

bicarboxylic acids failed [3]. In particular, the reaction of **2** with glutaric anhydride in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ mainly yielded three products [3], which could not be identified by NMR. The most abundant of the three was crystallized, its X-ray crystal structure determined, and the results are reported here.

The compound was identified as 25-deacetyl-27,28-didehydro-27-demethoxy-11-deoxy-11,29-epoxy-28,29-dihydro-21,23-*O*-isopropylidenerifamycin S (**3**), and the chemical structure of the other two new compounds was, thus, established [3].

Discussion. – Compound **3** crystallizes with two crystallographically independent molecules and one H_2O molecule in the asymmetric unit.

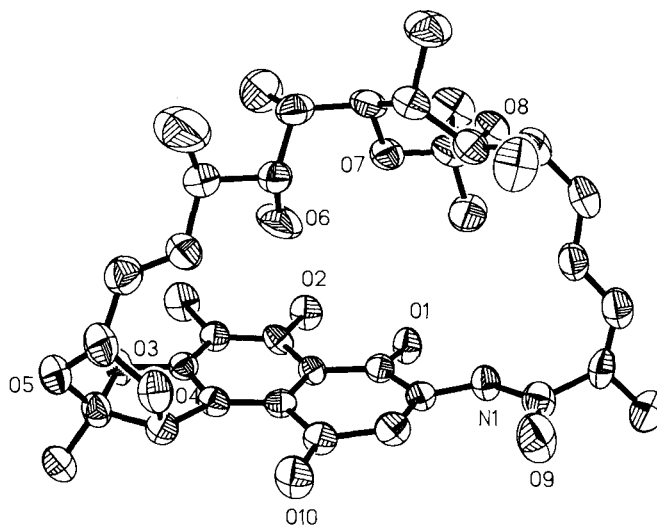


Fig. 1. A perspective view of molecule **a** of **3** (thermal ellipsoids are drawn at 50% probability level)

The structure of molecule **a** is shown in *Fig. 1*. The bond distances and angles are within the normal range and display a close parallel between equivalents in the two molecules. The values conform to those reported for other rifamycins [3–14]. Numbers will be quoted in pairs, the first referring to molecule **a** and the second to molecule **b**. The relative configuration of the new chiral centre C(29) is *S*.

The C(16)=C(17) and C(18)=C(19) bonds are (*Z*)- and (*E*)-configured, respectively, and their conformation is *s-trans* with respect to the C(17)–C(18) bond. The adjoining amide C(15)=O function is (*E*)-configured with respect to the C(16)=C(17) bond. The isolated new C(27)=C(28) bond has (*E*)-configuration.

The two molecules adopt very similar conformations, the major differences occurring at: C(18)–C(19)–C(20)–C(21): $-67(1)^\circ$, $-80(1)^\circ$; C(24)–C(25)–C(26)–C(27): $-179(1)^\circ$, $-169(1)^\circ$, and C(25)–C(26)–C(27)–C(28): $-160(1)^\circ$, $-171(1)^\circ$. The two torsion angles defining the junction of the *ansa*-chain to the naphthoquinone moiety are C(1)–C(2)–N(1)–C(15) $179(1)^\circ$ and $-180(1)^\circ$, and C(27)–C(28)–C(29)–O(5) $-135(1)^\circ$, $-126(1)^\circ$. The best plane through the 15 atoms of the skeleton of the *ansa*-

Table 1. Angles [°] between the Best Planes through the Atoms of the Ansa-Chain and of the Chromophore

Compound	Angle ^{a)}	Reference
1	114	[12]
Rifamycin SV	105	[10]
Rifamycin B	109	[4]
Rifamycin Y	103	[4]
Rifamycin P	90	[14]
Rifampicin	98	[13]
3-Methoxycarbonylrifamycin S	97	[5]
(11 <i>R</i>)-11-Deoxo-11-hydroxyrifamycin S	89/87 ^{b)}	[7]
(11 <i>R</i>)-21- <i>O</i> -Acetyl-11-deoxo-11-hydroxyrifamycin S	96	[8]
15-Deoxo-1,15-epoxyrifamycin SV	133	[11]
Rifamycin S iminomethyl ether	147/149 ^{b)}	[9]
4-Deoxy-3'-bromopyrido[1',2':1,2]imidazo[5,4- <i>c</i>]rifamycin S	123	[6]
2	48	[3]
3	67/66 ^{b)}	This work

^{a)} The reported values refer to the dihedral angle amplitude encompassing the region between the *ansa*-chain and the part of the chromophore nucleus containing the O(1)- and O(2)-atoms.

^{b)} Two molecules in the asymmetric unit.

bridge displays angles of 67.0(1)° and 66.4(1)° with the plane of the chromophore. The corresponding angles for related rifamycins are reported in *Table 1*. An analysis of these values, average 101(27)°, shows that, in **3**, the introduction of the 21,23-*O*-isopropylidene group, the additional presence of the 11,29-epoxy group, and the double-bond shift from C(28)–C(29) to C(27)–C(28), resulting in a rearrangement of the whole *ansa*-chain, gives to this molecule a spatial shape still close to most rifamycins.

The puckering parameters [15] of the dihydrofuran ring, $Q = 0.11(1) \text{ \AA}$, $0.10(1) \text{ \AA}$ and $\phi_2 = -124(3)^\circ$, $-123(3)^\circ$, indicate a *twist*-type conformation. In both molecules, the dioxolane ring, which includes the new chiral C(29)-atom, has a *twist*-type conformation with $Q = 0.27(1) \text{ \AA}$, $0.25(1) \text{ \AA}$ and $\phi_2 = -50(1)^\circ$, $-50(1)^\circ$. The dihedral angles between the least-squares plane through the atoms of the dioxolane ring and through those of the chromophore ring have values of 68.4(2)°, 70.8(2)°. The puckering parameters of the dioxane ring, $Q = 0.77(1) \text{ \AA}$, $0.76(1) \text{ \AA}$, $\phi_2 = 159(1)^\circ$, $161(1)^\circ$ and $\theta_2 = 85(1)^\circ$, $83(1)^\circ$, indicate a *twist-boat*-conformation, almost identical to that found in the crystal and molecular structure of **2** [3].

Strong attractive interactions between π systems have been known for a long time. They control phenomena such as the vertical base-base interactions which stabilize the double helical structure of DNA, the intercalation of drugs into DNA, the packing of aromatic molecules in crystals, the tertiary structure of proteins, the conformational preferences and binding properties of polyaromatic macrocycles, complexation in many host-guest systems, and porphyrin aggregation [16]. It has been suggested that a π - π interaction may occur in the inhibiting binding of rifamycins to an aromatic amino acid (tyrosine, phenylalanine, or tryptophan) of the bacterial enzyme-DNA-dependent RNA polymerase [12] [17] [18].

A dimeric π - π association analogous to those found in the crystal and molecular structures of 11-deoxo-11-hydroxyrifamycin S [7] and **2** [3] is once again shown in the solid state by **3**. It is worth mentioning that, to our knowledge, this type of association

occurred in the solid state only for rifamycins chemically reduced at C(11), *i.e.* 11-deoxy-11-hydroxyrifamycin S [7] and **2** [3] with the exception of 21-acetyl-11-deoxy-11-hydroxyrifamycin S [8]. In the crystal and molecular structure of **3**, pairs of independent molecules are faced one another through the naphthoquinone moieties and interact by means of the π -electron systems stacking. The best planes passing through the ten atoms of the chromophore are strictly parallel, displaying an angle of $0.7(1)^\circ$; the mean distance of the atoms of one moiety from the plane of the other is $3.40(4)$ Å. A view along the normal to the two chromophore nuclei is shown in *Fig. 2*.

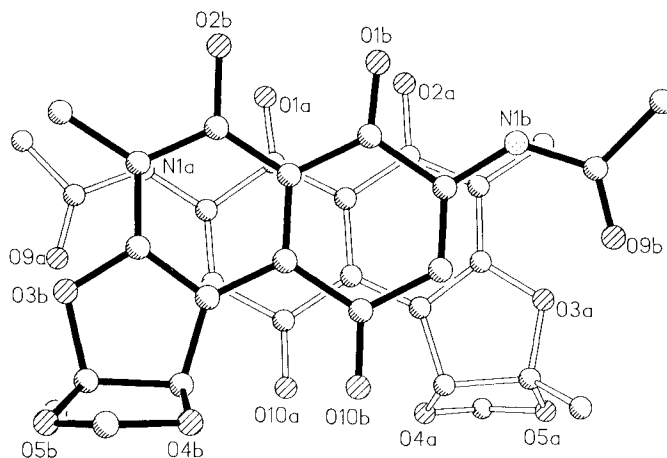


Fig. 2. A perspective view of the chromophore rings of the two molecules of **3** in the asymmetric unit along the perpendicular axis to the rings

It is worthy of note that the benzoquinone ring of molecule **a** shows a highly significant distortion from planarity, the ring being distorted towards the boat-like conformation. A pseudo mirror plane passes through C(1a) and C(4a); a second one passes through the middle points of bonds C(2a)–C(3a) and C(9a)–C(10a). The boat deformation of the benzoquinone ring results in an out-of-plane displacement of both the carbonyl O-atoms O(1a) and O(10a) of $0.154(4)$ Å and $0.201(5)$ Å, respectively. These displacements are on the opposite side of the *ansa*-bridge, towards the chromophore nuclei of the π - π complex. In molecule **b**, the benzoquinone ring is distorted towards an envelope-like conformation with C(2b) in the flap position. A pseudo mirror plane passes through C(2b) and C(10b). This displacement is on the same side of the *ansa*-bridge. Significant distortions of the benzoquinone moiety have been previously observed in **2** [3] and 11-deoxy-11-hydroxyrifamycin S [7].

The coordinates of the two molecules in the asymmetric unit provide evidence for the presence of two non-crystallographic pseudo two-fold axes (sum of the squared distances = 2.86 Å²). One axis is almost parallel to the *b* axis with a deviation of only 2.0° , characterized by $\rho = 180.5^\circ$ and a screwing length of 0.18 Å, and is located at $(0.46, y, 0.25)$. The second axis has the same orientation as the first but with a screwing length of 0.13 Å, and it is located at $(-0.04, y, 0.25)$. The quasi-symmetrical arrangement of the molecules is shown in *Fig. 3*. The first pseudo two-fold axis allows the molecules to

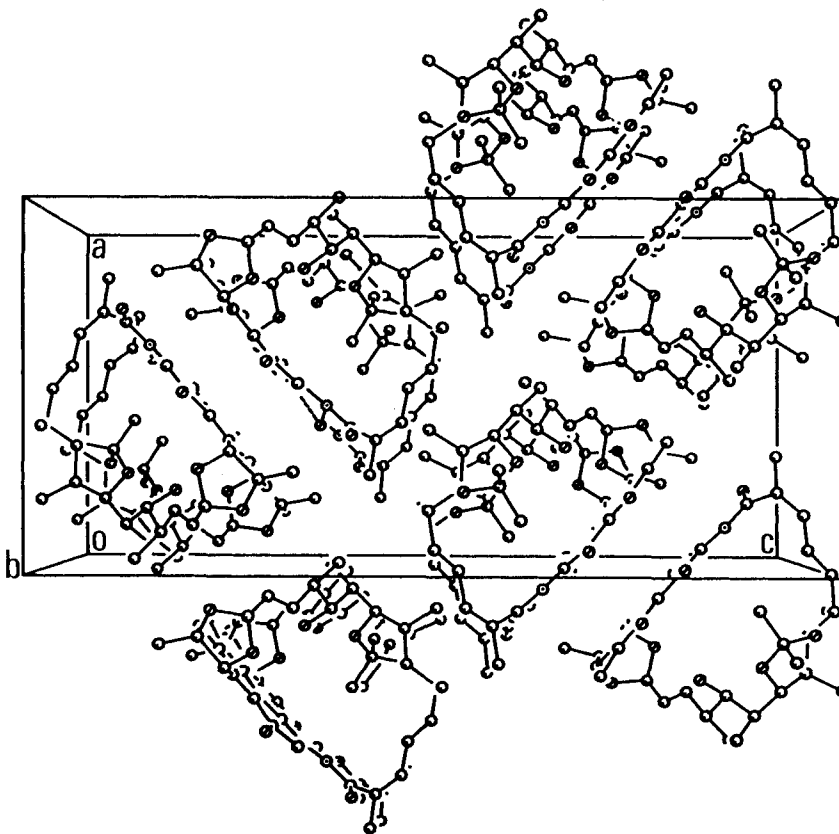


Fig. 3. A perspective view of the unit cell and of the spatial arrangement of the molecules around the two pseudo-binary axes

Table 2. Selected Intra- and Intermolecular Interactions ([Å], [°]) in the Crystal and Molecular Structure of 3

D—H···A	D···A	D—H	H···A	D—H···A
O(6a)—H—(O6a)···O(7a) ^{a)}	2.744(8)	0.85(1)	2.034(7)	140.5(7)
C(28a)—H—(28a)···O(5b) ^{b)}	3.491(8)	0.96(1)	2.665(8)	144.4(8)
C(28b)—H—(28b)···O(5a) ^{c)}	3.491(8)	0.96(1)	2.690(8)	141.2(7)
N(1a)—H—N(1a)···O(1W) ^{d)}	2.949(8)	0.90(1)	2.131(8)	150.7(6)
O(1a)···O(2b) ^{a)}	3.333(6)			
O(1b)···O(2a) ^{a)}	3.392(6)			
O(2a)···O(6a) ^{a)}	3.407(8)			
O(2b)···O(6b) ^{a)}	3.418(8)			
O(6b)···O(7b) ^{a)}	2.763(8)			
O(10b)···O(1W) ^{a)}	2.771(9)			
O(1a)···O(1W) ^{d)}	2.989(9)			
O(1b)···O(10a) ^{d)}	3.310(6)			
O(2b)···O(10a) ^{d)}	3.052(6)			

Symmetry code

^{a)} x, y, z ; ^{b)} $x - 1, y, z$; ^{c)} $x + 1, y, z$; ^{d)} $-x + 1, y - 1/2, -z + 1/2$.

interact by the π electrons of the chromophore rings; the second axis allows the molecules to face along the region of the *ansa*-chain spanning from C(12) to C(26). It is worth remarking that two short C–H \cdots O contacts involving C(28) and O(5) occur, as shown in Table 2. This type of contacts are attractive interactions which can be reasonably described as H-bonds [19]. The hydroxy O(6) is engaged in an intramolecular H-bond with O(7). The crystal packing is then built up by infinite columns, extending along the *b*-axis, of pseudo-symmetrical molecules spaced by $\sim b/2$ and bridged by H-bonds involving the H₂O molecule O(1W) and O(10b), O(1a) and N(1a) of two molecules related by the symmetry operator $(1-x, 1/2+y, 1/2-z)$. The columns are held together by $\pi-\pi$ interactions between chromophores, and O(5) \cdots H–C(28) short contacts and *van der Waals* forces between *ansa*-chains.

Experimental. – Orange prismatic crystals were grown from MeOH/H₂O at 277 K. Crystal data: C₃₇H₄₅NO₁₀ · 1/2H₂O, $M_r = 672.8$, space group orthorhombic $P2_12_12_1$, $a = 14.037(3)$, $b = 17.113(4)$, $c = 30.295(6)$ Å, $V = 7277(3)$ Å³, $F(000) = 2872$, $Z = 8$, $D_x = 1.228$ g · cm⁻³, $\text{CuK}\alpha$, $\lambda = 1.54184$ Å, $\mu = 7.00$ cm⁻¹. A crystal of dimensions $0.4 \times 0.4 \times 0.1$ mm was used for data collection and set on a *Siemens R3m/V* diffractometer (graphite-monochromated $\text{CuK}\alpha$ radiation). Intensity data were collected the experimental conditions being: $(\sin \theta/\lambda)_{\max} = 0.60$ Å⁻¹, $\theta - 2\theta$ scan mode, scan width $(2 + 0.14 \tan \theta)^\circ$, scan rate $0.75\text{--}14.65^\circ \cdot \text{min}^{-1}$ (depending on reflection intensity), background count time half of the total scan time. Accurate unit-cell parameters were determined by least-squares fit of the setting angles of 25 selected reflections with $48 \leq 2\theta \leq 80^\circ$. There was no significant intensity variation for the three check reflections $-2, 0, 0$, $0, -4, 0$, and $0, 0, -4$, monitored every hundred. The data were corrected for *Lorentz* and polarization effects, but no absorption or extinction corrections were made. Of the 7257 unique reflections measured (after averaging $R_{\text{int}} = 2.80\%$), 5928 with $I \geq 1.0\sigma(I)$ were considered as observed. The structure was solved by direct methods using the *SHELXTL-Plus* [20] program based on the multiple-permutation single-solution procedure, and refined on F_0 by full-matrix block least-squares methods (number of refined parameters was 874 and the data to parameter ratio 6.8:1). Attempts to locate H-atoms in the difference *Fourier* map were only partially successful, and so the H-atoms of the O(2), and O(6) OH groups, and those of the O(1W) H₂O molecule were not included in the refinement. After including H-atoms, kept fixed with isotropic temperature factors $U_{\text{iso}} = 0.08$ Å², and refining non-H-atoms anisotropically, the final *R* value was 0.070 and $R_w = 0.117$ minimizing the function $w|AF|^2$, with $w = [\sigma^2[(F_0) + 0.030346F_0^2]]^{-1}$. At convergence, the maximum shift/e.s.d. ratio was less than 0.25 and $S = 0.611$. Heights in final difference *Fourier* map $\rho_{\max} = 0.28$, $\rho_{\min} = -0.29$ e · Å⁻³. Atomic scattering factors were taken from [21]. Final positional and equivalent isotropic thermal parameters U_{eq} have been deposited with the *Cambridge Crystallographic Data Centre*. The *PARST* program [22] was used for the molecular-geometry calculations.

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