresponds very closely to that of RIFCM, RIFAS, RIFSV and RIFOLS. It is worth noting that in ARIFOLS the observed local conformation of this group occurs due to the unfavourable short contact that would arise between the H atom at C(29) in the overthrown orientation and the β-sited O(4).

The amide –HN(1)–C(15)–O(11)– is approximately coplanar with the naphthoquinone nucleus, the angle between the planes being 5·7 (3)°. The carbonyl group is turned in a *syn* arrangement with respect to the C(2)–C(3) bond (see Fig. 2). This type of conformation of the amide group has been found in the structure of RIFCM, RIFSV, RIFAS and RIFOLS.

These results suggest that the reduction of the carbonyl group to hydroxyl in the β position and the acetylation at O(10) do not induce relevant distortions of the geometrical features which are characteristic of the active compounds. The observed conformational variations are restricted to the same regions found in the rifamycin derivatives which have unchanged ansa-chains.

The crystal packing. The crystal packing projected along the *b* axis is shown in Fig. 3. Infinite chains extending along the *b* axis are formed by hydrogen bonds between N(1) and O(11) of two molecules of ARIFOLS related by twofold screw axes. The geometrical parameters are as follows: N(1)···O(11) 3·159 (6) Å, C(15)–O(11)···N(1) 121·3 (4), C(2)–N(1)···O(11) 128·3 (3) and C(15)–N(1)···O(11) 105·2 (3)°. The hydrogen-bond interaction is tightened by the further contact of O(1) and O(11) [3·205 (5) Å].

The chains related by screw axes interact with one another by means of a van der Waals contact between C(14) and C(29) of two different molecules, and form layers extending in a plane parallel to the *bc* plane. The layers are stacked along the *a* direction, with two normal contacts O(8)···C(11) and O(12)···C(32) which occur between molecules translated along the *a* axis.

The water and methanol molecules are located between the layers; the water is close to the O(6) and

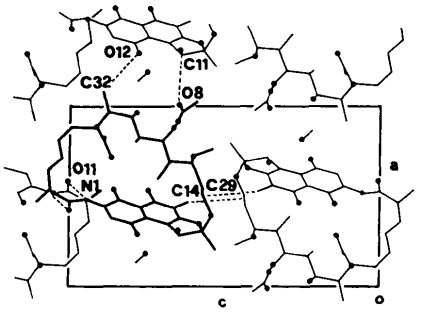


Fig. 3. The crystal packing of the molecules, projected along the *b* axis.

O(8) atoms; the methanol is near to the O(4) and O(12) atoms. Both guest molecules have distances larger than 3·6 Å (without considering hydrogens) from the surrounding atoms.

References

ARORA, K. S. (1981). *Acta Cryst.* B**37**, 152–157.

ARORA, K. S. (1983). *Mol. Pharmacol.* **23**, 133–140.

ARORA, K. S. (1984). *J. Antibiot.* **37**, 178–181.

ARORA, K. S. (1985). *J. Med. Chem.* **28**, 1099–1102.

BRIZZI, V., BRUFANI, M., CELLAI, L. & SEGRE, A. (1983). *J. Antibiot.* **36**, 516–521.

BRUFANI, M. (1977). In *Topics in Antibiotic Chemistry* 1, pp. 91–212, edited by P. G. SAMMES. Chichester: Ellis Horwood.

BRUFANI, M., CECCHINI, E., CELLAI, L., FEDERICI, M., GUISO, M. & SEGRE, A. (1985). *J. Antibiot.* **38**, 259–262.

BRUFANI, M., CELLAI, L., CERRINI, S., FEDELI, W. & VACIAGO, A. (1978). *Mol. Pharmacol.* **14**, 693–703.

BRUFANI, M., CELLAI, L., COZZELLA, L., FEDERICI, M., GUISO, M. & SEGRE, A. (1985). Proc. 2nd Cyprus Conf. on New Methods in Drug Research, Limassol, p. 27.

BRUFANI, M., CERRINI, S., FEDELI, W. & VACIAGO, A. (1974). *J. Mol. Biol.* **87**, 409–435.

CAMALLI, M., CAPITANI, D., CASCARANO, G., CERRINI, S., GIACOVAZZO, C. & SPAGNA, R. (1986). *SIR-CAOS* (Italian Patent No. 35403c/86): *User Guide.* Istituto di Strutturistica Chimica CNR, CP No. 10-00016 Monterotondo Stazione, Roma, Italy.

CASCARANO, G., GIACOVAZZO, C., BURLA, M. C., NUNZI, A., POLIDORI, G., CAMALLI, M., SPAGNA, R. & VITERBO, D. (1985). Abstr. 9th European Crystallogr. Meet., Torino, 1, p. 79.

CELLAI, L., CERRINI, S., LAMBA, D., BRIZZI, V. & BRUFANI, M. (1987). *J. Chem. Res.* (*S*), pp. 328–329.

CELLAI, L., CERRINI, S., SEGRE, A., BRUFANI, M., FEDELI, W. & VACIAGO, A. (1982*a*). *J. Chem. Soc. Perkin Trans.* 2, pp. 1633–1640.

CELLAI, L., CERRINI, S., SEGRE, A., BRUFANI, M., FEDELI, W. & VACIAGO, A. (1982*b*). *J. Org. Chem.* **47**, 2652–2661.

DUAX, W. L., WEEKS, C. M. & ROHRER, D. C. (1976). In *Topics in Stereochemistry*, Vol. 9, pp. 271–283, edited by N. L. ALLINGER & E. L. ELIEL. New York: Wiley–Interscience.

GADRET, M., GOURSOLLE, M., LEGER, J. & COLLETER, J. C. (1975). *Acta Cryst.* B**31**, 1454–1462.

HARTMANN, G., HONIKEL, K. O., KNUSEL, F. F. & NUESCH, J. (1967). *Biochim. Biophys. Acta*, **145**, 843–844.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor D. Reidel, Dordrecht.)

LEITICH, J., OPPOLZER, W. & PRELOG, V. (1964). *Experientia*, **20**, 343–344.

MAGGI, M., VIGEVANI, A., GALLO, G. G. & PASQUALUCCI, C. R. (1968). *J. Med. Chem.* **11**, 936–939.

MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1980). *MULTAN*80. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

UMEZAWA, H., MIZUNO, S., YAMAZAKI, H. & NITTA, K. (1968). *J. Antibiot.* **21**, 234–236.

Acta Cryst. (1988). C**44**, 495–497

Structure of 8-Methyl-8-azabicyclo[3.2.1]oct-3-yl 3,5-Dichlorobenzoate Methylsulfate Monohydrate (MDL 72222), an Antagonist at Neuronal 5-HT Receptors

BY A. CARPY, A. LEMRABETT AND J. C. COLLETER

Laboratoire de Chimie Analytique, UA 605 *CNRS, Faculté de Pharmacie,* 3 *Place de la Victoire,* 33076 *Bordeaux CEDEX, France*

(*Received* 30 *April* 1987; *accepted* 2 *November* 1987)

Abstract. $C_{15}H_{18}Cl_2NO_2^+.CH_3SO_3^-.H_2O$, $M_r = 428{\cdot}33$, triclinic, $P\bar{1}$, $a = 7{\cdot}457\ (2)$, $b = 8{\cdot}389\ (1)$, $c = 15{\cdot}916\ (3)$ Å, $\alpha = 79{\cdot}59\ (1)$, $\beta = 85{\cdot}63\ (2)$, $\gamma = 87{\cdot}16\ (2)°$, $V = 975{\cdot}8\ (2)$ Å^3, $Z = 2$, $D_x = 1{\cdot}46$ g cm^{-3}, $\bar{\lambda}$(Cu $K\alpha$) = 1·54178 Å, $\mu = 42{\cdot}32$ cm^{-1}, $F(000) = 448$, room temperature, $R = 0{\cdot}041$ for 2419 independent observed reflections. The cation can be described in terms of the tropane group and an approximately planar dichlorobenzoate group. This conformation is compared with those of some structurally related antichlolinergic agents.

Introduction. Among a series of substituted benzoic acid esters of tropine (Fozard & Gittos, 1983), the title compound named MDL 72222 exerts potent and selective blocking actions at certain excitatory 5-hydroxytryptamine receptors on mammalian peripheral neurones (Fozard, 1984). As it is related to atropine and to potent anticholinergics, we decided to investigate its structure and to compare it with models of anticholinergics.

Experimental. White crystal 0·15 × 0·12 × 0·10 mm (from ethanol). Density not determined. Unit-cell parameters and intensity data obtained on an Enraf–Nonius CAD-4 diffractometer with graphite-monochromated Cu $K\alpha$ radiation in ω/θ scan mode ($0 < \theta < 65°$). Cell dimensions refined by least-squares fitting of θ values of 25 reflections. No appreciable drop in intensity of two standard reflections (003 and 00$\bar{3}$)

0108-2701/88/030495-03$03.00