Reports

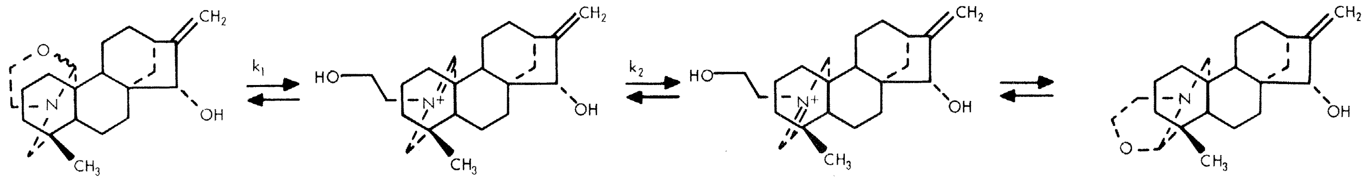
Veatchine: Coexistence of Epimers in a Crystal Structure

Abstract. *An x-ray crystal structure determination of veatchine, a C_{20}-diterpenoid alkaloid, reveals the coexistence of molecules which differ in configuration at one of seven asymmetric carbon atoms. This disorder between epimers demonstrates the stability of both forms, and accounts for the doubling of certain peaks in the magnetic resonance spectra of this and related alkaloids.*

X-ray crystal structure determinations are among the most precise and reliable sources of information about molecular structure. Usually, no doubt is left about the details of conformation and configuration in the solid state. When a single unit cell contains molecules in environments which are not symmetrically identical (that is, the asymmetric unit of the crystal contains more than one molecule), minor (and sometimes major) differences in conformation may be found. Similar differences in configuration, however, have not been observed, for diastereomeric molecules tend to separate on crystallization while enantiomeric molecules tend to crystallize as racemates. We are reporting here a highly unusual example of two configurationally distinct molecules (epimeric at only one of seven chiral centers) which cocrystallize in a disordered manner.

Veatchine (I in Fig. 1) is a C_{20}-diterpenoid alkaloid (*1*) which is found in the bark of *Garrya veatchii* Kellogg. The facile isomerization (I $\rightleftarrows$ IV) of the oxazolidine ring F in this and several related alkaloids has been the subject of chemical interest for many years (*2*). Spectral studies have been particularly difficult, for certain resonances in the nuclear magnetic resonance (NMR) spectra of these alkaloids are doubled (*3*). Explanations of this observation include an equilibrium between chair and boat conformations for ring E, and interconversion of epimeric molecules through a zwitterionic intermediate (*4*). Recent ^{13}C NMR spectral studies support the coexistence in solution of epimeric molecules in veatchine and the related alkaloid atisine (*5*), but indicate that the proposed interconversion does not occur. We favor this interpretation, since crystals of veatchine contain both 20*R* and 20*S* molecules, showing that both epimers are thermodynamically stable (see Figs. 2 and 3). This coexistence of C(20) epimers in the solid state is, of course, distinct from the possible coexistence in solution of veatchine (I) and garryine (IV), which differ in the fusion of rings E and F. Furthermore, the epimerization of veatchine at C(20) must not be confused with epimerization at C(15), which would give the alkaloid laurifoline.

Veatchine forms large, colorless crystals from acetone. Diffractometric measurements established that they belong to the orthorhombic system, space group $P2_12_12_1$. The density was found to be 1.239 g/cm^3 by flotation in a toluene-chloroform mixture. A least-squares fit



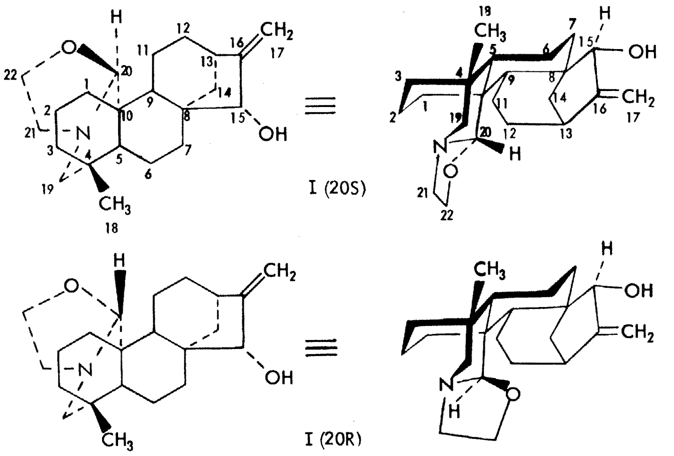
I
Veatchine

II

III

IV
Garryine

Fig. 1. Structures of veatchine, garryine, and intermediates.



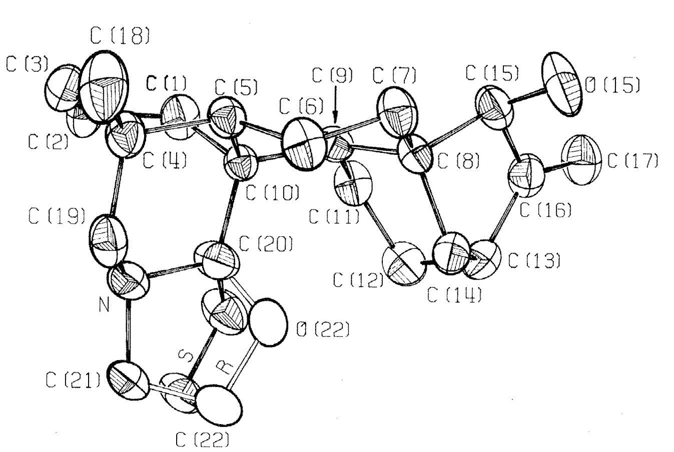


Fig. 2 (left). Structure and conformational drawings of C(20) veatchine epimers. Fig. 3 (right). Perspective drawing of the molecule of veatchine, with the major (20*S*) epimer shown as solid atoms. The open circles show the alternate positions for C(22) and O(22) in the minor (20*R*) epimer.

to 15 2θ values established the unit cell dimensions as $a = 9.934(3)$, $b = 21.581(8)$, and $c = 8.674(2)$ Å. Integrated intensities were measured on an Enraf-Nonius CAD-4 diffractometer (Mo$K\alpha$ radiation, $\lambda = 0.71069$ Å; $2\theta_{\max} = 54.90°$) for 2424 reflections, of which 1614 were significantly (2 standard deviations) above background. The structure was solved by a multisolution approach (*6*) and refined by least squares using a free-blocking approximation to the full matrix (*7*).

Initial atomic positions were found for all but one of the expected nonhydrogen atoms from an electron density map, with the remaining atom [the hydroxyl oxygen O(15)] being located from a difference electron density map. Refinement with anisotropic thermal parameters converged to an agreement residual $R = 0.149$. Two large peaks in the difference map corresponded to possible alternate positions for atoms C(22) and O(22) of the oxazolidine ring. A difference map, calculated under the assumption that these were correct, showed maxima at the original coordinates. Consequently, the four atoms were treated as half-occupied sites in subsequent refinement.

All but three of the hydrogen atoms were located from successive difference electron density maps; the missing atoms were expected to be disordered. Additional refinement converged at $R = 0.056$, with a weighted agreement residual $R_W = 0.066$ (*8*). In the last cycles, the site occupancy was allowed to vary for the disordered atoms and converged to values consistent with the predominance of one epimer by about a 60:40 ratio. This ratio is not only significantly different from random (50:50) disorder, based on the estimated standard deviations of the site occupancies, but also in agreement with the approximate 2:1 ratio found by integrating the doubled NMR peaks (*3, 5*). Although this work does not establish the absolute configuration of veatchine, the latter has been correlated with atisine (*9*), for which the absolute configuration has been established by x-rays (*10*). By analogy, the absolute configuration of veatchine is 4*S*, 5*S*, 8*R*, 10*R*, 13*R*, 15*R*, and 20*SR*, with the 20*S* epimer predominating.

Crystallization of two epimers in a disordered relationship is, as far as we can establish, a highly unusual observation (*11*). Such a manner of crystallization requires that both epimers exist in the solution and that their respective heats of crystallization be approximately the same. Furthermore, it seems unlikely that interconversion of the epimers occurs rapidly, since this would favor the growth of crystals which contain only a single epimer. In aprotic solvents, such interconversions may not occur at all. The only reasonable intermediate for such an epimerization is the normal form of the ternary iminium ion (II), the formation of which is favored in protic solvents. Kinetic studies of the isomerization of atisine clearly demonstrated the stability at room temperature of the iso- (III) over the normal-form of the iminium ion, but no information is available concerning the relationship of the rate constant for the ionization step (k_1) to that for the isomerization step (k_2). The fact that crystallization can occur more rapidly than epimerization suggests that in polar, aprotic solvents, the ionization step is sufficiently disfavored that it becomes rate-limiting. The reclosure of the oxazolidine ring (with the possibility of epimerization) thus becomes the preferred route to isomerization.

Even though veatchine (and, presumably, other similar diterpenoid alkaloids such as atisine, garryfoline, and cuachichicine) exists as a mixture of epimers, separation of the two molecules would be extremely difficult, if not impossible.

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11. Similar disorder has heretofore been observed only rarely, and has been limited to disorder between α and β anomers in mono- and disaccharides: *N*-acetyl-α-D-glucosamine (*12*), and various structures of α-lactose (*13*) and α-melibiose (*14*). In all these instances, the possibility for the hydroxyl group of the minor anomer to participate in the hydrogen bonding scheme without distortion appears to contribute to the stability of the structure. The present work, in contrast, shows no evidence of hydrogen bonding participation by O(22). We express our appreciation to R. E. Marsh for bringing these cases to our attention.
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Antarctica: A Deep-Freeze Storehouse for Meteorites

Abstract. *Meteorites that fall on the Antarctic ice cap are preserved for long periods of time under very clean conditions as they are carried toward the continental margin. If the host ice encounters a barrier it cannot flow over or around, it tends to dissipate by ablation, leaving an accumulation of meteorites on the surface.*

We have recovered 11 new meteorites in Antarctica during the period 15 December 1976 to 20 January 1977. At first glance, Antarctica would seem a poor place to search for meteorites. The vast, snow-covered Antarctic ice sheet moves radially outward, losing altitude and reaching zones having higher average temperatures as it approaches the edges of the continent. Cold, dense air spilling down over the surface also moves radially outward, creating winds that can attain hurricane force near the fringes of the ice sheet. Such winds can strip the ice bare of snow and promote local evaporation of the exposed ice surface. Blue ice patches appear and receive a rippled surface texture as evidence of working by the wind.

Wherever the ice sheet becomes thin enough, or the rocky surface of the continent rises high enough, mountains protrude through the ice. The vast Transantarctic Mountain Range, for example, is prominent above the ice in many places. The interface between the ice mass, which is moving slowly but inexorably off the polar plateau, and these mountains is a region where the ice sheet splits into ice streams that drop sharply in elevation over highly crevassed icefalls, then funnel into valley glaciers and pass through the mountains. On the plateau side, mountain peaks and ridges