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ABSOLUTE CONFIGURATION OF THE RUBIGINONES AND PHOTO-INDUCED OXIDATION OF THE C1 HYDROXYL OF THE ANTIBIOTICS TO A KETONE

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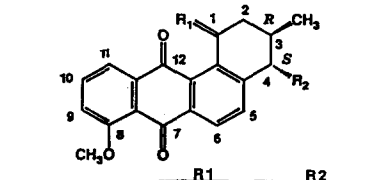
Abstract : The absolute stereochemistry of rubiginones A_1, A_2, B_1, B_2, C_1 and C_2 has been established by NMR spectral analysis using the O-methylmandelate method. A facile photo-induced oxidation of rubiginones A_1, B_1 and C_1 to rubiginones A_2, B_2 and C_2, respectively, is discussed in relation to the absolute stereochemistry.

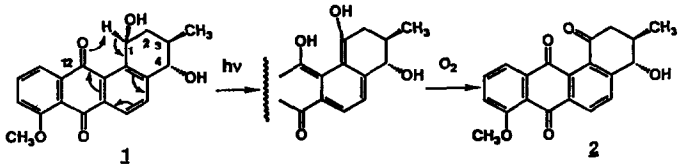
Rubiginones A_1(1, $C_{20}H_{18}O_5$), A_2(2, $C_{20}H_{16}O_5$), B_1(3, $C_{20}H_{18}O_4$), B_2(4, $C_{20}H_{16}O_4$), C_1 (5, $C_{24}H_{24}O_6$) and C_2 (6, $C_{24}H_{22}O_6$) were isolated from the fermentation broth of *Streptomyces griseorubiginosus* and exhibited potentiation of vincristine-induced cytotoxicity against multi-drug-resistant tumor cells[1]. Analysis of their hetero- and homonuclear COSY and long-range COSY spectra has established that they are new members of the isotetracenone[2] (angucyclinone[3]) family of antibiotics with a 1,2,3,4-tetrahydro-3-methyl-8-methoxybenz-[a]anthraquinone nucleus. They differ from each other in the oxidation pattern at C1 and C4 and acylation at the C4 hydroxyl.

During the purification of 1, we observed that a bright yellow solution of 1 in CH_2Cl_2 rapidly changed to violet (λmax 540 nm) upon exposure to light; the color returned to the original yellow after putting the solution in the dark. This photochromism is probably caused by photoenolization[4], in which intramolecular hydrogen transfer from C1 to oxygen at C12 occurs yielding the enol (Norrish type II reaction). In fact, 1 was oxidized to 2 by irradiation with a medium pressure mercury lamp in the presence of oxygen (Scheme 1). Similarly, 3 and 5 were converted to 4 and 6, respectively, under light at room temperature. The formation of the enol suggests that the C12-quinone oxygen is close enough to the C1-hydrogen for the hydrogen to be transferred.



Rubiginone	R1	R2
A_1(1)	H, OH, (S)	OH
A_2(2)	O	OH
B_1(3)	H, OH, (S)	H
B_2(4)	O	H
C_1(5)	H, OH, (S)	$OCOCH(CH_3)_2$
C_2(6)	O	$OCOCH(CH_3)_2$

Scheme 1



NOESY experiments on 1 showed interaction of the protons on the cyclohexene ring as in Fig. 1. NOE observed in the two pairs of 1,3-diaxial protons (1-H and 3-H, and 2-H_{ax} and 4-H) and two large spin-spin couplings (J_{2ax-3} = 11.1Hz and J_{3-4} = 9.6Hz)indicated that the ring exists in a half-chair conformation. However, the dihedral angles between 1-H and 2-H_{eq} (24°), and 1-H and 2-H_{ax} (146°) calculated from the coupling constants (J_{1-2eq} = 6.8Hz and J_{1-2ax} = 7.6Hz) by the Karplus equation[5] suggested that the ring is twisted considerably to a boat form, in which 1-H and 12-O are in close proximity when a molecular model is constructed. This form might contribute to the facile photoenolization reaction of 1.

The ring protons of other rubiginone components exhibited similar spin-spin couplings indicating that they have the same configuration as that of 1.

Fig. 1 NOESY data of 1

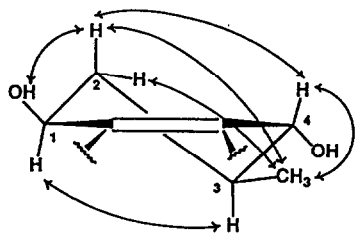


Table 1 Proton Chemical Shifts of (*R*) and (*S*)-O-Methylmandelate Esters of Rubiginone A_2

	Chemical shift (ppm in $CDCl_3$)						
	H_{2ax}	H_{2eq}	H_3	3-CH_3	H_4	H_5	H_6
(*R*)-O-Methylmandelate Ester	2.53	2.84	2.40	0.82	5.81	7.45	8.26
(*S*)-O-Methylmandelate Ester	2.64	3.03	2.51	1.11	5.84	6.76	7.96

In order to determine the absolute configuration of the rubiginones, (*S*)- and (*R*)-O-methylmandelate esters of 2 were synthesized (DCC and dimethylaminopyridine)[6] and their ^{1}H-NMR spectra compared. Upfield shifts of 2-H_{ax}, 2-H_{eq}, 3-H and 3-CH_3 were observed in the 4-(*R*)-ester relative to the 4-(*S*)-ester, whereas 5-H and 6-H of the 4-(*S*)-ester were observed at significantly higher field than those of the 4-(*R*)-ester. These shielding effects of the mandelate phenyl group indicated that 2 has the *S* configuration at the C-4 center. Since 1, 3 and 5, were converted to 2, 4 and 6, respectively and the relative stereochemistry of the substituents on C-1, C-3 and C-4 of rubiginones have been established as above, the rubiginones must have the absolute configurations of 1(1*S*, 3*R*, 4*S*), 2 (3*R*, 4*S*), 3(1*S*, 3*R*), 4(3*R*), 5(1*S*, 3*R*, 4*S*) and 6(3*R*, 4*S*).

This is the first example from a natural source of isotetracenones having a hydroxyl group at the C-1 position of the cyclohexene ring (rubiginones A_1, B_1 and C_1). Since the hydroxyl groups on C-1 are readily oxidized to ketones in the presence of light as discussed above, rubiginones A_2, B_2 and C_2 may not be true metabolites but artifacts produced during the fermentation under light with aeration and subsequent extraction process. The isotetracenone antibiotics with an ester substituent at C-4 (rubiginones C_1 and C_2) have never been previously reported.

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