# RELATIVE AND ABSOLUTE CONFIGURATION OF PSEUDOIVALIN[1]

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The isolation from a chemical race of _Iva microcephala_ Nutt. of microcephalin (_1_)[2] and pseudoivalin (_2a_)[3] has so far remained the only instance in which a guaianolide has been found to co-occur with a eudesmanolide.  While the stereochemistry of microcephalin was established by chemical and physical means, our assignment of stereochemistry _2a_ to pseudoivalin was speculative and based primarily on the assumption that a common ten-membered ring precursor was involved.  The nature of this precursor has been discussed.[4]

To place speculations concerning the biogenetic origin of these and other sesquiterpene lactones[5] on a firmer footing, we undertook an X-ray crystallographic analysis of pseudoivalin bromoacetate (_2b_) the results of which confirm formula _2a_ and support the hypothesis that _1_ and _2a_ are formed by processes simulating Markownikow and anti-Markownikow oriented cyclization of the same (_cis_-$\Delta^{1,10}$?)[4] germacradienoid precursor.



_1_

2a,  R=H
2b,  R= -C CH₂Br
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            O
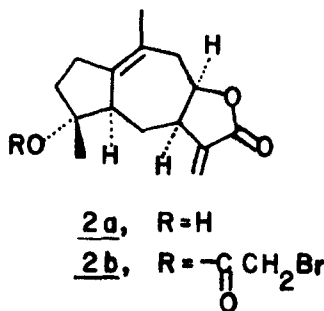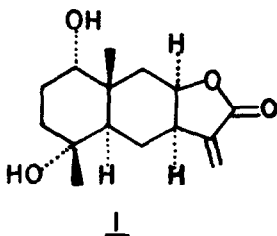
A single approximately equidimensional crystal of pseudoivalin bromoacetate (0.4 x 0.6 x 0.7 mm) obtained by crystallization from methanol was shown to belong to the orthorhombic space group $P2_1 2_1 2_1$ from precession and Weissenberg photographs. The crystal was examined on a Hilger-Watts Y290 automatic diffractometer using molybdenum $K\alpha$ radiation. The unit cell dimensions obtained by a least squares fit of observed angles were a = 13.219 (3), b = 8.835 (4), c = 14.367 (4), which for four molecules per unit cell gave a crystallographic density of 1.461 g/ccm. This compared favorably with the density of 1.47 g/ccm determined by floatation in aqueous potassium iodide.

Of the total of 2908 reflections measured, 1130 were independent and had a positive, nonzero intensity. Structure factors were obtained for the independent reflections after the standard corrections had been applied ($\mu = 26$ cm$^{-1}$, spherical approximation).

The structure was solved by the heavy atom method using the XRAY-72 System of programs devised by Stewart[6]. The bromine position was obtained from the Patterson map. Considerable difficulties were encountered in extending the phasing model due to the highly anisotropic character of the bromine atom (It is also possible that the bromine atom is disordered which would give the same electron density distribution.). Examination of the F map showed that the bromine peak was extremely elongated along the y axis and examination of the delta-F map indicated that a large concentration of electron density was at the same x and z co-ordinate as the bromine but with the y co-ordinates of the two peaks above and below that of the bromine position. When two bromine atoms, each having a population parameter of 0.5, were introduced at these locations, the phasing model extended rapidly and smoothly. All of the carbon and oxygen atoms were

found from a series of F maps. A structure factor calculation with all twenty-one of these atoms being assigned a maximum scattering factor of 6.0 and the two bromine positions assigned a population parameter of 0.5 gave a conventional R factor of 0.342.

When the F maps obtained from the one bromine model were re-examined, it was found that the light atom positions did appear on the maps but they were not as readily recognizable as those in the maps for the two bromine model.

Assignment of the appropriate scattering factors to the light atoms, inclusion of the bromine position as that obtained from the Patterson map, and definition of "less-thans" as those reflections having an intensity less than three times the estimated standard deviation of the measurement, followed by four cycles of full matrix least squares refinement using individual isotropic temperature factors and four cycles of full matrix least squares refinement using individual anisotropic temperature factors reduced the R factor to 0.10 excluding the 69 "less-thans".

A difference map showed no feature greater than 0.5 electrons/ $Å^3$. All bond lengths and angles are as expected. Further refinement is under way; full details of the X-ray analysis will be published at a later date.

The CD curve of pseudoivalin exhibited a strong negative Cotton effect at 250 nm ($\theta = -5500$). Since there are no unusual factors affecting the chirality of the lactone ring, i.e. no allylic double bond, the empirical rule relating the sign of the lactone Cotton effect to the nature of the lactone ring fusion[7] may be expected to hold and the absolute configuration is as shown in 2a.
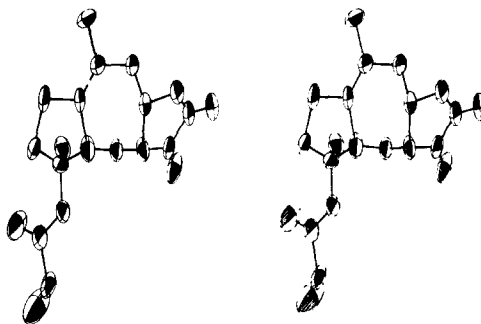
FIGURE I.   Three-dimensional view of pseudoivalin bromoacetate.

## References

1.  Part XV in the series "Constituents of Iva Species".  For Part XIV, see H. Chikamatsu and W. Herz, J. Org. Chem., 38, 585 (1973).

2.  W. Herz, G. Högenauer and A. Romo de Vivar, J. Org. Chem., 29, 1700 (1964).

3.  W. Herz, A. Romo de Vivar and M. V. Lakshmikantham, J. Org. Chem., 30, 118 (1965).

4.  W. Parker, J. S. Roberts and R. Ramage, Quart. Rev., 21, 331 (1967).

5.  W. Herz in Pharmacognosy and Phytochemistry (H. Wagner and L. Hörhammer, eds.), Springer Verlag, Berlin-Heidelberg-New York, p. 64 (1971).

6.  Programs used were local modifications of the XRAY System, Version of June 1972, (Technical Report TR-192 of the Computer Science Center, University of Maryland, June 1972, J. M. Stewart, G. J. Kruger, H. L. Ammon, C. Dickinson, and S. R. Hall, eds.) and ORTEP (ORNL-3794 second revision) written by Carroll K. Johnson, Oak Ridge National Laboratory. All computations were carried out on a CDC 6500 computer.  Plots were prepared on a Stromberg-Carlson CRT plotter at Eglin Air Force Base through the courtesy of Mr. Terry Blanchard.

7.  W. Stöcklin, T. G. Waddell and T. A. Geissman, Tetrahedron, 26, 2397 (1970)