

THE STRUCTURE OF AN EPIDERMAL
GROWTH FACTOR-RECEPTOR
KINASE INHIBITOR, ERBSTATIN

Sir:

The discovery, isolation and biological studies of erbstatin (**1**) have been reported in the preceding paper in this journal¹⁾. In this communication, spectral studies of **1** and the result of crystal structure determination by X-ray diffraction methods are reported.

¹H NMR spectroscopy of **1** in acetone-*d*₆ at 400 MHz (internal TMS reference) gave duplicate (4: 1 mixture) spectrum, resulting from restricted rotation around the N-C bond of an amide. In the spectrum of the main component in the mixture, 3 aromatic and 2 olefinic protons were shown at δ 6.4~7.7. Two of them, δ 6.64 (1H, d, $J=15$ Hz, H-7) and δ 7.63 (1H, dd, $J=11$ Hz, 15 Hz, H-8) were assigned to *trans* olefinic protons and the others, δ 6.51 (1H, dd, $J=3$ Hz, 9 Hz, H-5), 6.68 (1H, d, $J=9$ Hz, H-6) and 6.80 (1H, d, $J=3$ Hz, H-3) were assigned to 1,2,4-trisubstituted benzene ring protons. The protons at δ 7.72 (1H, br, OH), 8.02 (1H, br, OH) and 9.30 (1H, br d, $J=11$ Hz, NH) were exchangeable by addition of deuterium oxide. The signal at δ 8.17 (1H, s) was assigned to an

Table 1. ¹³C NMR chemical shifts of **1** in ppm from TMS in acetone-*d*₆ at 100 MHz.

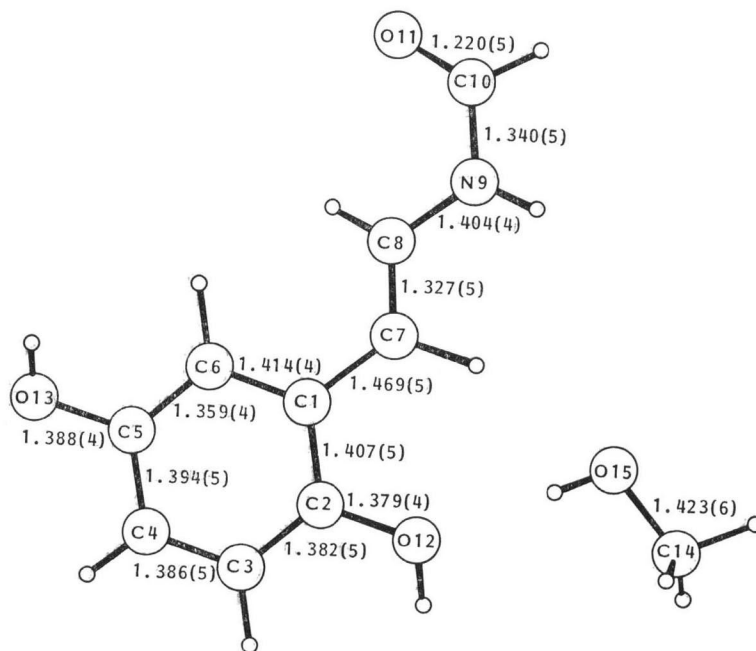
Chemical shifts (multiplicity)	Assignment
110.3 (d)	7
113.2 (d)	6
115.0 (d)	4
117.2 (d)	3
122.5 (d)	8
124.7 (s)	1
148.2 (s)	2
151.4 (s)	5
159.2 (d)	10

N-formyl group attached to the olefinic carbon H-8 by a spin-spin decoupling experiment irradiating at δ 9.30 and by the ¹³C NMR spectrum of **1** (δ 159.2, d).

After the structure determination by X-ray crystallographic analysis described later, the ¹³C NMR spectrum was assigned by long range selective proton decoupling experiments as listed in Table 1.

Crystals of **1** were grown in methanol-chloroform solution as brown in color. A small fragment of approximate dimensions 0.55×0.25×0.1 mm was mounted on a Philips PW1100 diffractometer and its unit cell dimensions and in-

Fig. 1. Molecular structure.
Bond lengths between the heavier atoms are shown.



tensity data were obtained using $\text{CuK}\alpha$ radiation monochromated by a graphite plate. The crystal data are: erbstatin methanol solvate, $\text{C}_9\text{H}_8\text{NO}_3 \cdot \text{CH}_3\text{OH}$, $\text{FW}=211.2$. Monoclinic, space group $\text{P}2_1$, $a=6.536(4)$, $b=15.074(8)$, $c=5.473(4)$ Å, $\beta=104.39(5)^\circ$, $U=522.3$ Å³. $Z=2$, $D_{\text{calc}}=1.344$ gcm⁻³, μ for $\text{CuK}\alpha$ radiation = 8.38 cm⁻¹.

Intensities of 1106 reflections out of 1163 theoretically possible ones in a 2θ range 6° through 156° were observed as above the 2σ (I) level. Intensities of three reference reflections decreased only by about 1% throughout the measurement. The structure was determined by the direct method using the MULTAN²⁾ procedure and refined by the method of least-squares with block-diagonal approximations.

The final R value was 0.04 with anisotropic temperature factors for 15 heavier atoms and isotropic ones for 13 hydrogen atoms[†].

The structure of the molecule with bond lengths indicated is shown in Fig. 1. There is no unusual feature in the molecular dimensions. The amide group is *trans* with respect to the carbonyl group and imino hydrogen atom. Double bond nature is extended to C1-C7 and also to C8-N9-C10 bonds. Thus the molecule consists of two planar groups; one formed by the six atoms of benzene ring, C1 through C6 and the other formed by six atoms of the side chain, C1 and C7 through O11. The mean value of the atomic displacements from the least-squares plane is calculated to be ± 0.00 Å for the former and ± 0.040 Å for the later planar group. Both planes are nearly coplanar but the side chain is

twisted a little from benzene ring; the dihedral angle between the two planes is 12.1° . The solvation molecule is hydrogen bonded to O12 [O15 \cdots O12, 2.831(4); HO15 \cdots O12, 1.97(4) Å] and O13 [O13 \cdots O15ⁱ, 2.735(4); HO13 \cdots O15ⁱ, 1.91(4) Å] where i is at \bar{x} , $\frac{1}{2}+y$, \bar{z} . The molecules are held together by intermolecular hydrogen bonds described above and also O12 \cdots O11ⁱⁱ, 2.662(4) Å [HO12 \cdots O11ⁱⁱ, 1.74(5) Å] and N9 \cdots O13ⁱⁱⁱ, 3.000(4) Å [HN9 \cdots O13ⁱⁱⁱ, 2.07(4) Å] where ii is at $1+x$, y , $-1+z$ and iii is at \bar{x} , $-\frac{1}{2}+y$, \bar{z} .

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(Received September 9, 1985)

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- 2) MAIN, P.; M. M. WOOLFSON & G. GERMAIN: MULTAN, A Computer Program for the Automatic Solution of Crystal Structures. University of York (England) and Leuven (Belgium), 1971

[†] Final atomic coordinates will be compiled in the Cambridge Crystallographic Data-base and a list of thermal parameters and F_o , F_c tables may be obtained from one of the authors (HIKARU NAKAMURA) on request.