

The Determination of the Conformation of a Germacranolide (Dihydotamaulipin-A Acetate) with the Aid of Nuclear Overhauser Effects

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WE report the determination of the conformation of dihydotamaulipin-A acetate (I) in solution by the use of nuclear Overhauser effects (NOE).¹ The acetate (I) is a member of a series of newly investigated^{2,3} germacranolides whose structure and stereochemistry was reported earlier.

A number of these *trans,trans*-cyclodeca-1,5-diene derivatives exhibit anomalous u.v.-absorption at *ca.* 210 nm; due to an interaction of the double bonds across the ring (transannular conjugation).²⁻⁵ Models for these medium rings indicate that the planes of the double bonds must be approximately perpendicular to the plane of the ring. In addition, the double bonds can either have a parallel or a crossed spatial arrangement. Therefore, cyclodeca-1,5-diene derivatives with substituted double bonds, such as germacranolides with methyl groups at C-4 and C-10, may theoretically have four different major conformations.

From earlier studies,⁴ a parallel orientation of the double bonds was inferred. The stereochemical course in certain chemical conversions, such as the Cope rearrangements, of a number of germacranolides to compounds of the elemene type^{2,3,5} and transannular addition reactions which produce *trans*-decalin derivatives⁶ suggest, however that, at least in the transition state, the double bonds in the cyclodeca-1,5-dienes must have a crossed orientation with the methyl

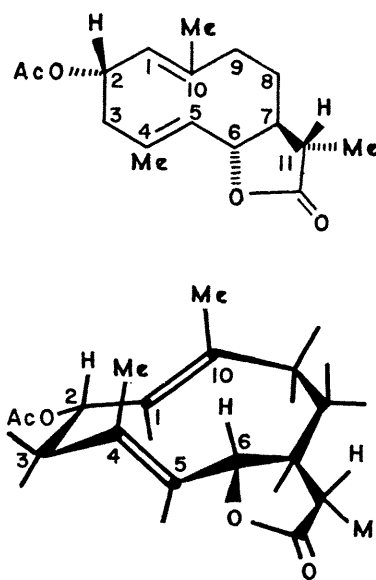


FIGURE. The molecular conformation of (I).

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groups at C-4 and C-10 on the same side of the plane of the medium ring.

The relationship of the double bonds to each other as well as to the two methyl groups at C-4 and C-10 in the germacranolide was determined by performing the NOE experiments¹ on a [²H₆]benzene solution of dihydrotamulipin-A acetate at 100 MHz.

The resonances of interest in the n.m.r. spectrum[‡] are (a) two intense signals at 1.26 (d, *J* 1.0) and 1.39 (d, *J* 1.5) corresponding to 10-Me and 4-Me respectively, (b) a lactonic hydrogen absorption at 3.96 (dd, *J* 8.5 and 10.0), (c) two broad peaks (*ca.* 10 c./sec.) at 4.55 and 4.71 representing the two olefinic protons at C-5 and C-1, and (d) a doublet of triplets at 5.66 (*J* 5.5 and 10.0) corresponding to HC-OAc. The signal assignments were confirmed by spin-decoupling experiments.

Low-intensity irradiation§ of a C₆D₆ solution of dihydrotamulipin-A acetate at a frequency corresponding to the absorbance of the 4-Me group caused an increase in the integrated intensity of the C-6 lactonic proton signal (15%

NOE) and a 10% increase of the 2-H signal. Irradiation of the 10-Me signal resulted in 15% enhancement of the signal intensity of the 2-H proton. Interactions between the 4-Me group and the C-1 olefinic proton and between the 10-Me group and the 5-H were not detected.

These results clearly indicate that the 4-Me group has the same direction in space as do the β-oriented C-6 lactonic proton and the 2-H proton.¶ The interaction of both the 4-Me and the 10-Me groups with the β-oriented proton at C-2 requires the methyl groups to have a *syn*-orientation. Therefore, the planes of the olefinic linkages are approximately perpendicular to the plane of the medium ring, with a crossed orientation of the double bonds, and the 4-Me and 10-Me are on the same side of the plane of the medium ring (Figure). A similar conformation has been reported recently for the 1:1 adduct of germacatriene with silver nitrate.⁷

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‡ The chemical shifts are reported in p.p.m. relative to internal reference tetramethylsilane and coupling constants (*J* values) are in c./sec. d = doublet, dd = doublet of doublets.

§ NOE data were obtained with the assistance of Mr. W. Wegner on a Varian HA-100 n.m.r. spectrometer operating in frequency sweep mode. A drop of benzene was added to the sample solution for internal lock.

¶ Because the 4-Me group is in proximity to the hydrogens at C-2 and C-6, and 6-H is known to be β-oriented,² it follows that 2-H must also have a β-configuration. These results are in agreement with our previous assignments for the stereochemistry at C-2 in dihydrotamulipin-A acetate.³

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