*Journal of Natural Products*
*Vol. 51, No. 2, pp. 221-228. Mar-Apr 1988*



# CONFORMATIONAL ANALYSIS OF ACHILLIN AND LEUKODIN

MARIANO MARTÍNEZ V., ALEJANDRA MUÑOZ-ZAMORA,

*Instituto de Química. Universidad Nacional Autónoma de México. Circuito Exterior. Ciudad Universitaria. Coyoacán 04510. México. D.F., México*

and PEDRO JOSEPH-NATHAN*

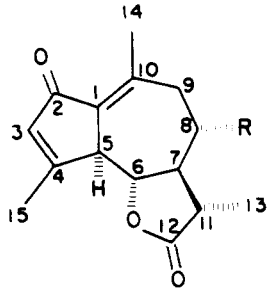
*Departamento de Química. Centro de Investigación y de Estudios Avanzados. Instituto Politécnico Nacional. Apartado 14-740. 07000 México. D.F., México*

ABSTRACT.—The guaianolide leukodin was isolated from *Stevia pilosa*, this being the first time that leukodin has been isolated from a *Stevia* species. The total assignments of $^{1}$H- and $^{13}$C-nmr spectra of leukodin, achillin, matricarin, and desacetylmatricarin were achieved with the aid of single-frequency experiments and heteronuclear (HETCOR) $^{1}$H-$^{13}$C two-dimensional experiments. The results establish the molecular conformations in solution, which for achillin and leukodin were compared with those obtained by single crystal X-ray diffraction.

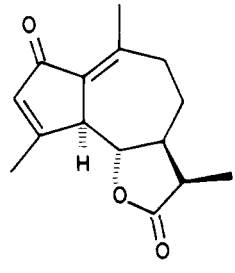
*Stevia* is one of the largest (200 species) and most easily recognized genera in the tribe Eupatorieae (1). However, this morphologically well-delimited genus is surprisingly heterogeneous regarding chemical composition. To our knowledge, until 1986 the phytochemical studies of 17 species showed that labdane diterpenes have been found in 4 species (2–4), clerodanes in 2 (5), sweet glycosides in 4 (6), and sesquiterpenoids, mainly of the longipinane type, in 16 (7–9). However, only seven species contain sesquiterpene lactones: guaianolides in *Stevia boliviensis* (10), *Stevia serrata* (11), *Stevia setifera* (10), *Stevia mercedensis* (9), and *Stevia achalensis* (8,9); a heliangolide in *Stevia monaerdifolia* (12); a germacranolide in *S. serrata* (13), and eudesmanolides, eremophilanolides, and eudesmanolides in *S. achalensis* (9). All these compounds can be classified at the first or second level in their biogenetic complexity (14). Only one species, *Stevia rhombifolia* (15), has been reported to contain a pseudoguaianolide.

We wish to report here the isolation of leukodin [**1**], a known guaianolide-type sesquiterpene lactone, from the aerial parts of *Stevia pilosa* Lag. This is the first time that **1** has been isolated from a *Stevia* species.

A review of the literature showed that leukodin has been isolated from *Achillea eriophora* (16) and *Achillea millefolium* (17), and also from *Artemisia leukodes* (18), *Artemisia tridentata* Nutt (19), *Artemisia tridentata* var. *tridentata* (20), and *Artemisia austriaca* (21,22), both genera belonging to the Anthemideae tribe. Regardless of the extensive distribution of leukodin, there are some confusing or even contradictory interpretations of its $^{1}$H-nmr spectrum (23,24), and, surprisingly, to our knowledge no $^{13}$C-nmr data have been reported. Furthermore, the $^{1}$H-nmr interpretations leave some




**1** R=H
**3** R=OAc
**4** R=OH




**2**

lack of confidence regarding stereochemistry at C-11, although the molecular structure and stereochemistry have been settled by chemical means (24,25). Thus, we report here the total assignments of both the $^1$H- and $^{13}$C-nmr spectra of **1** and of the related compounds achillin [**2**], matricarin [**3**], and desacetylmatricarin [**4**]. Furthermore, we also report single crystal X-ray diffraction studies of **1** and **2**, which allow comparison of the solution conformations deduced from $^1$H-nmr measurements with those in the solid state.

## RESULTS AND DISCUSSION

Leukodin [**1**] was obtained when the hexane extracts of *S. pilosa* were concentrated under reduced pressure, while its C-11 epimer, achillin [**2**], was isolated from *Achillea millifolium* L. (17).

The $^1$H-nmr spectra of **1–4** were assigned, including the spin-spin interactions that were determined by homonuclear double resonance experiments (Table 1). The high values of $J_{5,6}$ and $J_{6,7}$ confirmed the *trans* arrangement of H-5, H-6, and H-7. It has been shown recently (26) that in *trans*-guaianolides H-6 appears at characteristic chemical shifts in the 3.2–3.9 ppm region and that the geminal interaction $J_{9,9'}$ is on the order of 13–14 Hz when measured in $CHCl_3$ solutions. These observations are also in full agreement with those found for **1–4** (Table 1).

TABLE 1. $^1$H-nmr Data[a] of Leukodin [**1**], Achillin [**2**], Matricarin [**3**], and Desacetylmatricarin [**4**].

| Proton | Compound | | | | | |
|---|---|---|---|---|---|---|
| | **1** ($CDCl_3$) | **1** ($C_6D_6$) | **2** ($CDCl_3$) | **2** ($C_6D_6$) | **3** ($CDCl_3$) | **4** ($CDCl_3$) |
| H-3 | 6.187 dq | 6.035 dq | 6.167 dq | 6.038 dq | 6.179 dq | 6.169 dq |
| H-5 | 3.433 d | 2.674 d | 3.417 d | 2.683 d | 3.416 d | 3.387 d |
| H-6 | 3.645 t | 2.688 t | 3.810 t | 3.134 t | 3.728 dd | 3.653 t |
| H-7 | 1.964 dddd | 1.064 m | 2.491 m | 1.398 dddd | 2.347 ddd | 2.135 ddd |
| H-8β | 1.380 dddd | 0.430 dddd | 1.440 dddd | 0.560 dddd | 4.830 t | 3.743 dt |
| H-8α | 2.040 m | 1.582 dddd | 1.861 dddd | 0.827 dddd | | |
| H-9β | 2.370 ddd | 1.064 m | 2.337 m | 1.576 ddd | 2.375 dd | 2.379 dd |
| H-9α | 2.445 ddd | 1.607 ddd | 2.382 m | 1.614 ddd | 2.726 dd | 2.802 dd |
| H-11 | 2.275 dq | 1.482 dq | 2.702 dq | 2.065 dq | 2.458 dq | 2.602 dq |
| H-13 | 1.296 d | 0.892 d | 1.136 d | 0.612 d | 1.340 d | 1.540 d |
| H-14 | 2.456 s | 2.382 s | 2.428 s | 2.379 s | 2.423 s | 2.429 s |
| H-15 | 2.318 d | 1.967 d | 2.278 d | 1.983 d | 2.296 d<br>2.117 s | 2.349 d |

[a]At 300 MHz, chemical shifts as δ values from internal TMS. Coupling constants (Hz): **1** $J_{3,15}=2.0$, $J_{5,6}=10.1$, $J_{6,7}=9.7$, $J_{7,8\beta}=11.9$, $J_{7,11}=12.2$, $J_{8\alpha,8\beta}=13.2$, $J_{8\alpha,9\alpha}=1.3$, $J_{8\beta,9\alpha}=12.9$, $J_{8\beta,9\beta}=1.8$, $J_{9\alpha,9\beta}=13$, $J_{11,13}=6.8$; **2** $J_{3,15}=1.6$, $J_{5,6}=10.2$, $J_{6,7}=10.2$, $J_{7,8\alpha}=2.3$, $J_{7,8\beta}=11.0$, $J_{7,11}=7.2$, $J_{8\alpha,8\beta}=13.7$, $J_{8\alpha,9\alpha}=2.0$, $J_{8\alpha,9\beta}=5.2$, $J_{8\beta,9\alpha}=11.6$, $J_{8\beta,9\beta}=2.5$, $J_{9\alpha,9\beta}=14.5$, $J_{11,13}=7.0$; **3** $J_{3,15}=1.8$, $J_{5,6}=10.8$, $J_{6,7}=11.3$, $J_{7,8\beta}=9.2$, $J_{7,11}=11.2$, $J_{8\beta,9\alpha}=11.1$, $J_{8\beta,9\beta}=3.4$, $J_{9\alpha,9\beta}=13.2$, $J_{11,13}=6.0$; **4** $J_{3,15}=2.5$, $J_{5,6}=10.2$, $J_{6,7}=10.5$, $J_{7,8\beta}=10.3$, $J_{7,11}=11.6$, $J_{8\beta,9\alpha}=11.0$, $J_{8\beta,9\beta}=2.0$, $J_{9\alpha,9\beta}=14.1$, $J_{11,13}=6.8$.

It is accepted that in cycloheptanes the twist-chair conformation is the most stable one (27). However, in the guaianolides **1–4** the seven-membered ring, in addition to having a double bond, is further conformationally restricted by two five-membered rings. Therefore, it can only adapt a chair-like or a boat-like conformation. The hydrogen-hydrogen dihedral angles in the C-5–C-9 framework given in Table 2 were derived from the $^1$H-nmr measurements using a generalized Karplus equation (28) and are consistent only for a chair-like conformation of the seven-membered ring. Furthermore, it is known (29,30) that for allylic protons such as those at C-9, the value of the geminal coupling constant depends on the orientation of the methylene hydrogens with respect to the π electrons of the double bond. The observed value of $J_{9,9'}=13$–14 Hz is also in full agreement with chair-like conformations for **1–4**.

TABLE 2. Hydrogen-Hydrogen Dihedral Angles for Compounds **1–4**.

| Atom | | X-ray values | | Nmr | Measurement[a] | | |
|---|---|---|---|---|---|---|---|
| X | Y | **1** | **2** | **1** | **2** | **3** | **4** |
| 5 | 6 | 162.3(0) | 169.3(0) | 159 | 160 | 171 | 160 |
| 6 | 7 | −156.2(1) | −153.5(0) | −156 | −160 | −157 | −152 |
| 7 | 8α | −61.8(1) | −71.3(1) | na[b] | −67 | — | — |
| 7 | 8β | 178.9(1) | 169.5(1) | 171 | 160 | 150 | 160 |
| 7 | 11 | 152.2(1) | 35.0(0) | 171 | 36 | 158 | 161 |
| 8α | 9α | 76.8(2) | 74.2(1) | 72 | 67 | — | — |
| 8α | 9β | −42.0(2) | −43.9(1) | na | −48 | — | — |
| 8β | 9α | −163.9(0) | −166.6(0) | −164 | −156 | −161 | −160 |
| 8β | 9β | 77.3(2) | 75.3(1) | 68 | 63 | 65 | 77 |

[a]Estimated using a generalized Karplus equation (28); coupling constants as in Table 1.
[b]Not assigned.

The $^{13}$C-nmr spectra of **1–4** (Table 3) show the 15 carbon atoms of the guaianolide skeleton and the acetate signals of **3**. The assignments for **2** were achieved as follows: The ketone and lactone carbonyls were assigned from their chemical shifts. Comparison of a proton-coupled $^{13}$C-nmr spectrum with single frequency irradiation experiments at H-3 provided confirmatory evidence for C-2 and allowed assignment of C-1, C-4, C-5, and C-15 from the modification of the long-range multiplicities. Thus, the assignments for C-7, C-10, and C-14 follow. The assignments for C-6, C-11, and C-13 also became evident, and C-8 and C-9 were assigned taking into account the data of similar compounds (31,32). Confirmative evidence for the protonated carbons of the seven-membered ring and of the heterocycle was obtained from the heteronuclear (HETCOR) $^{1}$H-$^{13}$C two-dimensional chemical shift plot shown in Figure 1. The spectra of **1**, **3**, and **4** were assigned using the data of **2** as the model compound. Their $^{13}$C-nmr chemical shifts are shown in Table 3.

TABLE 3. $^{13}$C-nmr Chemical Shifts[a] of Leukodin [**1**], Achillin [**2**], Matricarin [**3**], and Desacetylmatricarin [**4**].

| Carbon | Compound | | | |
|---|---|---|---|---|
| | **1** | **2** | **3** | **4** |
| 1 | 131.9 s | 131.8 s | 133.3 s | 133.1 s |
| 2 | 195.8 s | 195.7 s | 195.1 s | 195.0 s |
| 3 | 135.5 d | 135.4 d | 135.8 d | 135.7 d |
| 4 | 169.9 s | 170.1 s | 169.6 s | 170.0 s |
| 5 | 52.6 d | 52.9 d | 51.6 d | 51.7 d |
| 6 | 84.2 d | 83.5 d | 81.1 d | 81.1 d |
| 7 | 56.4 d | 51.9 d | 59.1 d | 61.6 d |
| 8 | 26.0 t | 23.6 t | 70.4 d | 69.6 d |
| 9 | 37.6 t | 37.6 t | 44.7 t | 41.4 t |
| 10 | 152.1 s | 152.1 s | 145.0 s | 145.3 s |
| 11 | 41.1 d | 39.3 d | 40.7 d | 41.4 d |
| 12 | 177.5 s | 178.3 s | 176.6 s | 177.5 s |
| 13 | 12.3 q | 9.9 q | 15.0 q | 15.5 q |
| 14 | 21.6 q | 21.5 q | 21.1 q | 21.6 q |
| 15 | 19.8 q | 19.7 q | 19.8 q | 19.8 q |
| 16 | — | — | 169.7 s | — |
| 17 | — | — | 21.3 q | — |

[a]At 75.4 MHz in $CDCl_3$ from internal TMS.

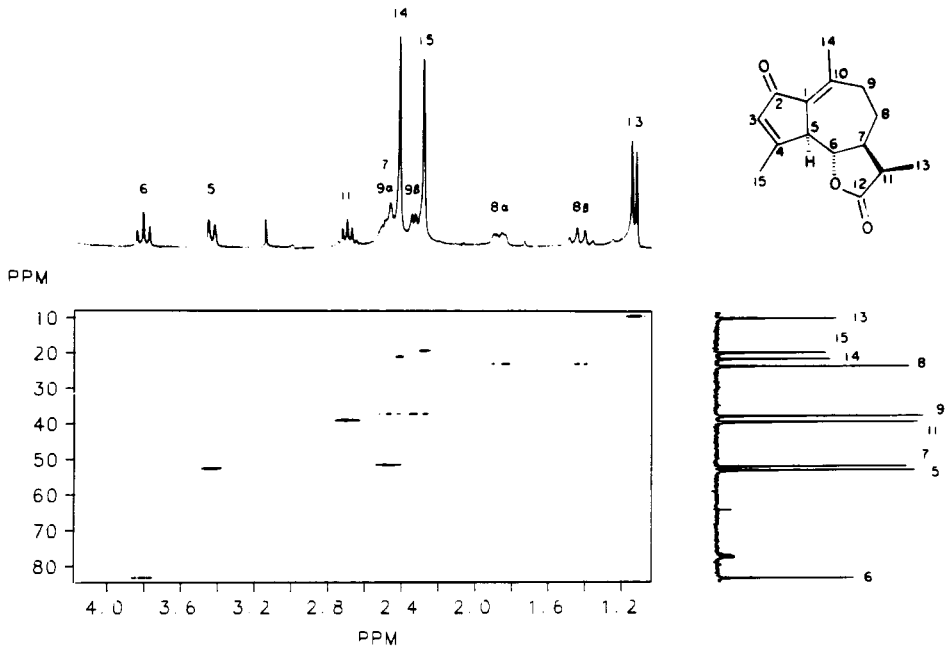



FIGURE 1. HETCOR $^{13}C$-$^{1}H$ contour plot for achillin [**2**].

CRYSTAL STRUCTURE ANALYSIS OF LEUKODIN [**1**].—The molecular structure of **1** is illustrated in Figure 2, and its atomic coordinates are listed in Table 4. The configuration is such that H-5 and H-7 are both below the approximate plane of the seven-membered ring (i.e., they are α), and, hence, the configuration is confirmed as being 5α-H, 6β-H, and 7α-H. The seven-membered ring adopts approximately a chair conformation with the atoms C-5, C-1, C-10, and C-9 approximately coplanar, while the atoms C-6, C-7, and C-8 are all above that plane.

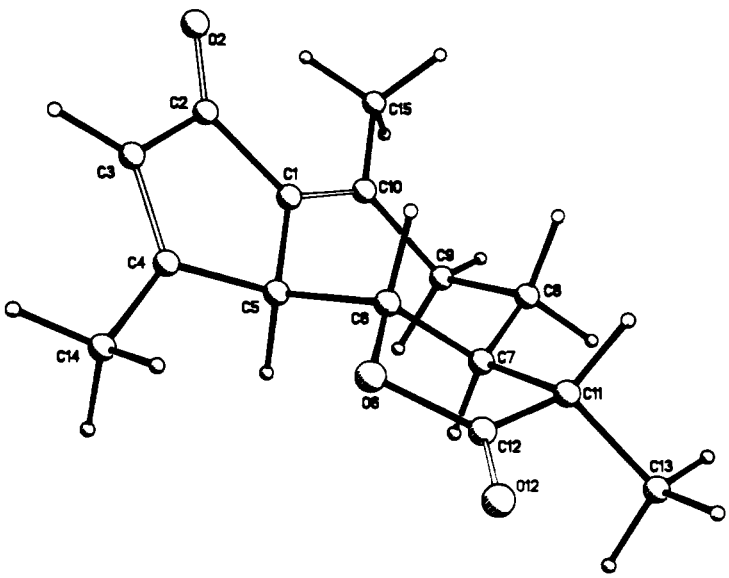



FIGURE 2. The molecular structure of leukodin [**1**].

TABLE 4. Experimentally Refined Fractional Atomic Coordinates ($\times 10^4$) of Leukodin [**1**].

| Atom | *x* | *y* | *z* |
|---|---|---|---|
| C-1 | 5134(7)[a] | 2076(5) | 5017(4) |
| C-2 | 4864(8) | 3042(5) | 4366(4) |
| C-3 | 5012(8) | 2583(5) | 3433(4) |
| C-4 | 5301(8) | 1443(5) | 3443(4) |
| C-5 | 5269(7) | 997(4) | 4440(4) |
| C-6 | 3749(8) | 222(4) | 4673(4) |
| C-7 | 3932(7) | −489(4) | 5529(4) |
| C-8 | 3843(8) | 182(5) | 6440(4) |
| C-9 | 5352(8) | 1040(5) | 6530(4) |
| C-10 | 5116(8) | 2112(5) | 5948(4) |
| C-11 | 2538(8) | −1382(5) | 5362(4) |
| C-12 | 2706(8) | −1583(5) | 4332(4) |
| C-13 | 2685(9) | −2496(6) | 5933(5) |
| C-14 | 5650(9) | 704(5) | 2626(4) |
| C-15 | 4923(8) | 3201(5) | 6519(4) |
| O-2 | 4596(5) | 4059(3) | 4570(3) |
| O-6 | 3477(5) | −640(3) | 3940(3) |
| O-12 | 2279(7) | −2382(4) | 3863(4) |

[a]Estimated standard deviations in the least significant digits are shown in parentheses.

Inspection of the torsion angles shows that the cyclopentenone ring is approximately planar, while the lactone ring, which shows values of 40.8°, 38.4°, 22.7°, 3.0°, and 28.2°, has an envelope conformation (33). Bond distances and bond angles are normal.

CRYSTAL STRUCTURE ANALYSIS OF ACHILLIN [**2**].—The molecular structure of **2** is illustrated in Figure 3, and its atomic coordinates are listed in Table 5. The results of the X-ray analysis of **2** are similar to those for **1** except at C-11, since the methyl

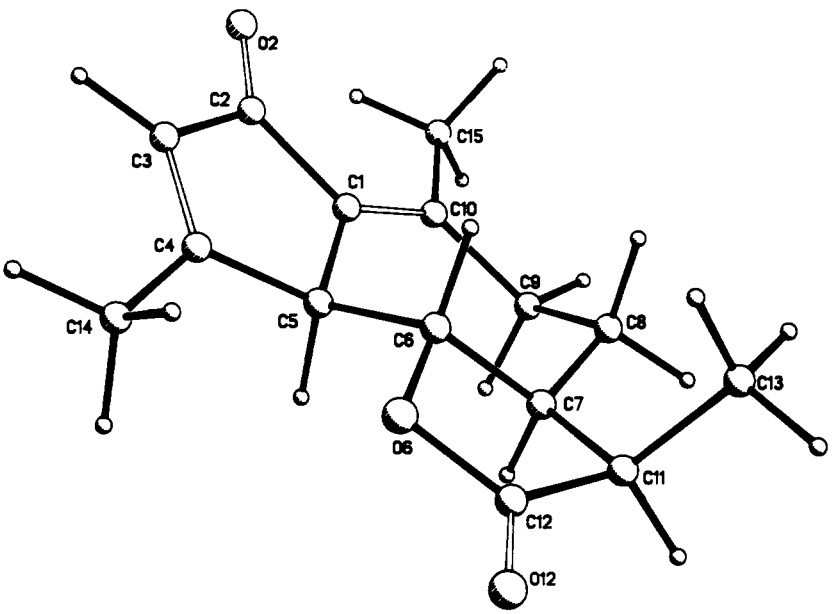



FIGURE 3. The molecular structure of achillin [**2**].

TABLE 5. Experimentally Refined Fractional Atomic Coordinates ($\times 10^4$) of Achillin [**2**].

| Atom | x | y | z |
|---|---|---|---|
| C-1 | 9605(6)[a] | 9516(2) | 8580(1) |
| C-2 | 10794(6) | 8896(2) | 9195(2) |
| C-3 | 9498(6) | 7984(2) | 9220(2) |
| C-4 | 7637(5) | 7978(2) | 8708(2) |
| C-5 | 7471(5) | 8942(2) | 8249(2) |
| C-6 | 7529(5) | 8830(2) | 7329(2) |
| C-7 | 6914(6) | 9766(2) | 6871(2) |
| C-8 | 8851(7) | 10527(2) | 6882(2) |
| C-9 | 9076(8) | 11018(2) | 7711(2) |
| C-10 | 10263(6) | 10423(2) | 8369(2) |
| C-11 | 6058(6) | 9351(2) | 6054(2) |
| C-12 | 4887(6) | 8419(2) | 6319(2) |
| C-13 | 8038(8) | 9137(3) | 5439(2) |
| C-14 | 5853(7) | 7191(2) | 8617(2) |
| C-15 | 12233(7) | 10979(2) | 8812(2) |
| O-2 | 12559(5) | 9085(2) | 9611(1) |
| O-6 | 5722(4) | 8149(1) | 7058(1) |
| O-12 | 3447(5) | 7928(2) | 5977(2) |

[a]Estimated standard deviations in the least significant digits are shown in parentheses.

group in **1** is α and that in **2** is β. The torsion angles of **2** provide conformational conclusions similar to those of **1**.

The hydrogen-hydrogen dihedral angles derived from the X-ray analyses of **1** and **2** are compared (Table 2) with those deduced from $^1$H-nmr measurements. Although results from both methods were obtained independently, their agreement indicates that the conformation of the molecules is similar in the solid state and in solution.

## EXPERIMENTAL

*S. pilosa* was collected on November 5, 1985, along the México-Puebla highway (30 km) (Martínez No. 28; voucher specimen deposited at the Herbario Nacional del Instituto de Biología, Universidad Nacional Autónoma de México). The air-dried plant material (122 g) was extracted with hexane (3 liters). Leukodin [**1**] precipitated when the hexane extract was concentrated under reduced pressure. Recrystallization from $CHCl_3$/hexane afforded 260 mg of **1**, mp 199–200° [lit. (17) 200–201°, $CHCl_3$/hexane]. Its identity was confirmed by direct comparison.

*A. millefolium* was collected on October 12, 1986, along the México-Puebla highway (55 km) (Martínez No. 32; voucher specimen deposited at the Herbario Nacional del Instituto de Biología, Universidad Nacional Autónoma de México). Powdered and dried aerial parts of *A. millefolium* (254 g) were extracted with hexane and worked up as previously described (17), providing 142 mg of achillin [**2**] and 118 mg of leukodin [**1**].

NMR MEASUREMENTS.—Nmr measurements were performed in 5-mm (o.d.) sample tubes on a Varian Associates XL-300GS spectrometer operated with software version 6.1D at ambient probe temperature (22°). The $^{13}$C measurements were Waltz-16 $^1$H decoupled (34). The two-dimensional $^{13}$C-$^1$H-chemical shift correlated spectra were obtained using the standard HETCOR pulse sequence provided by the spectrometer manufacturer, which incorporates quadrature detection in both domains. The fixed delays correspond to a coupling constant $^1J(^{13}C\text{-}^1H)$ of 130 Hz. Other parameters were as follows: spectral widths 5770.3 Hz ($^{13}$C axis), 943.5 ($^1$H axis); data matrix 1024 × 512 data points, recycle delay 1.0 sec; number of transients 32; increments of the delay time 128.

X-RAY DATA.[1]—Data collection for leukodin [**1**] and achillin [**2**] were done in the θ:2θ scanning

[1]Atomic coordinates for these structures have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

mode on a Nicolet R3m four circle diffractometer using $CuK_\alpha$ radiation ($\lambda = 1.54178$ Å). The crystal data for compounds **1** and **2** are summarized in Table 6. The collected reflections were corrected for background, Lorentz, and polarization effects; crystal decay was negligible and no absorption corrections were applied. The structures were solved by direct methods using the software provided by the diffractometer manufacturer and refined by full-matrix least squares based on F, using data for which $I \geq 2.5\ \sigma(I)$. The least squares weighting scheme used is $w = 1/\sigma^2(F_0) = G(F_0)^2$, where $\sigma$ is the standard deviation of observed amplitudes based on counting statistics, and G is a variable adjusted after each cycle to minimize the function $\Sigma\ w(\Delta F)^2$. Final G values are given in Table 6.

TABLE 6. Crystal Data of Leukodin [**1**] and Achillin [**2**].

| Crystal parameters | Compound | |
|---|---|---|
| | **1** | **2** |
| Chemical formula | $C_{15}H_{18}O_3$ | $C_{15}H_{18}O_3$ |
| Molecular weight | 246.309 | 246.309 |
| Crystal system | orthorhombic | orthorhombic |
| Space group | $P2_12_12_1$ | $P2_12_12_1$ |
| Crystal size (mm) | $0.12 \times 0.08 \times 0.04$ | $0.48 \times 0.46 \times 0.34$ |
| Crystal color | white | white |
| Cell constants | | |
| a (Å) | 7.7658(34) | 5.5951(16) |
| b (Å) | 11.7249(80) | 13.7963(44) |
| c (Å) | 14.4317(142) | 16.5314(58) |
| Cell volume, Å$^3$ | 1314.06(166) | 1276.08(70) |
| $\rho$ (calcd) (g/cm$^3$) | 1.25 | 1.23 |
| Z | 4 | 4 |
| F (000) ($e^-$) | 528 | 528 |
| Data collection parameters | | |
| $\mu$ (cm$^{-1}$) | 7.0 | 7.2 |
| Scan width below $K_{\alpha_1}$, above $K_{\alpha_2}$ (deg) | 0.9, 1.1 | 1.0, 1.1 |
| $2\theta$ limits (deg) | 3°–110° | 3°–110° |
| Scan speed (deg min$^{-1}$) | 4.0, 29.3 | 4.0, 29.3 |
| Exposure time (h) | 23.78 | 13.70 |
| Reflections collected | 1004 | 966 |
| Unique reflections | 706 | 925 |
| Structure refinement | | |
| Reflections for final refinement | 700 | 905 |
| Parameters refined | 174 | 174 |
| R(F) (%) | 5.37 | 5.00 |
| $R_w$(F) (%) | 5.09 | 6.07 |
| Goodness of fit for the last cycle | 1.141 | 1.196 |
| Final G | 0.00084 | 0.00495 |

## ACKNOWLEDGMENTS

The authors thank Dr. A. Romo de Vivar, University of Mexico, for samples of matricarin and desacetylmatricarin, Dr. J.L. Villaseñor, University of Mexico, for botanical classification of plant materials, and R.E. del Río and M. Rojas, CINVESTAV-México, for technical assistance. Partial financial support from Proyectos Estratégicos SEP-México and CoNaCyT-México is also acknowledged.

## LITERATURE CITED

1. R.M. King and H. Robinson, *Phytologia*. **46**, 446 (1980).
2. L. Quijano, J.S. Calderón, F. Gómez, J.L. Vega, and T. Ríos, *Phytochemistry*. **21**, 1369 (1982).
3. A. Ortega, R. Martínez, and C.L. García, *Rev. Latinoam. Quím.*. **11**, 45 (1980).
4. M. Salmón, A. Ortega, G. García de la Mora, and E. Angeles, *Phytochemistry*. **22**, 1512 (1983).
5. E. Angeles, K. Fotting, P.A. Grieco, J. Huffman, R. Miranda, and M. Salmón, *Phytochemistry*. **21**, 1804 (1982).

6. N. Kaneda, H. Khoda, K. Yamasaki, O. Tanako, and K. Nishi, *Chem. Pharm. Bull.*, **26**, 2266 (1978).
7. L.U. Román, R.E. del Río, J.D. Hernández, P. Joseph-Nathan, V. Zabel, and W.H. Watson, *Tetrahedron*, **37**, 2769 (1981).
8. J.C. Oberti, V.E. Sosa, W. Herz, J.S. Prasad, and V.L. Goedken, *J. Org. Chem.*, **48**, 4038 (1983).
9. F. Bohlmann, C. Zdero, R.M. King, and H. Robinson, *Ann. Chem.*, 799 (1986).
10. F. Bohlmann, L.M. Dutta, W. Dorner, R.M. King, and H. Robinson, *Phytochemistry*, **18**, 673 (1979).
11. M. Salmón, E. Díaz, and A. Ortega, *J. Org. Chem.*, **38**, 1759 (1973).
12. F. Gómez, L. Quijano, J.S. Calderón, A. Perales, and T. Ríos, *Phytochemistry*, **22**, 197 (1983).
13. M. Salmón, A. Ortega, and E. Díaz, *Rev. Latinoam. Quím.*, **6**, 45 (1975).
14. W. Herz, in: "The Biology and Chemistry of the Compositae." Ed. by V.H. Heywood, J.B. Harborne, and B.L. Turner, Vol. 1, Academic Press, London, 1977, pp. 337–357.
15. T. Ríos, A. Romo de Vivar, and J. Romo, *Tetrahedron*, **23**, 4265 (1967).
16. A. Rustaiyan and L. Nazarian, *Fitoterapia*, **48**, 175 (1977).
17. A. Romo de Vivar and F. Olmos, *Rev. Soc. Quím. Mex.*, **12**, 212 (1968).
18. M. Holub and V. Herout, *Collect. Czech. Chem. Commun.*, **27**, 2980 (1962).
19. T.A. Geismann, T. Stewart, and M.A. Irwin, *Phytochemistry*, **6**, 901 (1967).
20. M.A. Irwin, "Sesquiterpene Lactones of *Artemisa*," Ph.D. dissertation, University of California, Los Angeles; *Chem. Abstr.*, **75**, 137459z (1971).
21. K.S. Rybalko, *Zh. Obshch. Khim.*, **33**, 2734 (1963); *Chem. Abstr.*, **60**, 5561 (1964).
22. K.S. Rybalko and P.S. Massagetov, *Med. Prom. SSSR*, **15**, 25 (1961); *Chem. Abstr.*, **56**, 15607 (1962).
23. S.J. Smolenski, L.C. Bell, and L. Bauer, *Lloydia*, **30**, 144 (1967).
24. J.N. Marx and E.H. White, *Tetrahedron*, **25**, 2117 (1969).
25. E.H. White, S. Eguchi, and J.N. Marx, *Tetrahedron*, **25**, 2099 (1969).
26. U. Rychlenska, D.J. Hodgson, M. Holub, M. Budesinsky, and Z. Smitalova, *Collect. Czech. Chem. Commun.*, **50**, 2607 (1985).
27. R. Bucourt, in: "Topics in Stereochemistry." Ed. by E.L. Eliel and N.L. Allinger, Vol. 8, John Wiley & Sons, New York, 1974, pp. 159–224.
28. C.A.G. Haasnoot, F.A.A.M. de Leeuw, and C. Altona, *Tetrahedron*, **36**, 2783 (1980).
29. M. Barfield and D.M. Grant, *J. Am. Chem. Soc.*, **85**, 1899 (1963).
30. S. Sternhell, *Quart. Rev., Chem. Soc.*, **23**, 236 (1969).
31. P.S. Pregosin, E.W. Randall, and T.B.H. McMurry, *J. Chem. Soc., Perkin Trans. 1*, 299 (1972).
32. A.J.R. da Silva, M. García, P.M. Baker, and J.A. Rabi, *Org. Magn. Reson.*, **16**, 230 (1981).
33. C. Romers, C. Altona, H.R. Buys, and E. Havinga, in: "Topics in Stereochemistry." Ed. by E.L. Eliel and N.L. Allinger, Vol. 4, John Wiley & Sons, New York, 1969, pp. 39–97.
34. A.J. Shaka, J. Keeler, and R. Freeman, *J. Magn. Reson.*, **53**, 313 (1983).

*Received 10 June 1987*