X-Ray Crystal Structure of Sarothralin, a Novel Antibiotic Compound from *Hypericum japonicum*

Kyoko Ishiguro,[a] Masae Yamaki,[a] Shuzo Takagi,*[a] Yuriko Yamagata,[b] and Ken-ichi Tomita[b]

[a] *Faculty of Pharmaceutical Sciences, Mukogawa Women's University, Edagawa-cho, Nishinomiya, Hyogo 663, Japan*

[b] *Faculty of Pharmaceutical Sciences, Osaka University, Yamadaoka, Suita, Osaka 565, Japan*

A novel antibiotic compound, sarothralin, from *Hypericum japonicum* Thunb. (*Sarothra japonica* Thunb.) has been isolated and its stereostructure elucidated using spectroscopic and *X*-ray crystallographic techniques.

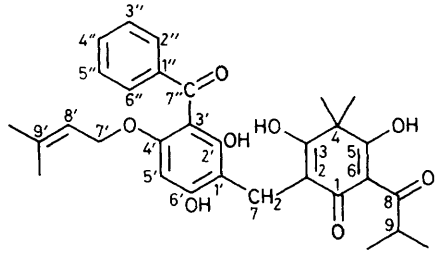
Hypericum japonicum Thunb. (*Sarothra japonica* Thunb.) is a Chinese herbal medicine for the treatment of several bacterial diseases, infectious hepatitis, gastro-intestinal disorders, and tumours. From the diethyl ether extract of the dried whole plant possessing significant inhibition against *Bacillus cereus*, *Staphylococcus aureus*, and *Genus citrobactor*, a new active compound, sarothralin (**1**), was isolated together with albaspidin iBiB.[1]

This paper deals with the isolation and structure analysis of (**1**). The diethyl ether extract of *H. japonicum* was carefully chromatographed on silica gel, followed by recrystallization (in ethanol–ethyl acetate) to purify (**1**)† (m.p. 140—145 °C, $[\alpha]_D$ 0°). The i.r. spectrum of (**1**) showed the presence of an enolic 1,3-diketo system or a 2-hydroxyaryl ketone (3300—3000 and 1640—1595 cm^{-1}). The ^1H n.m.r. spectrum indicated the presence of four hydroxylic protons (δ 9.70, 11.43, 14.64, and 18.75) [one of which (at δ 18.75) is characteristic of a β-triketone], a monosubstituted benzene ring (δ 7.35 and 7.46), an aromatic proton (δ 6.02), methylene protons (δ 3.58 and 3.60), geminal methyl groups (δ 1.50 and 1.56), isopropyl groups (δ 1.18 and 4.48), and isopentenyl groups (δ 1.54, 4.16, and 4.64). From a total of 31 signals present in the ^{13}C n.m.r. spectrum, three were ascribed to carbonyl carbon atoms, eighteen to aromatic or olefinic carbon atoms, and ten to aliphatic carbon atoms. The ^1H and ^{13}C n.m.r. spectra of (**1**) indicate certain anomalies which can be explained by tautomerization of an acylfilicinic acid system.[2]

The spectral data for (**1**) indicate that it contains phloroglucinol and filicinic acid and benzoyl residues, but the spectral data alone could not provide us with the aromatic substitution pattern in (**1**). Therefore, an *X*-ray analysis of (**1**) was carried out and its novel molecular structure was unequivocally determined.

Crystal data: $C_{31}H_{34}O_8$, M = 534.6, monoclinic, space group $P2_1$, a = 8.254(1), b = 10.260(2), c = 16.712(2) Å, β = 92.78(1)°, U = 1413.6(3) $Å^3$, Z = 2, D_c = 1.256 g cm^{-3}.‡ 2398 Independent reflections ($\sin\theta/\lambda < 0.58$ $Å^{-1}$) were collected on a Rigaku automatic four-circle diffractometer using Cu-K_α radiation. The structure was solved by direct and Fourier methods and refined by block diagonal least-squares. All hydrogen atom positions were located from a difference Fourier map and the final R factor is 0.076 for 1795 reflections with $|F_o| > \sigma(F_o)$.

The molecular structure of (**1**) is illustrated in Figure 1. The filicinic acid and phloroglucinol moieties are linked together by the methylene carbon atom C(7) such that their planes, with a dihedral angle of 56.6(3)°, are fixed rigidly by four intramolecular O–H- - -O hydrogen bonds as shown in Figure 1. This particular molecular conformation is very similar to



(**1**)

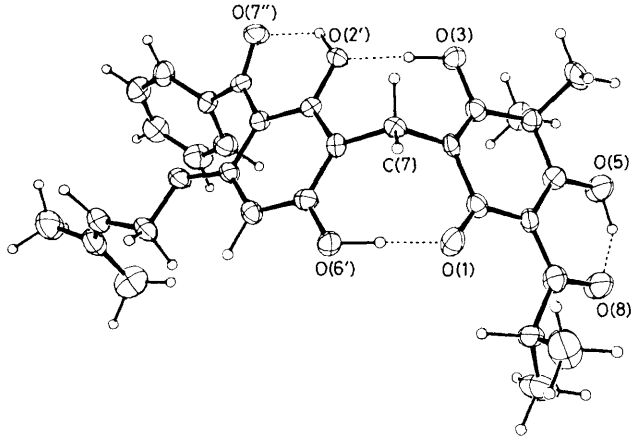


Figure 1. Molecular structure of (**1**). Dotted lines indicate the intramolecular hydrogen bonds. Hydrogen bond distances (Å) are: O(3)–H - - - O(2') 2.734(7), O(6')–H- - -O(1) 2.643(9), O(5)–H - - - O(8) 2.386(11), and O(2')–H - - - O(7'') 2.519(7).

† Sarothralin (**1**): i.r. ($CHCl_3$) $\nu_{max.}$ 3300—3000, 1640, 1652, 1625, 1595 cm^{-1}; u.v. (EtOH) $\lambda_{max.}$ (log ε) 245 (4.25), 362 (4.15) nm; ^1H n.m.r. (360 MHz, $CDCl_3$) δ 1.18 (6H, d, *J* 6.5 Hz, 9-Me), 1.40 (s), 1.50 (3H, s, 4-Me), 1.54 (6H, s, 9'-Me), 1.56 (3H, s, 4-Me), 3.58 (1H, s, 7-H), 3.60 (1H, s, 7-H), 4.16 (2H, d, *J* 6.1 Hz, 7'-H), 4.18 (1H, m, *J* 6.5 Hz, 9-H), 4.64 (1H, tq, *J* 6.1, 1.5 Hz, 8'-H), 6.02 (1H, s, 5'-H), 7.35 (2H, m, 2'',6''-H), 7.46 (3H, m, 3'',4'',5''-H), 9.70 (1H, s, C-3–OH), 11.43 (1H, s, C-6'–OH), 14.65 (1H, s, C-2'–OH), 18.75 (1H, s, C-5–OH); ^{13}C n.m.r. (25.2 MHz, $CDCl_3$) δ 16.8 (t, C-7), 18.0 (q, C-4–Me), 19.0 (q, C-9'–Me), 19.2 (q, C-4–Me), 25.5 (q, C-9–Me), 36.7 (d, C-9), 44.4 (s, C-4), 65.1 (t, C-7'), 94.2 (d, C-5'), 104.5 (s, C-1' or -3'), 106.2 (s, C-2 or -6), 107.1 (s, C-1' or -3'), 111.2 (s, C-2 or -6), 118.3 (d, C-8'), 127.3 (d, C-2'' or -6''), 127.5 (d, C-3'' or -5''), 130.2 (d, C-4''), 137.2 (s, C-1'' or -9''), 142.0 (s, C-1'' or -9''), 161.0 (s, C-2', -4', or -6'), 162.0 (s, C-2', -4', or -6'), 164.9 (s, C-2', -4', or -6'), 171.5 (s, C-3), 187.3 (s, C-5), 199.4 (s, C-7''), 199.6 (s, C-1), 210.8 (s, C-8).

‡ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

that of bromouliginosin B,[3] an analogous antibiotic compound extracted from *H. uliginosum,* and it may have some correlations with its biological activity.

Received, 2nd July 1984; Com. 935

References

1 A. Penttilä and J. Sundman, *Acta Chem. Scand.*, 1964, **18**, 344.
2 S. Forsén, M. Nilsson, and C. A. Wachtmeister, *Acta Chem. Scand.*, 1962, **16**, 583.
3 W. L. Parker, J. J. Flynn, and F. P. Boer, *J. Am. Chem. Soc.*, 1968, **90**, 4723.