be determined. The magnitudes of the induced activity when measurable could not be reproduced reliably due to variations in sample thickness and temperature.

Acknowledgment. The financial support for this work from the Research Corp. and the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Registry No. 2a, 2627-86-3; **2b**, 3789-59-1; **2c**, 68906-26-3; **2d**, 32908-36-4; **2e**, 82729-98-4; **2f**, 3082-58-4; **2g**, 4187-53-5; **2h**, 27298-97-1; **2i**, 27298-98-2; **2j** (isomer 1), 27948-34-1; **2j** (isomer 2), 22038-88-6; **2k** (isomer 1), 3082-62-0; **2k** (isomer 2), 3906-16-9; **2m**, 10420-89-0; **2n**, 82679-49-0; **2o**, 15185-02-1; **3a**, 74879-40-6; **3b**, 74879-41-7; **3e**, 82679-50-3; **3o**, 82679-51-4.

Crystal Structure and Stereochemistry of Ivaxillin[1]

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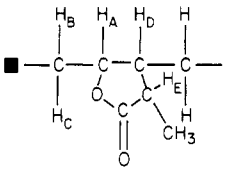
Received April 13, 1982

A number of years ago[2] one of us described isolation from *Iva axillaris* of the three cyclopropanoid guaianolides axivalin (**1**), ivaxillarin (**2**), and anhydroivaxillarin (**3**) which have so far remained the only representatives of their type (see Chart I). The stereochemistry of axivalin which has been correlated with **2** and **3** was subsequently[3] established by X-ray crystallography.

Two other constituents of *I. axillaris* were the previously known[4] eudesmanolide microcephalin (**4**) and a saturated sesquiterpene lactone $C_{15}H_{22}O_4$ (mp 173–176 °C) which appeared to be new and was named ivaxillin. As the substance lacked hydroxyl and ketone groups, it was tentatively formulated as a diepoxyguaianolide,[2] but this is clearly incompatible with the empirical formula which, if the presence of two oxirane functions is postulated, imposes an upper limit of one alicyclic ring.

Indeed, ^{13}C NMR and 270-MHz ^1H NMR spectra of the small sample of ivaxillin still extant from the earlier work suggested that the substance was a diepoxygermacranolide of structural type **5**, exclusive of stereochemistry. The presence of partial structure A was deduced by spin de-



A

Chart I

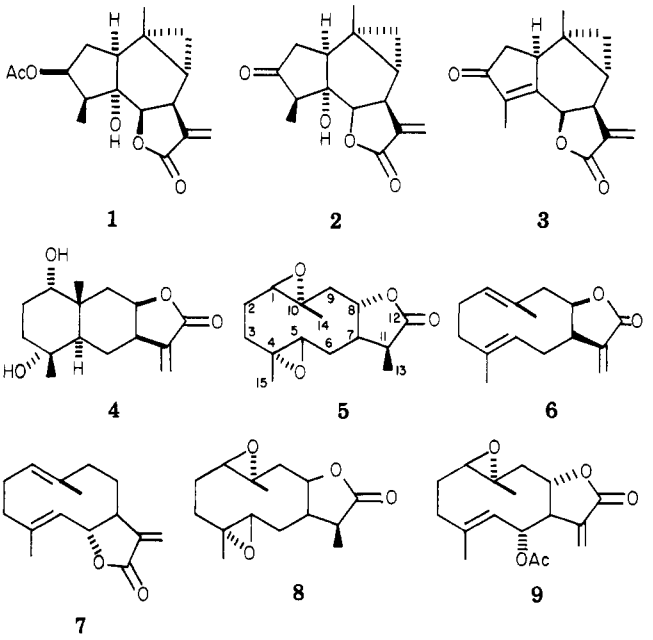


Table I. ^{13}C NMR Spectral Data of Ivaxillin[a]

shift, δ	carbon	shift, δ	carbon
177.91 s	C-12	40.59 d	C-11[b]
82.02 d	C-8[b]	35.73 t	C-3[c]
65.13 d	C-1,5	26.33 t	C-6[c]
64.39 d		24.00 t	C-2[c]
61.02 s	C-4[c]	18.19 q	C-14[c]
57.66 s	C-10[c]	16.33 q	C-15[c]
45.57 d	C-7[b]	11.54 q	C-13[b]
45.11 t	C-9[c]		

[a] Run at 67.9 MHz in $CDCl_3$. [b] Assignment by selective decoupling. [c] Assignment based on predicted shifts and comparison with the ^{13}C NMR spectrum of **9** (Joseph, Nathan-P. *Rev. Latinoam. Quim.* **1978**, *9*, 36).

coupling. In $CDCl_3$, H_A (ddd at 4.30 ppm) was coupled to H_B (br d at 2.78 ppm, $J_{A,B}$ 1.5 Hz) and H_C (partially buried in a four-proton multiplet centered at 1.45 ppm but clearly visible in C_6D_6 as a dd at 1.08 ppm, $J_{A,C}$ = 10 Hz) as well as to H_D (m at 2.45 ppm, $J_{A,D}$ = 10 Hz). H_B and H_C were mutually coupled ($J_{B,C}$ = 14 Hz), the absence of further splitting indicating that the neighboring carbon was quaternary. H_D was also coupled to H_E (quintet at 2.82 ppm, $J_{D,E}$ = 7.5 Hz) which in turn was coupled to a methyl doublet at 1.23 ppm. The appearance of the H_D signal indicated that it adjoined a methylene, at least one of whose protons was part of the four-proton multiplet at 1.45 ppm.

As the ^1H NMR spectrum of ivaxillin also displayed two methyl singlets at 1.39 and 1.27 ppm and two signals at 2.79 (br d, J = 14 Hz) and 2.74 ppm (br d, J = 10 Hz) characteristic of protons on an oxirane ring, gross structure **5** which was consonant with the ^{13}C NMR spectrum (Table I) and biogenetically plausible seemed likely. As to stereochemistry, if ivaxillin were derived by epoxidation of a *trans*-1(10),*trans*-4,5-germacradienolide and hence in the favored crown conformation when in solution,[5,6] the lactone ring had to be trans-fused to account for the observed coupling constants involving H-7 and H-8. Furthermore, the value of $J_{7,11}$ (7.5 Hz) and the large solvent shift observed for the C-11 methyl signal ($\delta_{CDCl_3} - \delta_{C_6D_6}$ = −0.46

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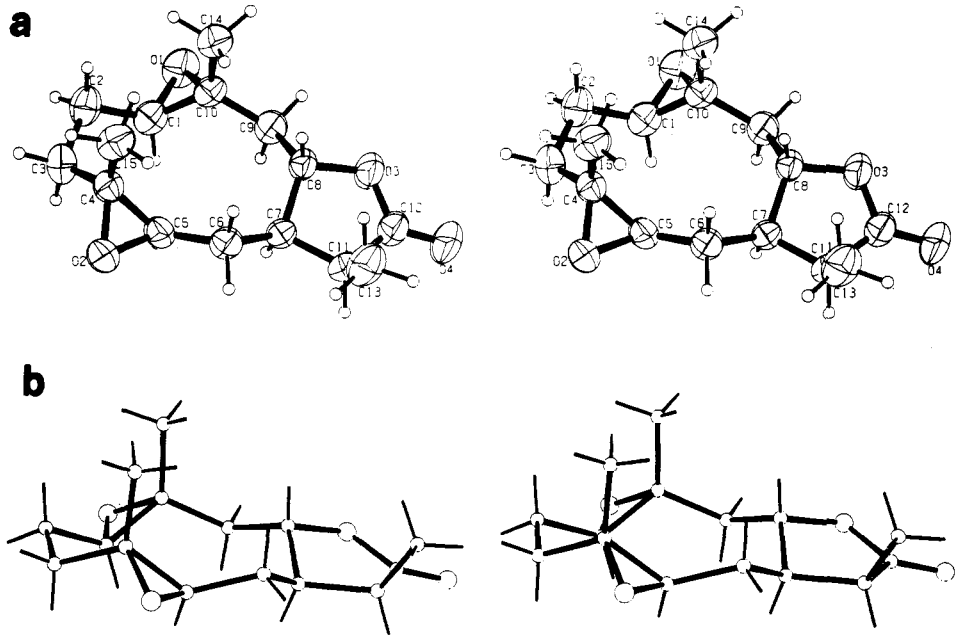

Figure 1. (a) Stereoscopic view of the ivaxillin molecule with ellipsoids of thermal motion. (b) side view of atom framework.

ppm) suggested[7] that the C-11 methyl group was pseudoaxial and hence β for the absolute configuration depicted in **5**.

Two substances of gross structure **5** are described in the literature, but the sparse physical data recorded for them do not allow for a very satisfactory comparison with ivaxillin. One of them, eriolin, a naturally occurring compound of unknown stereochemistry,[8] appears to be different from ivaxillin because of its much higher melting point, 238–240 °C. The second substance, presumably a cis lactone (mp 205–206 °C) of uncertain stereochemistry at C-1, C-4, C-5, C-10, and C-11, was obtained[9] by hydrogenation and epoxidation of inunolide (presumably **6**) and also seems to differ from ivaxillin. To provide a basis for a comparison of our compound with these and other possible stereoisomers and to verify our proposed formula, we undertook an X-ray analysis of ivaxillin.

Crystal data for ivaxillin are listed in the Experimental Section. Figure 1a is a stereoscopic drawing of the molecule which probably also represents the absolute configuration on the basis of the generalization that H-7 in sesquiterpene lactones from higher plants is axial and α.[5] Figure 1b shows a side view of the atom framework. Tables II–V listing final atomic and final anisotropic thermal parameters, bond lengths and bond angles are available as supplementary material; Table VI presents selected torsion angles.

The lactone ring and the epoxide rings of ivaxillin are fused trans to the ten-membered ring, and the C-11 methyl group is pseudoaxial and β. The γ-lactone ring is an envelope with C-7 as the flap. The C-4 and the C-10 methyl group lie β to the plane of the molecule; this is evident from Figure 1b which also shows that ivaxillin can be viewed as being derived by enzymic bis-epoxidation from the "outside" of a trans,trans-C(8)-lactonized germacradienolide precursor in the crown conformation. This is also the predominant stereochemical course taken by chemical epoxidation of costunolide (**7**) and its analogues[10] and may

Table VI. Torsion Angles (deg) in 5 with Standard Deviations in Parentheses

C(10)-C(1)-C(2)-C(3)	-104.6 (4)
C(1)-C(2)-C(3)-C(4)	54.9 (4)
C(2)-C(3)-C(4)-C(5)	-88.7 (4)
C(3)-C(4)-C(5)-C(6)	153.6 (4)
C(4)-C(5)-C(6)-C(7)	-122.5 (4)
C(5)-C(6)-C(7)-C(8)	81.8 (4)
C(7)-C(8)-C(9)-C(10)	86.1 (4)
C(8)-C(9)-C(10)-C(1)	-104.9 (3)
C(9)-C(10)-C(1)-C(2)	154.4 (3)
C(7)-C(8)-O(3)-C(12)	-16.2 (3)
C(8)-O(3)-C(12)-C(11)	-3.4 (4)
O(3)-C(12)-C(11)-C(7)	21.6 (4)
C(12)-C(11)-C(7)-C(8)	-29.7 (3)
C(11)-C(7)-C(8)-O(3)	28.1 (3)

be presumed to be involved as well in the transformation of 11,13-dihydroinunolide to the bis-epoxide of melting point 205–206 °C.[9] Therefore the latter can most probably be formulated as **8**.[11]

The conformation of ivaxillin is very similar to that of an adduct formed between pyrethrosin (**9**) and *o*-chlorobenzonitrile oxide.[12] Its conformation in solution does not appear to depart significantly from that observed in the crystal as judged by the coupling constants involving H-2, H-5, H-7, and H-8.

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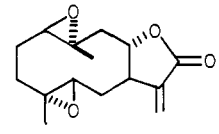

i

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Experimental Section

Slow crystallization from $CHCl_3$–hexane of the small sample of ivaxillin remaining from the earlier work[2] gave single crystals which melted somewhat higher than reported previously: mp 181–182 °C; ^1H NMR spectrum ($CDCl_3$, 270 MHz) 4.30 (ddd, J = 10, 10, 1.5 Hz, H-8), 2.82 (quintet, J = 7.5 Hz, H-11), 2.78 (br d, J = 10 Hz, H-9a), 2.79 (br d, J = 14 Hz) and 2.74 (br d, J = 10 Hz, H-1 and H-5), 2.42 (br q, J = 7 Hz, H-7), 2.25 (dt, J = 14, 3 Hz), 2.14 (dt, J = 12.5, 3 Hz), 2.11 (br d, J = 14.5 Hz), 1.45 (dd, J = 14, 10 Hz, H-9b in 4p multiplet at 1.53–1.34 ppm), 1.39 and 1.27 (C-4 and C-10 Me), 1.23 (d, J = 8 Hz, C-11 Me); ^1H NMR spectrum (C_6D_6, 270 MHz) 3.75 (ddd, J = 11, 9, 1.5 Hz, H-8), 2.60 (br d, J = 14 Hz), 2.28 (br d, J = 10 Hz) and 2.13 (br, J = 10 Hz, H-2, H-5, and H-9a), 2.17 (quintet, J = 7.5 Hz, H-11), 1.75 (m, 2 H), 1.51 (br d, J = 15.5 Hz), 1.46 (br q, J = 7 Hz, H-7), 1.08 (dd, J = 13, 10 Hz, H-9b), 0.95 (m, 3 H), 0.89 and 0.79 (C-4 and C-10 Me), 0.77 (d, J = 5 Hz, C-11 Me).

The crystals of ivaxillin were monoclinic, space group $P2_1$, with a = 9.920 (1) Å, b = 8.743 (2) Å, c = 9.256 (1) Å, β = 117.02 (1)°, and d_{calcd} = 1.237 g cm^{-3} for Z = 2 ($C_{15}H_{22}O_4$, M_r = 266.34). The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans, pulse-height discrimination). The size of the crystal used for data collection was approximately 0.30 × 0.30 × 0.30 mm. A total of 1037 independent reflections were measured for θ < 57° of which 1008 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple solution procedure[13] and was refined by full-matrix least-squares methods. In the final refinement anisotropic thermal parameters were used for the nonhydrogen atoms, and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are R = 0.033 and R = 0.043 for the 1008 observed reflections. The final difference map has no peaks greater than 0.2 e Å^{-3}.

Registry No. 5, 11014-50-9.

Supplementary Material Available: Tables II–V listing final atomic parameters, final anisotropic thermal parameters, bond lengths, and bond angles for compound **5** (4 pages). Ordering information is given on any current masthead page.

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Conformational Analysis of 1,4-Cyclohexadienes: Effect of a Single Bulky Substituent

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Received March 9, 1982

The conformational analysis of 1,4-cyclohexadiene (**1**), its derivatives and related compounds, has been the subject of considerable controversy.[1] Substantial efforts have been made to characterize the large, conformationally dependent, homoallylic coupling constants ($J_{1,4}$ and $J_{1,4'}$)[2] in an effort to determine geometric preferences between boat and planar forms. However, theoretical predictions as to the expected ratio of $J_{1,4}/J_{1,4'}$ for various folding angles have not always been in agreement.[3-6] There now exists sufficient experimental data to deduce preferred geometries, and it appears as though small substituents (e.g., **2**) cause little distortion from planarity. This compares favorably to the parent system itself which has been shown by far infrared,[7] force field calculations,[8] and NMR[5] to vibrate around a planar energy minimum.

Table I. Coupling Constant Data (Hertz) for **3**[a,b]

$J_{1,4}$ (cis)	$J_{1,4'}$ (trans)	$J_{3,4}$	$J_{3,4'}$	$J_{1,2}$	$J_{4,4'}$
7.4	7.7	4.0	2.9	3.4[c]	22.8

[a] Run at 360 MHz in the presence of Eu(fod)$_3$. PANIC spectrum simulation indicates that first-order treatment is warranted. [b] $H_{4'}$ was assigned to the methylene signal that moved downfield fastest upon Eu(fod)$_3$ addition. See ref 13. [c] Measured both in the presence and absence of Eu(fod)$_3$.

It has been assumed that a bulky substituent at C-1 may produce a boat-shaped conformation as the energy minimum. Moreover, early suggestions[9] based on inspection of models as well as a preliminary X-ray crystallographic study with *trans*-1,4-dihydro-4-tritylbiphenyl led to the suggestion that bulky groups would preferentially occupy the pseudoequatorial position. This is in contrast with the related, 1,4-dihydronaphthalene and 9,10-dihydroanthracene systems for which pseudoaxial preference has been demonstrated.[1,10] However, since these latter systems provide considerably greater "peri" interactions than dihydrobenzenes, pseudoequatorial preference had been accepted without challenge. Recently, however, Grossel et al.[11] have reexamined the X-ray crystallographic structure of *trans*-1,4-dihydro-4-tritylbiphenyl, and their results indicate a pseudoaxial preference for the trityl group, which is, of course, assumed to be the more bulky substituent. In addition, force field calculations of 1-*tert*-butyl-1,4-dihydrobenzene indicated a boat conformation (folding angle = 160°) with the *tert*-butyl group in the pseudoaxial position.[8c] In view of these recent results, we felt that it would be important to examine (experimentally) a 1,4-cyclohexadiene with a single large substituent to determine the shape of the ring and any preferred position of the substituent. We selected **3**, since the dimethylcarbinol substituent is large and provides a suitable system for the use of shift reagents.[12,13] NMR analysis (360 MHz) was accomplished with proton–proton

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