# *X*-Ray Structures of Hymenoxon and Hymenolane: Pseudoguaianolides isolated From *Hymenoxys Odorata* DC. (Bitterweed)

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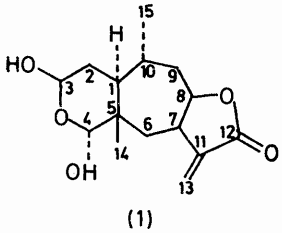
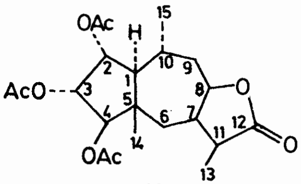
The structures of two sesquiterpene lactones isolated from *Hymenoxys Odorata* DC. have been determined by *X*-ray methods. In hymenoxon (1) the tricyclic skeleton consists of a six- and a five-membered ring fused on opposite sides of a seven-membered ring, which itself has a distorted twisted-boat conformation. The stereochemistry of hydroxy-groups attached to the six-membered ring is established. In hymenolane (2) the tricyclic skeleton consists of two five-membered rings fused on opposite sides of a seven-membered ring, again in a distorted twisted-boat conformation. The stereochemistry of three acetate groups attached to the carbocyclic five-membered ring is established. Both compounds crystallize in space group $P2_12_12_1$, with $Z = 4$ in unit cells of dimensions: (1) $a$ = 7.500(2), $b$ = 8.011(4), $c$ = 24.549(5) Å; (2) $a$ = 8.963(3), $b$ = 9.265(4), $c$ = 26.292(11) Å. Structures were solved from diffractometer data by direct methods and refined by block-diagonal least squares to $R$ 0.035 [(1), 902 reflections] and 0.043 [(2), 1 509 reflections].

IN the chemical study of a Texas poisonous plant, *Hymenoxys odorata* DC. (Compositae),[1] two new pseudoguaianolides were isolated: hymenoxon [2] (1), $C_{15}H_{22}O_5$, and hymenolane (2), $C_{21}H_{30}O_8$, in 0.5 and 0.04% yield of the dried plant, respectively. The isolations of several pseudoguaianolides from *H. odorata* DC. which were collected in Mexico and New Mexico have been reported.[3,4] A general review of pseudoguaianolides in compositae has been published.[5]



(1)



(2)

Hymenoxon (1) was poisonous to sheep (intraperitoneal $LD_{50}$ *ca.* 7 mg kg$^{-1}$) and its structure was suggested, devoid of stereochemistry, on the basis of chemical and spectral evidence.[2] Hymenoxon (1) melted at 135—142 °C even after several recrystallizations from acetone, but further recrystallizations from acetonitrile provided suitable crystals (m.p. 135.5—136.5 °C) for a single-crystal *X*-ray analysis to clarify the stereochemistry.

The $^1$H n.m.r. (100 MHz; three singlets of 3 H each at δ 2.12, 2.06, and 2.02), i.r. (1 750 cm$^{-1}$), and mass spectra [*m*/*e* at 410 ($M^+$)], 350, 308, 292, 290, 280, 266, 248, *etc.*) indicated hymenolane (2) to be a sesquiterpene lactone triacetate. A suitable crystal (m.p. 215.5—216.5 °C) for single-crystal *X*-ray analysis was obtained by recrystallization from ethyl acetate.

## EXPERIMENTAL

(*a*) *Hymenoxon* (1).—*Crystal data.* $C_{15}H_{22}O_5$, $M = 282.3$, m.p. 135.5—136.5 °C. Orthorhombic, $a = 7.500(2)$, $b = 8.011(4)$, $c = 24.549(5)$ Å, $U = 1\,475.0(9)$ Å$^3$, $D_c = 1.27$ g cm$^{-3}$, $Z = 4$, $D_m = 1.24$ g cm$^{-3}$. Mo-$K_\alpha$ radiation, $\lambda = 0.710\,69$ Å, $\mu$(Mo-$K_\alpha$) = 1.02 cm$^{-1}$. Crystal size: 0.23 × 0.40 × 0.52 mm. Space group $P2_12_12_1$.

Unit-cell dimensions were determined from a refinement of carefully measured 2θ angles for 26 independent reflections. The 2θ angles and subsequent intensity data were obtained with a General Electric XRD 7 manual diffractometer equipped with balanced Zr/Y filters. Data were collected by the stationary-crystal–counter-method with a 5.0° take-off angle. Peak intensities were counted for two intervals of 10 s each with a zirconium and then yttrium filter in place between the crystal and the detector. Of 1 523 measurements, 902 were considered observed having $[I_{Zr} - 2\sigma(I)_{Zr}] - [I_Y + 2\sigma(I)_Y] \geqslant 100$ counts, where $I_{Zr}$ and $I_Y$ are the counts for the zirconium and yttrium filters respectively, and $\sigma(I)_{Zr}$ and $\sigma(I)_Y$ are the usual standard errors from counting statistics. A weight $w$ was assigned to each reflection where $w = 1/\sigma^2_{F_0}$ and $\sigma(F_0) = \frac{1}{2}\{(LP^{-1}) \,.\, [I_{Zr} + I_Y + (KI_{Zr})^2]/(I_{Zr} - I_Y)\}^{\frac{1}{2}}$, $LP$ is the Lorentz-polarization factor, and $K$, an empirical instrumental factor was assigned a value of 0.03. The intensities of five strong reflections measured periodically during data collection showed no significant variations. Intensity data were processed by the program INCON.[6]

The structure was solved by use of a recent version of MULTAN.[7-9] Using phases from the set with the largest combined figure of merit, an $E$ map was calculated and all carbon and oxygen atoms located, except the methyl carbon C(15), the positional co-ordinates for which were determined geometrically.[10]

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[1] J. M. Kingsbury, ' Poisonous Plants of the United States and Canada,' Englewood Cliffs, New Jersey, Prentice-Hall, 1964.

[2] H. L. Kim, L. D. Rowe, and B. J. Camp, *Res. Comm. Chem. Pathol. Pharmacol.*, 1975, **11**, 647.

[3] W. Herz, K. Aota, M. Holub, and Z. Samek, *J. Org. Chem.*, 1970, **35**, 2611.

[4] A. Ortega, A. Romo de Vivar, and J. Romo, *Canad. J. Chem.*, 1968, **46**, 1538.

[5] W. Herz, *Nobel*, 1973, **25**, 153.

[6] R. E. Davis, 1965. INCON 2, ' A Fortran IV Program for I to F conversion,' personal communication.

[7] G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1971, **A27**, 368.

[8] J. P. Declerq, G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1973, **A29**, 231.

[9] M. J. H. Koch, *Acta Cryst.*, 1974, **B30**, 67.

[10] P. Roberts and G. Sheldrick, Program XANADU, personal communication.

The structure was refined by block-diagonal least-squares calculations, atomic scattering factors for neutral atoms being taken from ref. 11. Refinement converged to a conventional $R$ of 0.035 and weighted $R'$ of 0.045 $\{R' = [\Sigma w|F_o - |F_c||^2/\Sigma w F_o^2]^{\frac{1}{2}}\}$; the error in an observation of unit weight was 1.88. Values for all 1 523 reflections included gave $R$ 0.082, $R'$ 0.047, and error 1.44. The difference in the structure between the two refinements was insignificant.

Carbon and oxygen atoms were refined with anisotropic temperature factors. Calculated positions for the 22 hydrogen atoms[10] and isotropic temperature factors of 7.0 were introduced during the later stages of refinement. Several cycles of refinement allowed hydrogen atom co-ordinates and temperature factors to vary, along with those for carbon and oxygen. Four hydrogen atoms, two from the methylene group and two from the two hydroxy-groups, did not refine well and were fixed in positions determined from a difference-Fourier map. All hydrogen parameters were held fixed in the final cycles of refinement. A final-difference Fourier map indicated a maximum residual electron density of 0.16 eÅ$^{-3}$. Table 1 contains the structural parameters, with estimated errors in parentheses, for hymenoxon (refinement with only the 902 significant reflections). The maximum shift-to-error ratio on the last cycle of refinement was 0.35 and most were <0.10. Tables of observed and calculated structure factors and anisotropic thermal parameters for both compounds (1) and (2) are listed in Supplementary Publication No. SUP 21738 (21 pp., 1 microfiche).*

TABLE 1

(*a*) Fractional co-ordinates of non-hydrogen atoms for hymenoxon (1), with estimated standard errors in parentheses

| | $x$ | $y$ | $z$ |
|---|---|---|---|
| C(1) | 0.381 0(4) | 0.554 6(4) | 0.608 7(1) |
| C(2) | 0.483 3(5) | 0.718 8(4) | 0.608 4(1) |
| C(3) | 0.514 9(5) | 0.784 7(4) | 0.665 8(1) |
| C(4) | 0.497 6(4) | 0.512 4(4) | 0.702 0(1) |
| C(5) | 0.475 6(4) | 0.427 1(4) | 0.646 5(1) |
| C(6) | 0.371 5(5) | 0.263 5(4) | 0.655 9(1) |
| C(7) | 0.169 3(4) | 0.267 3(4) | 0.645 1(1) |
| C(8) | 0.124 5(5) | 0.276 4(5) | 0.583 4(1) |
| C(9) | 0.278 4(5) | 0.315 3(5) | 0.545 3(1) |
| C(10) | 0.347 1(5) | 0.494 0(5) | 0.549 7(1) |
| C(11) | 0.086 2(5) | 0.108 9(5) | 0.662 6(1) |
| C(12) | 0.024 4(6) | 0.019 1(5) | 0.613 0(1) |
| C(13) | 0.065 2(6) | 0.045 3(6) | 0.711 3(1) |
| C(14) | 0.664 0(5) | 0.382 4(5) | 0.626 2(1) |
| C(15) | 0.221 8(7) | 0.614 6(7) | 0.519 3(1) |
| O(1) | 0.059 0(4) | 0.109 9(4) | 0.569 2(1) |
| O(2) | −0.046 0(4) | −0.118 2(4) | 0.610 3(1) |
| O(3) | 0.329 7(3) | 0.539 5(3) | 0.725 4(1) |
| O(4) | 0.597 0(3) | 0.661 5(3) | 0.699 2(1) |
| O(5) | 0.629 9(3) | 0.922 6(3) | 0.666 6(1) |

(*b*) Hydrogen atom parameters

| Bonded to | $x$ | $y$ | $z$ | $B$/Å$^2$ | C–H/Å |
|---|---|---|---|---|---|
| C(1) | 0.253 | 0.583 | 0.625 | 2.9 | 1.06 |
| C(2) | 0.417 | 0.814 | 0.591 | 3.9 | 1.00 |
| C(2) | 0.598 | 0.698 | 0.593 | 4.1 | 0.95 |
| C(3) | 0.398 | 0.822 | 0.682 | 3.3 | 1.01 |
| C(4) | 0.573 | 0.441 | 0.723 | 3.3 | 0.96 |
| C(6) | 0.379 | 0.235 | 0.692 | 3.2 | 0.93 |
| C(6) | 0.420 | 0.162 | 0.635 | 3.4 | 1.03 |
| C(7) | 0.109 | 0.369 | 0.662 | 3.7 | 1.01 |
| C(8) | 0.027 | 0.350 | 0.575 | 4.4 | 0.96 |
| C(9) | 0.243 | 0.272 | 0.508 | 6.4 | 1.01 |
| C(9) | 0.382 | 0.251 | 0.548 | 3.2 | 0.93 |
| C(10) | 0.465 | 0.502 | 0.532 | 5.1 | 0.99 |
| C(13) | 0.038 | 0.067 | 0.720 | 7.0 | 0.95 |
| C(13) | 0.124 | 0.092 | 0.742 | 7.0 | 0.95 |
| C(14) | 0.661 | 0.342 | 0.590 | 3.9 | 1.00 |
| C(14) | 0.742 | 0.468 | 0.623 | 4.2 | 0.91 |
| C(14) | 0.707 | 0.293 | 0.646 | 6.3 | 0.92 |
| C(15) | 0.118 | 0.639 | 0.540 | 5.4 | 0.95 |
| C(15) | 0.262 | 0.728 | 0.524 | 7.3 | 0.97 |
| C(15) | 0.179 | 0.574 | 0.486 | 8.4 | 0.93 |
| O(3) | 0.330 | 0.535 | 0.758 | 7.0 | 0.79 |
| O(5) | 0.724 | 0.893 | 0.651 | 7.0 | 0.84 |

(*b*) *Hymenolane* (2).—*Crystal data*. $C_{21}H_{30}O_8$, $M$ = 410.4, m.p. = 215.5—216.5 °C. Orthorhombic, $a$ = 8.963(3), $b$ = 9.265(4), $c$ = 26.292(11) Å, $U$ = 2 813.4(1.5) Å$^3$, $D_c$ = 1.25 g cm$^{-3}$, $Z$ = 4, $D_m$ = 1.23 g cm$^{-3}$. Mo-$K_\alpha$ radiation; $\mu$(Mo-$K_\alpha$) = 1.03 cm$^{-1}$. Crystal size: 0.4 × 0.5 × 0.5 mm. Space group $P2_12_12_1$.

The experimental procedure was similar to that described for (1). Of 2 309 intensity measurements, 1 509 were considered observed by the previously described criterion. No significant variation was noted in five reflections monitored during data collection.

The structure was solved as before by use of MULTAN.[7-9] The largest peaks from an $E$ map computed using phases from the set with the highest combined figure of merit could be assembled to give the entire structure (2) with the exception of the C(15) methyl carbon, which was found in a subsequent difference map. The structure was refined by block-diagonal least-squares calculations. Calculated positions[10] and isotropic temperature factors ($B$ 6.0 Å$^2$) were introduced for the 30 hydrogen atoms after the carbon and oxygen atoms had been refined with anisotropic temperature factors. All parameters except the hydrogen atom temperature factors were refined for several cycles. The final cycles of refinement held all hydrogen parameters fixed and varied only those for carbon, oxygen, and the scale factor. $R$ was then 0.043 and $R'$ 0.056. The error in an observation of unit weight was 2.21. When all reflections were used in the refinement, corresponding values were $R$ 0.078, $R'$ 0.057, and the error in unit weight 1.75. Structural differences between the two refinements were again insignificant. The maximum shift-to-error in the last cycle of either refinement was 0.69, but most were <0.10. A final difference map gave a maximum residual electron density of 0.21 eÅ$^{-3}$. Structural parameters, with estimated standard errors in parentheses, are listed in Table 2 (from refinement with observed reflections only).

## RESULTS AND DISCUSSION

Bond lengths and valency angles for both molecules are presented in Tables 3 and 4,[12] and torsion angles in Table 5.[10] An ORTEP[13] plot of each molecule is shown in Figures 1 and 2. The two molecules exhibit

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* For details see Notice to Authors No. 7, in *J.C.S. Perkin II*, 1975, Index issue.

[11] 'International Tables for $X$-Ray Crystallography,' vol IV, Kynoch Press, Birmingham, 1974.

[12] W. R. Busing, K. O. Martin, and H. Levy, 'ORFFE: A Fortran Crystallographic Function and Error Program,' Report ORNL TM-306 Oak Ridge National Laboratory, Oak Ridge, Tennessee, U.S.A.

[13] C. K. Johnson, 1965, ORTEP, Oak Ridge National Laboratory, Report ORNL 3794.

the same relative stereochemistry: the ring junctions at C(7)–C(8) are both *cis*, and at C(1)–C(5) are both *trans*.

TABLE 2

(*a*) Fractional co-ordinates of non-hydrogen atoms for hymenolane, with estimated standard errors in parentheses

| | *x* | *y* | *z* |
|---|---|---|---|
| C(1) | 0.119 6(4) | 0.488 2(4) | 0.091 3(1) |
| C(2) | 0.108 3(4) | 0.616 2(4) | 0.071 1(1) |
| C(3) | 0.094 9(4) | 0.721 9(4) | 0.116 1(1) |
| C(4) | 0.145 1(4) | 0.631 8(4) | 0.161 7(1) |
| C(5) | 0.275 4(4) | 0.543 2(4) | 0.141 1(1) |
| C(6) | 0.318 5(4) | 0.418 6(4) | 0.178 2(1) |
| C(7) | 0.249 8(3) | 0.273 8(4) | 0.166 3(1) |
| C(8) | 0.316 5(4) | 0.200 8(4) | 0.118 3(1) |
| C(9) | 0.398 0(4) | 0.296 6(5) | 0.080 4(1) |
| C(10) | 0.302 7(4) | 0.411 3(4) | 0.053 4(1) |
| C(11) | 0.276 8(4) | 0.156 0(4) | 0.206 8(1) |
| C(12) | 0.414 0(5) | 0.081 3(5) | 0.188 3(1) |
| C(13) | 0.286 7(5) | 0.202 7(5) | 0.262 5(1) |
| C(14) | 0.409 9(4) | 0.640 1(4) | 0.130 4(1) |
| C(15) | 0.210 6(6) | 0.347 2(6) | 0.010 1(1) |
| C(16) | −0.120 3(4) | 0.626 9(5) | 0.023 4(1) |
| C(17) | −0.267 9(5) | 0.561 2(5) | 0.018 1(2) |
| C(18) | −0.083 7(5) | 0.911 0(5) | 0.110 8(1) |
| C(19) | −0.244 6(5) | 0.945 9(6) | 0.119 0(1) |
| C(20) | 0.144 3(4) | 0.688 5(5) | 0.250 8(1) |
| C(21) | 0.197 1(6) | 0.797 9(6) | 0.287 8(1) |
| O(1) | 0.430 2(3) | 0.101 3(3) | 0.137 8(1) |
| O(2) | 0.501 1(3) | 0.008 1(4) | 0.212 2(1) |
| O(3) | −0.037 5(2) | 0.557 9(3) | 0.058 2(1) |
| O(4) | −0.078 7(4) | 0.732 7(4) | 0.001 9(1) |
| O(5) | −0.054 5(3) | 0.773 3(3) | 0.123 8(1) |
| O(6) | 0.006 6(3) | 0.991 5(3) | 0.094 8(1) |
| O(7) | 0.186 4(3) | 0.726 0(3) | 0.203 0(1) |
| O(8) | 0.074 4(3) | 0.582 2(3) | 0.260 5(1) |

(*b*) Hydrogen atom parameters

| Bonded to | *x* | *y* | *z* | C–H/Å |
|---|---|---|---|---|
| C(1) | 0.125 | 0.431 | 0.099 | 0.88 |
| C(2) | 0.158 | 0.663 | 0.041 | 1.00 |
| C(3) | 0.156 | 0.801 | 0.113 | 0.92 |
| C(4) | 0.065 | 0.570 | 0.172 | 0.96 |
| C(6) | 0.429 | 0.414 | 0.178 | 0.99 |
| C(6) | 0.299 | 0.451 | 0.213 | 0.98 |
| C(7) | 0.125 | 0.281 | 0.165 | 1.12 |
| C(8) | 0.233 | 0.147 | 0.102 | 1.00 |
| C(9) | 0.492 | 0.347 | 0.103 | 1.13 |
| C(9) | 0.434 | 0.236 | 0.057 | 0.89 |
| C(10) | 0.367 | 0.471 | 0.041 | 0.86 |
| C(11) | 0.193 | 0.083 | 0.204 | 1.01 |
| C(13) | 0.200 | 0.241 | 0.272 | 0.89 |
| C(13) | 0.356 | 0.252 | 0.268 | 0.78 |
| C(13) | 0.293 | 0.127 | 0.284 | 0.91 |
| C(14) | 0.393 | 0.721 | 0.111 | 0.91 |
| C(14) | 0.500 | 0.592 | 0.119 | 0.97 |
| C(14) | 0.439 | 0.678 | 0.162 | 0.93 |
| C(15) | 0.139 | 0.414 | 0.010 | 1.03 |
| C(15) | 0.159 | 0.264 | 0.021 | 0.94 |
| C(15) | 0.263 | 0.304 | 0.007 | 0.77 |
| C(17) | 0.329 | 0.541 | 0.057 | 1.16 |
| C(17) | 0.269 | 0.479 | 0.020 | 0.76 |
| C(17) | 0.300 | 0.577 | 0.011 | 0.82 |
| C(19) | −0.269 | 0.935 | 0.156 | 1.00 |
| C(19) | −0.291 | 0.890 | 0.101 | 0.81 |
| C(19) | −0.269 | 1.041 | 0.110 | 0.94 |
| C(21) | 0.157 | 0.870 | 0.284 | 0.77 |
| C(21) | 0.286 | 0.828 | 0.276 | 0.91 |
| C(21) | 0.178 | 0.756 | 0.317 | 0.88 |

* All H atoms have an isotropic temperature factor *B* 6.0 (see text).

The relative stereochemistry of the basic three-ring skeleton including the characteristic methyl groups attached to C(5) and C(10), is in agreement with the *X*-ray structures of bromohelenalin [14] and autumnolide.[15]

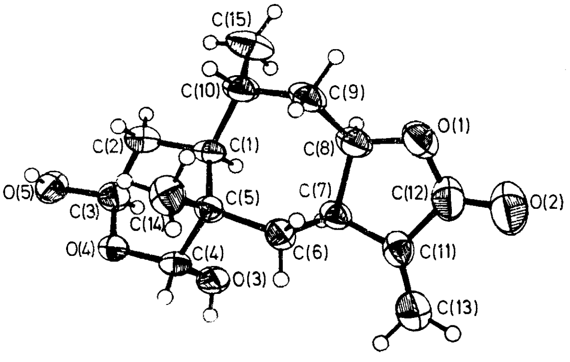

FIGURE 1 Molecular structure of hymenoxon (1)

Other *X*-ray structures of pseudoguaianolides are found to vary in their stereochemistry: *e.g.* bromoisotenulin [16] contains a *trans* C(7)–C(8) ring junction, but both ring junctions [C(1)–C(5) and C(7)–C(8)] are *cis* in helenalin oxide [17] and bromomexicanin-E.[18]

TABLE 3

Bond distances and valency angles for hymenoxon (1)

(*a*) Bonds (Å)

| | | | |
|---|---|---|---|
| C(1)–C(2) | 1.523(5) | C(6)–C(7) | 1.540(5) |
| C(1)–C(5) | 1.553(5) | C(7)–C(8) | 1.553(5) |
| C(1)–C(10) | 1.548(5) | C(7)–C(11) | 1.478(6) |
| C(2)–C(3) | 1.523(5) | C(8)–C(9) | 1.519(6) |
| C(3)–O(4) | 1.424(4) | C(8)–O(1) | 1.464(6) |
| C(3)–O(5) | 1.401(5) | C(9)–C(10) | 1.526(6) |
| C(4)–C(5) | 1.534(5) | C(10)–C(15) | 1.540(7) |
| C(4)–O(3) | 1.401(4) | C(11)–C(12) | 1.488(6) |
| C(4)–O(4) | 1.410(5) | C(11)–C(13) | 1.309(6) |
| C(5)–C(6) | 1.543(5) | C(12)–O(1) | 1.324(6) |
| C(5)–C(14) | 1.540(5) | C(12)–O(2) | 1.222(6) |

(*b*) Angles (°)

| | | | |
|---|---|---|---|
| C(2)–C(1)–C(5) | 109.9(3) | C(6)–C(7)–C(11) | 110.4(3) |
| C(2)–C(1)–C(10) | 110.4(3) | C(8)–C(7)–C(11) | 103.4(3) |
| C(5)–C(1)–C(10) | 115.4(3) | C(7)–C(8)–C(9) | 116.5(3) |
| C(1)–C(2)–C(3) | 112.0(3) | C(7)–C(8)–O(1) | 105.3(3) |
| C(2)–C(3)–O(4) | 111.1(3) | C(9)–C(8)–O(1) | 107.1(3) |
| C(2)–C(3)–O(5) | 112.5(3) | C(8)–C(9)–C(10) | 114.0(3) |
| O(4)–C(3)–O(5) | 105.8(3) | C(1)–C(10)–C(9) | 114.5(3) |
| C(5)–C(4)–O(3) | 113.0(3) | C(1)–C(10)–C(15) | 110.9(4) |
| C(5)–C(4)–O(4) | 109.7(3) | C(9)–C(10)–C(15) | 110.4(4) |
| O(3)–C(4)–O(4) | 111.3(3) | C(7)–C(11)–C(12) | 108.0(3) |
| C(1)–C(5)–C(4) | 106.7(3) | C(7)–C(11)–C(13) | 130.5(4) |
| C(1)–C(5)–C(6) | 114.7(3) | C(12)–C(11)–C(13) | 121.4(4) |
| C(1)–C(5)–C(14) | 112.3(3) | C(11)–C(12)–O(1) | 109.8(4) |
| C(4)–C(5)–C(6) | 107.4(3) | C(11)–C(12)–O(2) | 127.8(4) |
| C(4)–C(5)–C(14) | 107.0(3) | O(1)–C(12)–O(2) | 122.4(4) |
| C(6)–C(5)–C(14) | 108.4(3) | C(8)–O(1)–C(12) | 111.8(3) |
| C(5)–C(6)–C(7) | 117.1(3) | C(3)–O(4)–C(4) | 112.8(3) |
| C(6)–C(7)–C(8) | 112.5(3) | | |

[14] Mazhar-Ul-Haque, and C. N. Caughlan, *J. Chem. Soc.* (*B*), 1969, 956.

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[17] A. T. McPhail, K. D. Onan, K. H. Lee, H. Furukawa, S. H. Kim, and C. Piantodosi, *Tetrahedron Letters*, 1973, 4641.

[18] Mazhar-Ul-Haque, and C. N. Caughlan, *J. Chem. Soc.* (*B*), 1967, 355.

The absolute configurations for (1) and (2) were not determined experimentally, but a choice was made to be in agreement with that determined by *X*-ray methods for bromoisotenulin.[16] Although the latter contains a *trans* C(7)–C(8) ring junction, the remainder of the molecule allows a unique choice to be made for hymenoxon and hymenolane. This choice is also in agreement with the usual representations of the pseudoguaianolides.[5]

TABLE 4

Bond distances and valency angles for hymenolane (2)

(*a*) Bonds (Å)

| | | | |
|---|---|---|---|
| C(1)–C(2) | 1.537(6) | C(9)–C(10) | 1.538(6) |
| C(1)–C(5) | 1.561(5) | C(10)–C(15) | 1.525(6) |
| C(1)–C(10) | 1.536(6) | C(11)–C(12) | 1.492(6) |
| C(2)–C(3) | 1.542(6) | C(11)–C(13) | 1.530(6) |
| C(2)–O(3) | 1.453(5) | C(12)–O(1) | 1.350(5) |
| C(3)–C(4) | 1.528(6) | C(12)–O(2) | 1.209(6) |
| C(3)–O(5) | 1.435(5) | C(16)–O(3) | 1.340(5) |
| C(4)–C(5) | 1.526(5) | C(16)–O(4) | 1.192(6) |
| C(4)–O(7) | 1.441(5) | C(16)–C(17) | 1.463(7) |
| C(5)–C(6) | 1.560(6) | C(18)–C(19) | 1.494(7) |
| C(5)–C(14) | 1.530(6) | C(18)–O(5) | 1.347(6) |
| C(6)–C(7) | 1.510(6) | C(18)–O(6) | 1.178(6) |
| C(7)–C(8) | 1.552(6) | C(20)–C(21) | 1.483(7) |
| C(7)–C(11) | 1.542(6) | C(20)–O(7) | 1.358(5) |
| C(8)–C(9) | 1.521(6) | C(20)–O(8) | 1.195(6) |
| C(8)–O(1) | 1.467(5) | | |

(b) Angles (°)

| | | | |
|---|---|---|---|
| C(2)–C(1)–C(5) | 105.7(3) | C(9)–C(8)–O(1) | 105.2(3) |
| C(2)–C(1)–C(10) | 117.0(3) | C(8)–C(9)–C(10) | 116.0(4) |
| C(5)–C(1)–C(10) | 115.8(3) | C(1)–C(10)–C(9) | 110.7(3) |
| C(1)–C(2)–C(3) | 105.4(3) | C(1)–C(10)–C(15) | 109.8(4) |
| C(1)–C(2)–O(3) | 105.8(3) | C(9)–C(10)–C(15) | 112.1(4) |
| C(3)–C(2)–O(3) | 110.2(3) | C(7)–C(11)–C(12) | 103.5(3) |
| C(2)–C(3)–C(4) | 103.4(3) | C(7)–C(11)–C(13) | 117.9(3) |
| C(2)–C(3)–O(5) | 113.0(3) | C(12)–C(11)–C(13) | 113.2(4) |
| C(4)–C(3)–O(5) | 110.2(3) | C(11)–C(12)–O(1) | 110.2(4) |
| C(3)–C(4)–C(5) | 104.0(3) | C(11)–C(12)–O(2) | 128.6(4) |
| C(3)–C(4)–O(7) | 109.6(3) | O(1)–C(12)–O(2) | 121.2(4) |
| C(5)–C(4)–O(7) | 113.3(3) | C(17)–C(16)–O(3) | 111.6(4) |
| C(1)–C(5)–C(4) | 98.0(3) | C(17)–C(16)–O(4) | 125.4(4) |
| C(1)–C(5)–C(6) | 113.0(3) | O(3)–C(16)–O(4) | 122.9(4) |
| C(1)–C(5)–C(14) | 112.3(3) | C(19)–C(18)–O(5) | 110.9(4) |
| C(4)–C(5)–C(6) | 111.5(3) | C(19)–C(18)–O(6) | 125.3(5) |
| C(4)–C(5)–C(14) | 110.6(3) | O(5)–C(18)–O(6) | 123.8(4) |
| C(6)–C(5)–C(14) | 110.8(3) | C(21)–C(20)–O(7) | 110.2(4) |
| C(5)–C(6)–C(7) | 115.3(3) | C(21)–C(20)–O(8) | 126.2(4) |
| C(6)–C(7)–C(8) | 113.5(3) | O(7)–C(20)–O(8) | 123.6(4) |
| C(6)–C(7)–C(11) | 115.0(3) | C(8)–O(1)–C(12) | 110.8(3) |
| C(8)–C(7)–C(11) | 101.0(3) | C(2)–O(3)–C(16) | 118.7(3) |
| C(7)–C(8)–C(9) | 117.6(4) | C(3)–O(5)–C(18) | 117.4(3) |
| C(7)–C(8)–O(1) | 104.9(3) | C(4)–O(7)–C(20) | 118.1(3) |

A conformational analysis of the seven-membered ring indicates it to take on a distorted twisted-boat arrangement with an approximate $C_2$ axis passing through C(8) and the C(1)–C(5) bond in both molecules. Following the analysis as originally outlined by Hendrickson [19] and subsequently by McPhail and Sim,[20] $\Sigma_2$ is 244 for hymenoxon and 259 for hymenolane; the $\Sigma_s$ parameter is 60 and 81 respectively, where $\Sigma_2 = (|\omega_1 - \omega_5| + |\omega_2 - \omega_5| + |\omega_3 - \omega_4|)$, and $\Sigma_s = (|\omega_1 + \omega_7| + |\omega_2 + \omega_5| + |\omega_3 + \omega_5| + |\omega_4|)$. The $\omega_1 - \omega_7$ terms are the torsional angles for the seven-membered ring and appear in sequential order in Table 4; $\Sigma_2$ and $\Sigma_s$ represent deviations from ideal $C_2$ and $C_s$ symmetry, respectively. For the ideal boat and chair forms, the ring contains a mirror plane with $\Sigma_s$ 0 and $\Sigma_2$ 114 and 205, respectively. For the ideal twisted form, which is also the lower-energy form, the seven-membered ring contains a two-fold axis; $\Sigma_2$ 0 and $\Sigma_s$ 215 and 141 for the twisted boat and chair forms, respectively. Bromohelenalin [14] and autumnolide,[15] the two structures with similar relative stereochemistry to hymenoxon and hynenolane, take on a distorted twisted-chair and distorted twisted-boat arrangement, respectively, for their

TABLE 5

Torsion angles (°) for hymenoxon (1) and hymenolane (2) *

| 6-Membered ring | (1) | (2) |
|---|---|---|
| C(5)–C(1)–C(2)–C(3) | –54.2 | |
| C(1)–C(2)–C(3)–O(4) | 54.8 | |
| C(2)–C(3)–O(4)–C(4) | –58.1 | |
| C(3)–O(4)–C(4)–C(5) | 62.3 | |
| O(4)–C(4)–C(5)–C(1) | –58.9 | |
| C(4)–C(5)–C(1)–C(2) | 53.8 | |
| 7-Membered ring | | |
| C(10)–C(1)–C(5)–C(6) | –61.3 | –72.0 |
| C(1)–C(5)–C(6)–C(7) | –21.4 | –13.7 |
| C(5)–C(6)–C(7)–C(8) | 72.5 | 71.7 |
| C(6)–C(7)–C(8)–C(9) | –12.0 | –19.9 |
| C(7)–C(8)–C(9)–C(10) | –70.8 | –64.5 |
| C(8)–C(9)–C(10)–C(1) | 48.9 | 44.5 |
| C(9)–C(10)–C(1)–C(2) | 42.7 | 48.5 |
| Lactone ring | | |
| O(1)–C(8)–C(7)–C(11) | –13.2 | –27.1 |
| C(8)–C(7)–C(11)–C(12) | 8.7 | 29.7 |
| C(7)–C(11)–C(12)–O(1) | –0.8 | –23.1 |
| C(11)–C(12)–O(1)–C(8) | –8.4 | 5.4 |
| C(12)–O(1)–C(8)–C(7) | 13.7 | 14.5 |
| 5-Membered ring | | |
| C(5)–C(1)–C(2)–C(3) | | –16.5 |
| C(1)–C(2)–C(3)–C(4) | | –13.4 |
| C(2)–C(3)–C(4)–C(5) | | 39.4 |
| C(3)–C(4)–C(5)–C(1) | | –48.1 |
| C(4)–C(5)–C(1)–C(2) | | 39.3 |

* The torsion angle *W*(IJKL) is defined as the angle between the vector JI and the vector KL when viewed along JK. The sign of *W* is positive if JI is to be rotated clockwise into KL and negative if anticlockwise.

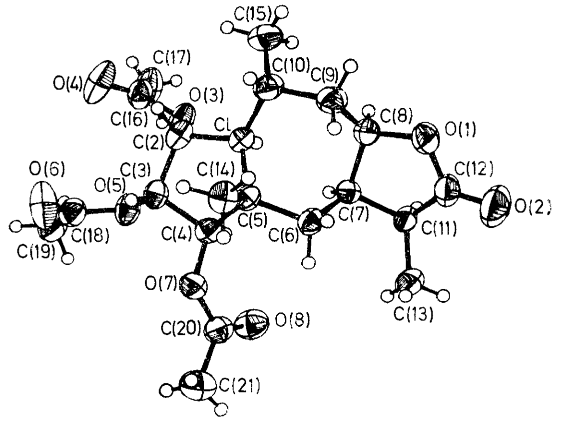

FIGURE 2 Molecular structure of hymenolane (2)

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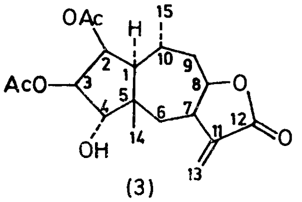
[19] J. B. Hendrickson, *Tetrahedron*, 1963, **19**, 1387.

[20] A. T. McPhail, and G. A. Sim, *Tetrahedron*, 1973, **29**, 1751.

seven-membered rings. Corresponding parameters are: bromohelenalin $\Sigma_2$ 40, $\Sigma_s$ 154; autumnolide $\Sigma_2$ 234, $\Sigma_s$ 50.5. For bromohelenalin the approximate $C_2$ axis passes through C(10) and the C(6)–C(7) bond, and in autumnolide through C(7) and the C(1)–C(10) bond. An analysis of the conformation of the seven-membered ring for several other pseudoguaianolides has been made.[20]

The lactone rings are somewhat puckered. The root-mean-square deviation from the best least-squares plane[10] containing atoms C(7), C(8), C(11), C(12), and O(2) is 0.06 for hymenoxon and 0.14 Å for hymenolane. The presence of a methylene group [C(13)] in hymenoxon results in a more planar lactone ring than for hymenolane where C(13) is a methyl group. The six-membered ring in hymenoxon is close to an ideal chair form (see torsion angles). The other five-membered ring of hymenolane is puckered and the root-mean-square deviation from the best least-squares plane containing atoms C(1) through C(5) is 0.21 Å.

Hymenolane is similar to hymenograndin, $C_{19}H_{26}O_7$, a pseudoguaianolide isolated from *Hymenoxys grandiflora* (T & G).[21] Hymenograndin is a diacetate and has been assigned structure and configuration (3) by means of $^{1}$H n.m.r. and other spectroscopic and chemical evidence. Note that the configuration at C(2)–(4) in (3) is the opposite of that determined for (2).



(3)

No hydrogen bonding is observed for the hymenolane structure. The shortest intermolecular contact is C(19) · · · O(1) 3.29 Å, between molecules related by unit-cell translations along *a* and *b*.

The hymenoxon structure (distances Å, angle °) indicates the following hydrogen-bonding scheme:

| | | | |
|---|---|---|---|
| O(3) · · · O(5) | 2.827(3) | O(5) · · · O(2) | 2.815(5) |
| O(3)–H(21) | 0.79 | O(5)–H(22) | 0.84 |
| O(5) · · · H(21) | 2.10 | O(2) · · · H(22) | 2.01 |
| O(3)–H(21) · · · O(5) | 155 | O(5)–H(22) · · · O(3) | 165 |
| C(4)–O(3)–H(21) | 114 | C(3)–O(5)–H(22) | 106 |

The O(3) · · · O(5) distance can be generated by the symmetry operation, $1 - x$, $y - \frac{1}{2}$, $1\frac{1}{2} - z$, and the O(5) · · · O(2) distance by unit-cell translations along *a* and *b*.

The relative configuration of the hydroxy-groups at positions 3 and 4 in hymenoxon indicates the latter to be in a situation of greater steric hindrance. It is possible that the sterically unhindered hydroxy-group at position 3 may play a significant role in the toxicity of hymenoxon.

After completion of this study, a paper appeared[22] describing the isolation and structure elucidation of hymenovin (m.p. 125—127 °C), as having structure (1); however, stereochemistry was not reported and the sample was said to be a mixture of two epimers.

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[6/088 *Received, January 14th*, 1976]

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[22] G. W. Ivie, D. A. Witzel, W. Herz, R. Kannan, J. O. Norman, D. D. Rushing, J. H. Johnson, L. D. Rowe, and J. A. Veech, *J. Agric. Food Chem.*, 1975, **23**, 841.