RELATIVE AND ABSOLUTE CONFIGURATION OF AXIVALIN AND ITS CONGENERS[1]

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Three novel cyclopropanoid guaianolides axivalin, ivaxillarin, and anhydroivaxillarin have been isolated from Iva axillaris Pursh. ssp. robustior, and were assigned gross structures I, II, and III, respectively.[2] To confirm the structures and to establish the stereochemistry, we undertook an X-ray crystallographic analysis of axivalin.
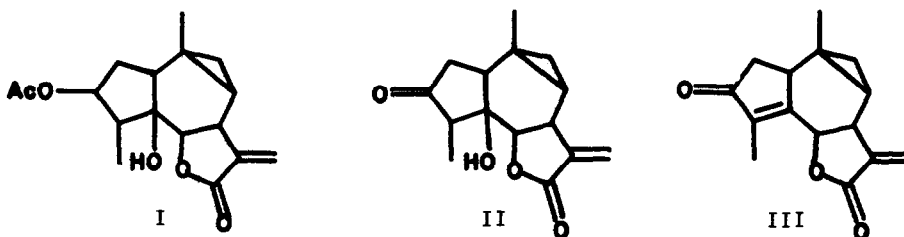
A single crystal of axivalin($C_{17}H_{22}O_5$) was obtained as the hydrate by crystallization from methanol-water. The crystal was shown to belong to the orthorhombic space group $P2_12_12_1$ from precession and Weissenberg photographs. The 0.8mm by 0.36mm by 0.04mm crystal, for which absorption was negligible was examined on a Hilger-Watts Y290 automatic diffractometer using molybdenum Kα radiation. The unit cell dimensions obtained by a least-squares fit of observed angles were: a = 8.601(3), b = 10.555(4), c = 18.734(9), which for four molecules of axivalin and four molecules of water gave a crystallographic density of 1.267 g/ccm. This compared favorably with the density of 1.26 g/ccm determined by floatation in heptane-carbon tetrachloride.

Of the total of 2911 reflections measured, 1285 were independent and had a positive, nonzero intensity. Structure factors were obtained for the independent reflections after the standard corrections had been applied.

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The structure was solved by direct methods using the X-Ray 70 System of programs devised by Stewart.[3]

Normalized structure factors were calculated using a linear isotropic temperature correction. All reflections having a positive, nonzero intensity were included as "observed" reflections for this calculation and for all steps in the phase determination.

A total of 7970 triplets were found for the 285 reflections having an E value of 1.2 or greater.

Three origin-defining reflections (0 3 2, E = 4.33; 2 0 7, E = 2.61; 0 2 1, E = 2.54) were selected and assigned phases of 90°, 90°, and 180° respectively. In addition, an enantiomer-defining reflection (3 0 1, E = 1.88) was assigned a phase of 90°. Reiterative application of the tangent refinement formula[4] led to the determination of 271 phases with an agreement factor of 0.24.

Use of these phases allowed the preparation of an E-map in which twenty-two of the twenty-four strongest unique peaks were recognizable as the molecular structure of axivalin. A structure factor calculation for carbon atoms at these twenty-two positions gave an R factor of 0.337. A Fourier map using the calculated phases and the observed structure amplitudes for all reflections showed the twenty-two unique peaks for axivalin as well as one unique peak corresponding to the stronger of the two not assigned in the E-map. Thus, this peak was accepted as the location of the oxygen atom of the water molecule. Inclusion of a carbon atom at this position followed by three cycles of full matrix least squares refinement using individual isotropic temperature factors and unit weights led to a value of 0.234 for the R factor. Replacing carbon atoms with oxygen atoms at the appropriate positions followed by four cycles of full matrix least squares refinement using individual anisotropic temperature factors and unit weights further reduced the R factor to 0.116.

At this point, "observed" reflections were redefined as those reflections for which the intensity was greater than three times the estimated standard deviation of the measurement. Hydrogen atoms were located by difference maps. Application of a new weighting scheme: $\{w = 1/(6.5 + F_0 + 0.005 \ F_0{}^2)\}$, inclusion of

an isotropic extinction correction, and further full matrix least squares refine-
ment using individual anisotropic temperature factors for carbon and oxygen and
an overall isotropic temperature factor for the hydrogen atoms gave a final R
factor of 0.077 excluding the 161 "less thans".

All bond lengths and angles were as expected. Full details of the
X-Ray analysis will be published at a later date.

The CD curve of axivalin exhibited a strong positive Cotton effect at
252 nm (θ = 4430). If a recently formulated empirical rule relating the sign of
the lactone Cotton effect to the nature of the lactone ring fusion[5] holds for
axivalin, the absolute stereochemistry is the same as that obtained through the
original phase assignment, i.e. the C-7 side chain of axivalin is β-oriented as
in all other guaianolides of established configuration. Model considerations
indicate that the pyrazoline of axivalin should be IV or its mirror image; the
negative Cotton effect (λ = 326mm, θ =-42940) requires the former.[6] The absolute
configuration of axivalin is shown in Figure I as that enantiomer deduced from the
optical data.
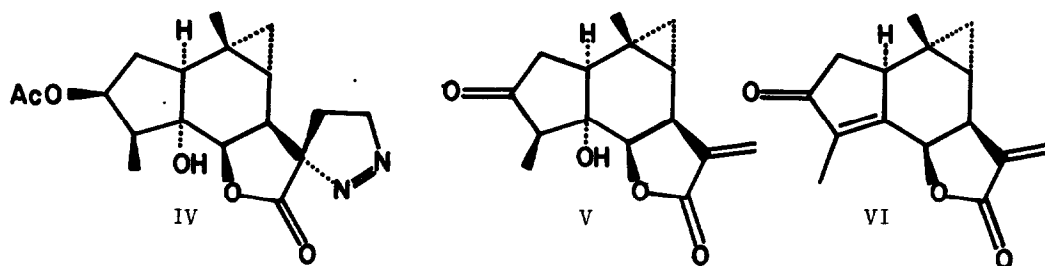
Since axivalin had been previously correlated with ivaxillarin
and anhydroivaxillarin, the stereochemistry of the latter compounds must be as
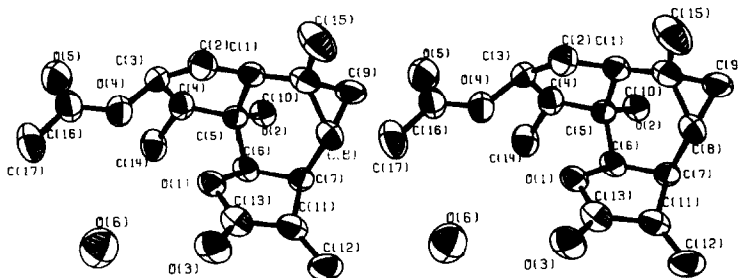shown in V and VI respectively.

FIGURE I.   Three-dimensional view of axivalin showing ellipsoids of thermal
            motion at 50% probability.

References

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