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CYCLIZATION OF POLYENES XXV[1]
CONFORMATIONAL STUDY OF CEMBRENE TYPE DITERPENES BY X-RAY ANALYSIS

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An X-ray crystallographic analysis of 15,16-dehydro epimukulol acetate has revealed that the exact stereostructure is indicated in figure 1, which can be depicted on the modified diamond lattice conformation model as shown in figure 2.

The conformational analysis of medium and large ring systems is an area of increasing investigation and interest. For typical examples a ten-membered sesquiterpene, laurenolide, was found to exist in solution as a mixture of four possible conformers at -15°C,[2] while a fourteen-membered macrolide such as kromycin was revealed to keep a single conformation[3].

Cembrenoid diterpenes are characterized by their uniquely functionalized macrocyclic skeleton. As exemplified by mukulol (I), all the natural cembrenoids possess, in addition to several double bonds, one isopropyl and three methyl groups or their biogenetical equivalents at the definite positions in the fourteen-membered ring. Owing to the characteristic feature of the cembrenoids, studies concerning the conformation are of special interest since several conformational isomers are possible when examined by Dreiding model. After completion of the biogenetic type synthesis of some natural cembrenoids including mukulol (I)[4] and neocembrene (II)[5], our attention was focused on the conformational analysis of these intriguing compounds.

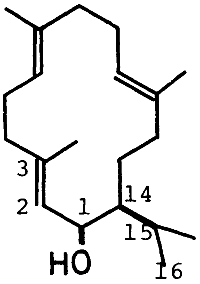
This paper concerns with the discussion on the conformation of 15,16-dehydro epimukulol acetate (III) by an X-ray crystallographic analysis.

X-RAY ANALYSIS OF DEHYDRO EPIMUKULOL ACETATE

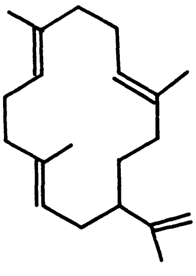
For the sake of establishment of the exact conformation and configuration of the cembrenoids, the crystalline acetate (III)[6] was submitted to the X-ray analysis and a resulting perspective view of the structure was presented in figure 1. The crystals of III are monoclinic with space group $P_{2/c}$, uniquely determined from the systematic absence for h0l with 2n+1. The unit cell dimensions are a = 21.488(3), b = 5.895(1), c = 18.971(3) Å, β = 120.4(2)°, and Z = 4. A total of 3660 reflections within 2θ = 14° were measured on a four circle diffractometer using CuKα radiation.

The structure was solved by the direct methods and refined by the block diagonal least squares methods. After several cycles of refinement with anisotropic thermal factors for non-hydrogen atoms, each position of hydrogen atoms was located by difference Fourier synthesis; some of the methyl hydrogens were poorly resolved. Hydrogen atom parameters were fixed in the following refinements and the final R value was 0.10 for the observed reflections. The observed bond lengths and angles are almost normal. It is, however, noteworthy that the principal features of the molecular vibration are clearly suggested from the thermal parameters although a detailed investigation of the anisotropic thermal vibration of III would be of value only if exceptionally good data were available. The markedly rigid sections of the ring are centered at C_1 and C_{10} while C_5 and C_{12} show the heavily anisotropic thermal parameters in the ring carbons. These observations suggest that the former two carbons behave like a bridgehead carbon in a relatively rigid ring and that the molecule vibrates with a maximum amplitude of oscillation at the latter two carbons.

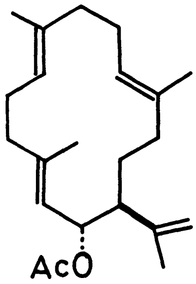
The most striking feature of the examined molecule is the beautiful arrangement of the three olefinic methyls, that is, C_3 and C_7 methyls protrude perpendicularly in the opposite directions while C_{11} methyl occupies the horizontal position, thus resulting in minimizing the non-bonded internal interaction of these methyl groups.



(I)



(II)



(III)

APPLICATION OF DIAMOND LATTICE CONFORMATION MODEL

It has been shown that a fourteen-membered macrolide antibiotics such as kromycin is present as a single conformation of a slightly modified diamond lattice type with the ring atoms occupying cyclohexane-like positions[7]. When the clarified conformation of III was applied to the model, the ring carbons can be set onto the modified diamond lattice conformation model. The new model was constructed by changing one of the chair type cyclohexanes into the boat form on which C_{14}-C_1-C_2- carbons are placed. The rest of carbons of III are placed onto the normal cyclohexane-like positions as shown in fig. 2. The fig. 3 shows the maps of dihedral angles. As evident, the shape and each of dihedral angles determined by X-ray analysis are in accord with those estimated from the Dreiding model.

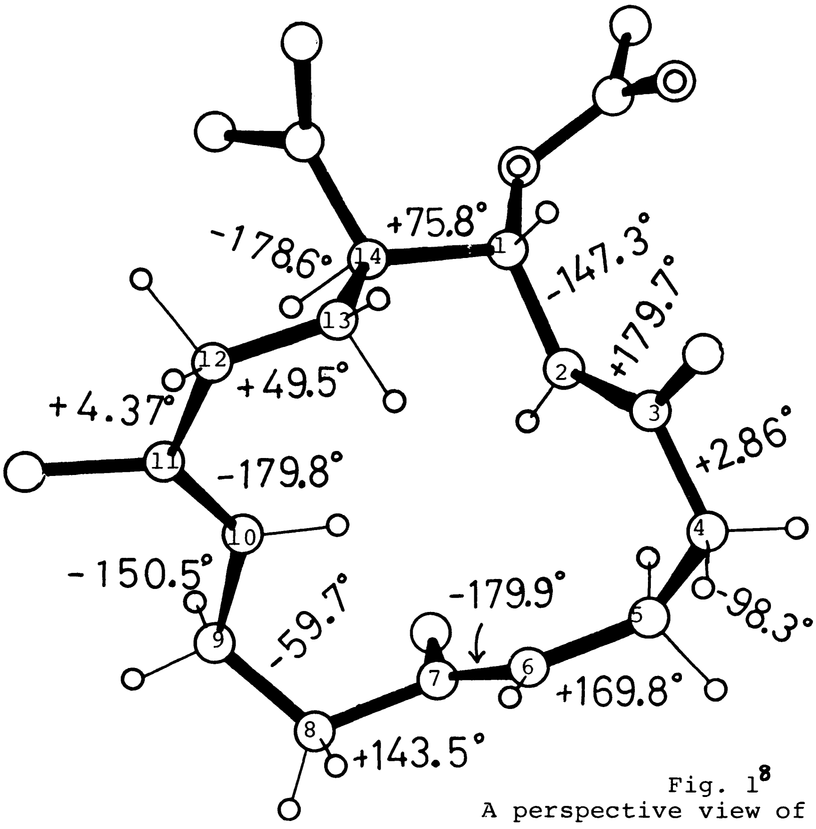


Fig. 1[8]
A perspective view of structure of III

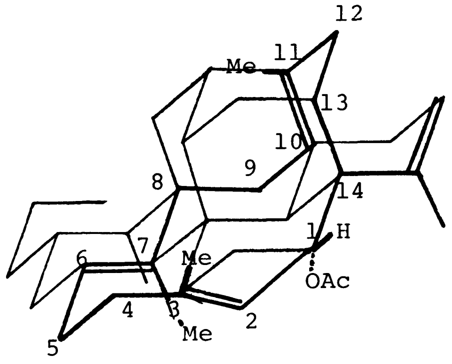


Fig. 2. Diamond lattice conformation model

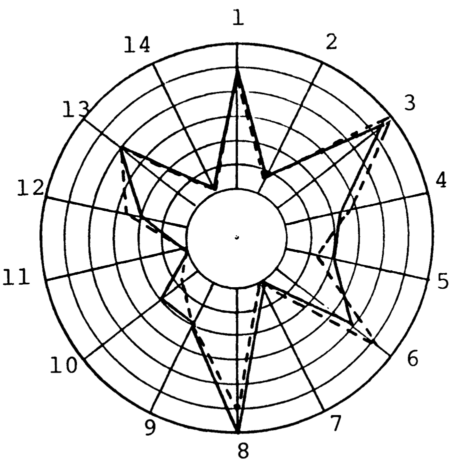


Fig. 3. Maps of dihedral angles[9]

It has thus made clear that the conformation of the cembrene type compound (III) is fixed in the crystalline state and can be set onto the modified diamond lattice conformation model.

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6. The relative stereochemistry of III was deduced from the coupling constants of the NMR spectra, the details of which will be published elsewhere.
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8. The value of each bond shows the dihedral angles.
9. An arbitrary but self-consistent set is defined for the sequence a-b-c-d as the positive clockwise rotation from a to d in the projection of the array down the line b-c. 1, 2, 3, --- on the outer circle show that a-b-c-d is C_{13}-C_{14}-C_1-C_2, C_{14}-C_1-C_2-C_3, and so on. The largest, the second, the third, ---and the smallest circles show the dihedral angles of +180°, +120°, +60°, --- and -180°, respectively. The solid and dotted lines show the dihedral angles estimated from Dreiding model and those observed by X-ray analysis, respectively.

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