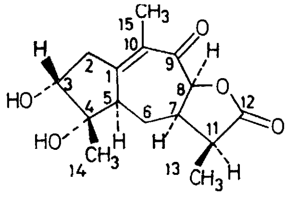
Crystal and Molecular Structure of Carolenalone, a Cycloheptenone Sesquiterpene Lactone from North Carolina *Helenium autumnale* L.

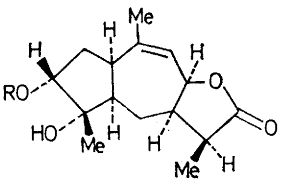
By **Andrew T. McPhail** * and **Kay D. Onan,** Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706, U.S.A.

X-Ray single crystal analysis has established the structure and relative stereochemistry of the title compound (I). Crystals are orthorhombic, space group $P2_12_12_1$, a = 7.31(1), b = 21.20(1), c = 9.21(1) Å, Z = 4. The structure was solved by direct methods and atomic positional and thermal parameters were refined by full-matrix least-squares calculations to R 0.078 over 476 reflections from diffractometer measurements. The cycloheptenone ring adopts a flattened twist-chair conformation in which the C:C·C:O system with a torsion angle of −157° is distinctly non-planar. The cyclopentane and γ-lactone rings are both in envelope conformations; the C(11) methyl group is β-oriented.

CAROLENALONE (I), $C_{15}H_{20}O_5$, a new sesquiterpene lactone was isolated as a minor component of North Carolina *Helenium autumnale* L. from which carolenalin (II) and its angelyl ester, carolenin (III), had been obtained previously.[1] Owing to the paucity of material available this new sesquiterpene lactone could not be fully characterized by chemical and spectral means so a diffraction study was undertaken to define the total constitution and relative stereochemistry, as well as to obtain details of the molecular conformation. A preliminary account has appeared.[2]



(I)



(II) R = H
(III) R = Angelyl

EXPERIMENTAL

Crystal Data.—$C_{15}H_{20}O_5$, M = 280.3. Orthorhombic, a = 7.31(1), b = 21.20(1), c = 9.21(1) Å, U = 1 427 Å^3, D_m (flotation) = 1.29, Z = 4, D_c = 1.305, $F(000)$ = 600. Cu-K_α radiation, λ = 1.542 Å, μ(Cu-K_α) = 8.2 cm^{-1}. Space group $P2_12_12_1$ (D_2^4) from systematic absences: $h00$ when $h \neq 2n$, $0k0$ when $k \neq 2n$, $00l$ when $l \neq 2n$.

Crystallographic Measurements.—Unit-cell dimensions were obtained initially from precession photographs taken with Mo-K_α (λ = 0.7 107 Å) and Weissenberg photographs taken with Cu-K_α radiation. The needle crystal, dimensions *ca.* 0.08 × 0.10 × 1.0 mm., was then mounted on an Enraf-Nonius CAD 3 automated diffractometer (Ni-filtered Cu-K_α radiation, take-off angle 3°) with the crystal c axis (needle axis) parallel to the instrument ϕ axis. More accurate cell dimensions were then obtained by least-squares treatment of the θ, χ, and ϕ angles for 32 high-order reflections. One octant of intensity data up to 2θ 114° was collected by use of the θ—2θ scan technique as described previously.[3] The intensity of a standard reflection checked periodically during data collection to monitor crystal and instrument stability showed no significant variation. Of the 1 149 reflections measured, 476 having $I > 2.0\sigma(I)$, were corrected for Lorentz and polarization effects, but not for absorption, and used in the structure analysis.

Structure Analysis.—The structure was solved by direct phase-determining methods with the MULTAN series of programs[4] and 210 reflections for which $|E| \geqslant 0.90$. The E-map based on that set of phases having the lowest R_K and one of the highest figures of merit revealed all the non-hydrogen atom positions. Structure factors calculated using these co-ordinates and B 3.5 Å^2 gave R 0.230. Full-matrix least-squares adjustment of the atomic parameters, initially varying isotropic and subsequently anisotropic thermal parameters, proceeded smoothly to R 0.110. A difference-Fourier synthesis was then calculated to confirm hydrogen atom positions which had been computed assuming C–H 1.05, O–H 1.0 Å and appropriate geometry. All except the C(15) methyl group hydrogen atoms appeared in regions of significant positive electron density. Inclusion of the contributions for those hydrogen atoms with confirmed positions, assuming B 4.0 Å^2, lowered R to 0.095. Further rounds of least-squares adjustment of positional and anisotropic thermal parameters of the non-hydrogen atoms brought the refinement to convergence at R 0.078.

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TABLE 1

Fractional atomic co-ordinates ($\times 10^4$), and anisotropic thermal parameters,* with estimated standard deviations in parentheses

Atom	x	y	z	10^3b_{11}	10^4b_{22}	10^3b_{33}	10^3b_{12}	10^3b_{13}	10^3b_{23}
C(1)	2 383(21)	3 495(6)	7 048(16)	17(3)	10(3)	3(2)	3(2)	−13(5)	−3(1)
C(2)	3 031(25)	3 186(8)	8 308(15)	22(4)	22(4)	1(2)	6(3)	2(5)	3(2)
C(3)	1 181(23)	3 399(6)	9 557(20)	19(3)	4(3)	10(2)	−7(2)	7(6)	2(2)
C(4)	−48(21)	3 618(7)	8 908(17)	15(3)	15(3)	7(2)	−10(2)	−20(5)	1(2)
C(5)	810(24)	3 932(7)	7 444(15)	24(4)	9(3)	5(1)	1(2)	−9(5)	3(1)
C(6)	−683(23)	4 070(16)	6 326(17)	24(4)	6(3)	3(2)	−1(2)	2(5)	0(1)
C(7)	−32(21)	4 554(6)	5 206(16)	12(3)	7(3)	8(2)	0(2)	3(5)	6(1)
C(8)	1 854(20)	4 428(16)	4 514(17)	8(3)	12(3)	3(2)	2(2)	−3(4)	−1(1)
C(9)	2 379(19)	3 684(6)	4 425(18)	16(3)	3(3)	13(2)	−6(2)	31(5)	−3(2)
C(10)	2 967(20)	3 356(6)	5 715(16)	12(3)	6(3)	5(2)	−5(2)	1(5)	1(1)
C(11)	−1 242(20)	4 702(8)	3 924(19)	7(3)	23(4)	12(2)	10(2)	8(5)	5(2)
C(12)	69(21)	4 861(6)	2 799(14)	12(3)	11(3)	3(2)	6(2)	−5(4)	3(1)
C(13)	−2 546(19)	4 180(10)	3 421(21)	6(6)	48(6)	12(3)	−8(3)	−12(5)	5(2)
C(14)	−1 206(31)	3 029(9)	8 562(18)	38(6)	30(5)	3(2)	−6(3)	−8(6)	3(2)
C(15)	4 415(17)	2 857(6)	5 384(16)	9(3)	8(3)	9(2)	9(2)	21(4)	1(1)
O(16)	2 655(16)	3 957(5)	10 247(13)	27(3)	23(3)	8(2)	4(2)	−4(4)	1(1)
O(17)	−946(14)	4 029(5)	9 709(10)	21(2)	19(3)	2(1)	2(2)	11(3)	−1(1)
O(18)	2 411(15)	3 473(5)	3 161(13)	20(3)	21(3)	8(1)	2(2)	8(4)	0(1)
O(19)	1 798(13)	4 690(4)	3 099(11)	10(2)	9(2)	8(1)	1(1)	8(3)	5(1)
O(20)	−242(16)	5 097(5)	1 653(11)	26(3)	17(3)	6(1)	5(2)	4(4)	5(1)

* In the form $B \sin^2\theta/\lambda^2 = b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl$.

For the structure-factor calculations atomic scattering factors for carbon and oxygen were taken from ref. 5, and for hydrogen from ref. 6. In the least-squares calculations $\Sigma w(|F_o| - |F_c|)^2$ was minimized with weights assigned according to the scheme $\sqrt{w} = 1$ when $|F_o| \leqslant 15.6$ and $\sqrt{w} = 15.6/|F_o|$ when $|F_o| > 15.6$. Analysis of this scheme showed only random variations of $<w\Delta^2>$ when analyzed in ranges of $|F_o|$. Final atomic positional and thermal parameters appear in Tables 1 and 2, interatomic distances and valency angles in Table 3, and displacements of selected atoms from least-squares planes in Table 4. Observed and calculated structure factors, and a table of torsion angles, are listed in Supplementary Publication No. SUP 21529 (7 pp., 1 microfiche).*

TABLE 2

Fractional atomic co-ordinates ($\times 10^3$) for the hydrogen atoms, labelled according to the atom to which they are bonded

Atom	x	y	z
H(2α)	441	327	852
H(2β)	289	267	819
H(3)	161	302	1 030
H(5)	130	437	771
H(6α)	−185	424	686
H(6β)	−102	365	578
H(7)	9	498	581
H(8)	280	464	519
H(11)	−207	510	425
H(13α)	−341	428	256
H(13β)	−346	407	429
H(13γ)	−173	379	317
H(14α)	−247	316	811
H(14β)	−170	279	954
H(14γ)	−47	269	797
H(16)	256	378	1 131
H(17)	−25	442	1 017

RESULTS AND DISCUSSION

The *X*-ray analysis establishes that carolenalone has the constitution and relative stereochemistry represented

TABLE 3

Interatomic distances (Å) and angles (deg.), with estimated standard deviations in parentheses

(*a*) Bond lengths

C(1)–C(2)	1.42(2)	C(7)–C(8)	1.54(2)
C(1)–C(5)	1.52(2)	C(7)–C(11)	1.51(2)
C(1)–C(10)	1.33(2)	C(8)–C(9)	1.63(2)
C(2)–C(3)	1.52(2)	C(8)–O(19)	1.42(2)
C(3)–C(4)	1.56(2)	C(9)–C(10)	1.44(2)
C(3)–O(16)	1.48(2)	C(9)–O(18)	1.25(2)
C(4)–C(5)	1.63(2)	C(10)–C(15)	1.53(2)
C(4)–C(14)	1.54(2)	C(11)–C(12)	1.45(2)
C(4)–O(17)	1.32(2)	C(11)–C(13)	1.53(2)
C(5)–C(6)	1.53(2)	C(12)–O(19)	1.34(2)
C(6)–C(7)	1.53(2)	C(12)–O(20)	1.19(2)

(*b*) Valency angles

C(2)–C(1)–C(5)	109.8(13)	C(6)–C(7)–C(11)	119.0(13)
C(2)–C(1)–C(10)	123.1(14)	C(8)–C(7)–C(11)	103.7(12)
C(5)–C(1)–C(10)	126.7(13)	C(7)–C(8)–C(9)	113.6(11)
C(1)–C(2)–C(3)	106.6(14)	C(7)–C(8)–O(19)	106.6(11)
C(2)–C(3)–C(4)	108.0(14)	C(9)–C(8)–O(19)	109.9(12)
C(2)–C(3)–O(16)	108.5(13)	C(8)–C(9)–C(10)	119.8(13)
C(4)–C(3)–O(16)	106.9(11)	C(8)–C(9)–O(18)	113.5(13)
C(3)–C(4)–C(5)	95.9(12)	C(10)–C(9)–O(18)	126.2(12)
C(3)–C(4)–C(14)	108.5(13)	C(1)–C(10)–C(9)	123.8(13)
C(3)–C(4)–O(17)	114.7(13)	C(1)–C(10)–C(15)	124.0(13)
C(5)–C(4)–C(14)	111.8(12)	C(9)–C(10)–C(15)	112.1(12)
C(5)–C(4)–O(17)	112.7(12)	C(7)–C(11)–C(12)	102.7(12)
C(14)–C(4)–O(17)	112.2(14)	C(7)–C(11)–C(13)	116.8(14)
C(1)–C(5)–C(4)	103.9(11)	C(12)–C(11)–C(13)	111.3(14)
C(1)–C(5)–C(6)	119.6(12)	C(11)–C(12)–O(19)	114.3(12)
C(4)–C(5)–C(6)	111.2(13)	C(11)–C(12)–O(20)	127.2(15)
C(5)–C(6)–C(7)	111.1(13)	O(19)–C(12)–O(20)	118.4(13)
C(6)–C(7)–C(8)	116.2(12)	C(8)–O(19)–C(12)	108.8(10)

TABLE 4

Displacements (Å) of atoms from least-squares planes through various groups of atoms; atoms not included in the derivation of the plane are italicized

Plane (*a*): C(1) 0.01, C(2) −0.01, C(3) 0.01, C(5) −0.01, *C(4) 0.64*

Plane (*b*): C(1) −0.04, C(2) −0.04, C(5) 0.07, C(9) −0.05, C(10) 0.01, C(15) 0.05, *C(8) −0.90, O(18) 0.38*

Plane (*c*): C(8) −0.01, C(11) 0.01, C(12) −0.01, O(19) 0.02, O(20) 0.00, *C(7) −0.31, C(13) 1.33*

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

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by (I) which is drawn in accord with the standard convention[7] [C(7) hydrogen atom α-oriented] and therefore probably also represents the absolute configuration. Carolenalone is novel among sesquiterpenes in that it appears to represent the first recorded instance of a naturally-occurring guaianolide containing a cycloheptenone ring. Figure 1 shows a view of the molecular conformation and atom-numbering scheme.

Owing to the small number of observed intensity data the results of the analysis do not lead to molecular dimensions upon which a meaningful discussion of apparent deviations of chemically equivalent bonds from the respective means may be based. All mean bond lengths are in good agreement with accepted values:[8] $C(sp^3)-C(sp^3)$ 1.54, $C(sp^3)-C(sp^2)$ 1.51, $C(sp^2)=C(sp^2)$ 1.33, $C(sp^2)-C(sp^2)$ 1.44, $C(sp^3)-O$ 1.41, $C(sp^2)-O$ 1.34, C=O 1.22 Å.

Analysis of the endocyclic torsion angles[9] in the cycloheptenone ring [$\omega_{1,5}$ 22, $\omega_{5,6}$ −78, $\omega_{6,7}$ 49, $\omega_{7,8}$ 29, $\omega_{8,9}$ −76, $\omega_{9,10}$ 32, and $\omega_{10,1}$ 11°] in the manner described previously[10] establishes that the ring approximates a twist-chair form [$\Sigma_2/(\Sigma_2 + \Sigma_s) = 0.19$] with the C_2 axis passing through C(7). Comparison of the individual torsion angles with the corresponding values (calculated by us from the co-ordinates of ref. 11) in the appropriate enantiomer of dimethyl 3-bromo-7-oxocyclohept-1-ene-1,2-dicarboxylate (18, −71, 43, 38, −79, 33, and 11°) indicates the close similarity of the ring conformations, the largest difference occurring at the C(7)–C(8) bond of carolenalone around which the torsion angle is slightly smaller (29 *vs.* 38°) probably owing to the presence of the *cis*-fused γ-lactone ring. Note the non-zero double-bond torsion angle of 11° in both compounds, giving an indication of the strain involved in the cycloheptenone moiety. Adoption of the flexible twist-chair form (IV) forces the C:C·C:O system to be distinctly non-planar with a torsion angle of −157°; a planar conjugated system would demand prohibitively short transannular H · · · H separations. Thus the observed conformation represents a compromise which allows for some degree of conjugation in the α,β-unsaturated ketone while minimizing the unfavourable non-bonded H · · · H interactions. Inspection of Dreiding molecular models shows that although the alternative chair conformation would lack these unfavourable H · · · H interactions it would still represent a higher energy form due not only to the torsional strain introduced by the C(7)–C(8) *cis*-fused γ-lactone but also because such a conformation forces the C=O group to lie almost perpendicular to the C=C double-bond thereby minimizing conjugation in the C:C·C:C system (V). In this respect it is of note that in the cycloheptene ring of bromogaillardin where a C(1)=C(10) double bond and a C(7)–C(8) *trans*-fused γ-lactone are present, a chair conformation is preferred.[12]

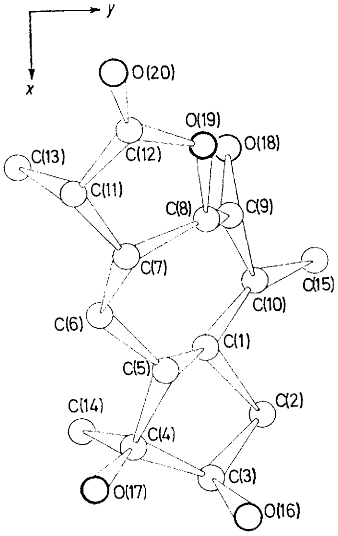
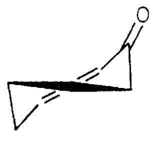
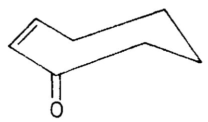


FIGURE 1 Molecular conformation and atom numbering scheme



(IV)



(V)

The mean valency angles in cycloheptane rings of sesquiterpene lactones are characteristically greater than tetrahedral, *e.g.* 114.5 in solstitialin,[13] 115.1 in euparotin bromoacetate,[10] 115.6 in bromohelenalin,[14] 115.9 in bromomexicanin E,[15] and bromogeigerin acetate.[16] Even larger mean values are encountered where steric overcrowding is present, *e.g.* 118° in plenolin *p*-iodobenzoate,[17] and the ring is flattened to minimize non-bonded interactions. In cycloheptene rings a similar variation is found and the magnitude of the mean valency angle is dependent upon several factors included among which are the location of the double bond with respect to ring fusions and the substitution pattern. For example, in bromogaillardin and deacetyldihydrogaillardin *p*-bromobenzoate[12] where the cycloheptene rings adopt distorted chair conformations the mean valency angle is 119.2° in the former [C(1)=C(10) double bond] in contrast to 116.4° in the latter [C(9)=C(10) double bond] and the ring is consequently flatter. The cyclo-

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[16] J. A. Hamilton, A. T. McPhail, and G. A. Sim, *J. Chem. Soc.* (*B*), 1962, 708.

[17] A. T. McPhail and K. D. Onan, *J.C.S. Perkin II*, 1975, 487.

heptenone rings of carolenalone and dimethyl 3-bromo-7-oxocyclohept-1-ene-1,2-dicarboxylate[11] with mean valency angles of 118.9 and 119.4° are likewise flattened. An alternative, and somewhat more striking, measure of the degree of flattening of these seven-membered rings is to be seen in the sums of the moduli of the endocyclic torsion angles, $\Sigma|\omega|$; the smaller is $\Sigma|\omega|$ the flatter is the ring. Thus $\Sigma|\omega|$ for the relatively less-puckered rings of carolenalone (297°) and dimethyl 3-bromo-7-oxocyclohept-1-ene-1,2-dicarboxylate[11] (293°) are significantly less than the corresponding values in the cyclo-heptane and -heptene rings of the sesquiterpene lactones already cited: solstitialin 454, euparotin bromoacetate 432, bromohelenalin 420, bromomexicanin E 402, bromogeigerin acetate 426, plenolin *p*-iodobenzoate 401, bromogaillardin 348, and deacetyldihydrogaillardin *p*-bromobenzoate 421°.

The cyclopentane ring (mean valency angle 105°) is puckered into an envelope conformation with C(4) displaced 0.64 Å from the least-squares plane through the other ring atoms (Table 4). Preference for this particular envelope form appears not to be dependent on the cycloheptenone ring conformation but is rather a consequence of the cycloheptenone ring fusion across the C(1)–C(5) bond and the presence of an sp^2 hybridized carbon atom at position (1). In support of this conclusion is the observation that a like cyclopentane conformation is found in bromogaillardin[12] where an identical ring fusion exists, but the cycloheptene ring adopts a chair conformation, in contrast to the twist-chair form in carolenalone.

In the γ-lactone ring the mean endocyclic valency angle is 107°, and the ring adopts the customary envelope conformation. However, it is less puckered than the saturated γ-lactone rings in other sesquiterpenes, C(7) being displaced by only 0.31 Å from the mean plane through C(8), C(11), C(12), O(19), and O(20). This contrasts with the more common form in which the mean valency angle is smaller and correspondingly the magnitude of the displacement of the out-of-plane atom is significantly greater: 105° and 0.54 Å in plenolin *p*-iodobenzoate,[17] 106° and 0.60 Å in deacetyldihydrogaillardin *p*-bromobenzoate,[12] and 106° and 0.63 Å in bromogeigerin acetate.[16]

A view of the packing of molecules in the crystal as seen in projection along the *a* axis is shown in Figure 2. The two shortest intermolecular separations [O(16) ··· O(18) 2.88, O(17) ··· O(20) 2.93 Å] are between hydroxy-groups in the reference molecule and carbonyl groups of the molecule (at $x, y, 1 + z$) related by a unit cell translation along the *c*-axis, and are typical of O–H ··· O hydrogen bonds. The preferential growth of the crystals as fine needles elongated along the crystal *c* axis is clearly a consequence of the association of molecules *via* hydrogen bonds in this direction. In addition to its involvement in the intermolecular O–H ··· O(carbonyl) hydrogen bond, the hydroxy-hydrogen atom H(16) is located *ca.* 2.34 Å from oxygen atom O(17) in the same molecule and the geometry is compatible with an intramolecular O–H ··· O(hydroxy) hydrogen bond. Thus the hydroxy-hydrogen atom H(16) appears to be involved in a bifurcated hydrogen bond involving intra- and inter-molecular acceptor groups.

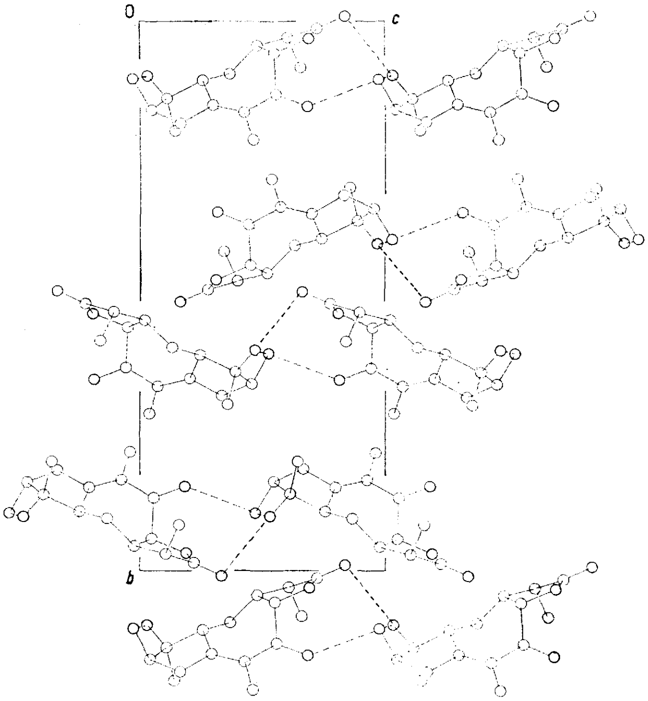

FIGURE 2 The crystal structure, viewed in projection along the *a*-axis; O–H ··· O hydrogen bonds denoted by dashed lines

We thank the U. S. National Science Foundation for funds towards the purchase of the diffractometer and the American Enka Company for a Graduate Fellowship (to K. D. O.). We also thank Professors K. H. Lee and H. Furukawa for supplies of the crystals. Calculations were performed on an IBM 370/165 computer located at the Triangle Universities Computation Centre, Research Triangle Park, North Carolina.

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