Structure of Icetexone,† a Diterpene Quinone From *Salvia ballotaeflorae*

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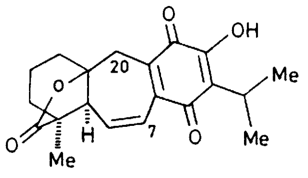
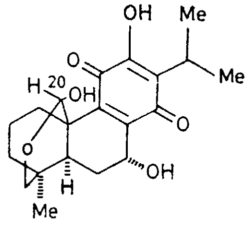
The title compound, a diterpenoid quinone isolated from *Salvia ballotaeflorae* Benth, crystallizes in space group $P2_12_12_1$ with cell dimensions $a = 20.991(7)$, $b = 10.359(7)$ and $c = 7.738(4)$ Å, with $Z = 4$. The structure was determined from diffractometer data by direct methods, and the model refined by least-squares techniques to R 0.037 for 1 331 observed reflections. The molecule contains a cyclohexane ring, a cycloheptadiene ring, a quinone moiety, and a γ-lactone. It is the first natural product of this structural type.

SALVIA species are used in many parts of the world in the treatment of disease,[1] and their effectiveness has been attributed to the presence of biologically active quinones. We have isolated several unique quinones from Salvia species and report the structure of one of them.

Icetexone (I) is an orange-red crystalline diterpene quinone isolated from the aereal parts of *Salvia ballotaeflora* Benth (Labiatae). Mass spectrum and chemical analysis established the formula as $C_{20}H_{22}O_5$. The structure of conacytone (II), a yellow crystalline quinone isolated from the same species, was determined earlier;[2] however, the structure of icetexone could not be established by analogy or by spectroscopic or chemical techniques. Although the biogenetic relationship of the two quinones can be visualized, the structures differ significantly. Conacytone contains two cyclohexane rings, a benzoquinone moiety, and a bridging six-membered hemiacetal function. Icetexone contains six- and seven-membered rings, in addition to the benzoquinone moiety, and a bridging γ-lactone function. Icetexone is the first natural product of this structural type.



(I)



(II)

EXPERIMENTAL

A crystal of dimensions 0.5 × 0.4 × 0.7 mm was mounted on a Syntex $P2_1$ diffractometer. The unit cell was found to be orthorhombic, and room-temperature cell dimensions were determined from a least-squares fit of 15 reflections.

Crystal Data.—$C_{20}H_{22}O_5$, $M = 342.39$, $a = 20.991(7)$, $b = 10.359(7)$, and $c = 7.738(4)$ Å, $U = 1\,683$ Å^3, $D_c = 1.351$ g cm^{-3}, $Z = 4$, $F(000) = 728$. Mo-K_α radiation, $\lambda = 0.710\,7$ Å; $\mu(\text{Mo-}K_\alpha) = 8.0$ cm^{-1}. Space group $P2_12_12_1$ (D_2^4, No. 19).

Intensity data were collected by the ω-scan technique with a scan range of 1.0° and a scan rate, S, varying from 2.0° to 29° min^{-1}. Backgrounds were counted for the same time as that required by the scan. Mo-K_α radiation and a graphite monochromator were used. Of 1 729 independent reflections measured, 1 331 had intensities $>3\sigma(I)$. The net intensity, I, and its estimated standard deviation, $\sigma(I)$, were calculated from: $I = S(P - B_1 - B_2)$; $\sigma^2(I) = S^2(P + B_1 + B_2)^2$. Lorentz and polarization factors were applied, but no absorption corrections were made. Structure-factor magnitudes, $|F_o|$, and normalized structure factor magnitudes, $|E_h|$, were computed. The scattering factors of ref. 3 were used for carbon and oxygen, those of ref. 4 for hydrogen.

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† Systematic name ($1S^*,4aS^*,11aS^*$)-2,3,4,4a,5,6,9,11a-octahydro-4a,7-dihydroxy-8-isopropyl-1-methyl-6,9-dioxo-1*H*-dibenzo[*a,d*]cycloheptene-1-carboxylic acid γ-lactone.

[1] 'Herbal Pharmacology in The People's Republic of China,' Committee on Scholarly Communication with People's Republic of China, National Academy of Sciences, Washington, D.C., 1975.

[2] Z. Taira and W. H. Watson, *Acta Cryst.*, 1976, **B32**, 2149.

[3] D. T. Cromer and J. T. Waber, *Acta Cryst.*, 1965, **18**, 104.

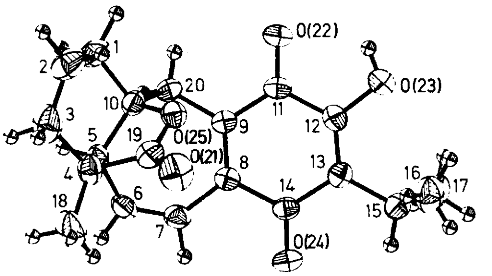
[4] R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.

Structure Determination and Refinement.—The MULTAN program package [5] was used to calculate phases for the 326 $|E|$ values >1.3. Three origin-defining reflections, four reflections with phases determined by Σ_1 relationships, and three other reflections were used in the starting set. From the 32 phase sets generated by MULTAN, the set with the largest absolute figure-of-merit generated an E map showing all 25 carbon and oxygen atoms. Five cycles of block-diagonal least-squares refinement with all atoms assigned carbon scattering factors reduced R to 0.153. Five additional cycles of isotropic refinement with oxygen scattering factors included reduced R to 0.099, and anisotropic refinement further reduced R to 0.074. All 22 hydrogen atoms were located in difference-Fourier maps through use of a peak search program. Five cycles of block-diagonal refinement reduced R to 0.037. The contributions of the hydrogen atoms to the structure factors were included but their co-ordinates were not refined. The function minimized in the refinement was $\Sigma w(\Sigma\Delta F_{\text{meas}})^2$ where $w = 1$.

All parameter shifts during the final cycle were $<0.1\sigma$. Atomic parameters, with estimated standard deviations, are given in Table 1. Observed and calculated structure factors and thermal parameters are listed in Supplementary Publication No. SUP 21806 (9 pp., 1 microfiche).*

DISCUSSION

The Figure shows the molecular structure of icetexone and gives the atom numbering system used. Table 2 lists bond distances and bond angles, while Table 3 gives torsion angles.



Molecular structure of icetexone and the atom numbering system used in the analysis

Icetexone (I) is a diterpene quinone closely related to conacytone, an abietane-type diterpene.[6] Schematically, interconversion of the structures requires insertion of the C(20) methyl carbon of conacytone into the six-membered ring B, loss of the C(7) hydroxy-group to produce a cycloheptadiene system, and replacement of the six-membered hemiacetal by a five-membered γ-lactone. The absolute configuration is known because of its relationship to the abietane-type diterpenes.[7]

The six-membered ring A is in the chair conformation, with distortion arising from fusion with the five- and seven-membered rings. The five-membered ring pulls the diaxial substituents together causing the two enclosed torsion angles to expand from the expected values of 56° to 70.6° and −73.8°. This is consistent with observations in other systems.[8] The connection of the diaxial substituents leads to angles in ring A of icetexone differing by $>3\sigma$ from those in conacytone. In particular, angle C(4)–C(5)–C(10) has contracted from 108.1(4) to 98.9(3)° and C(5)–C(10)–C(1) has expanded from 105.6(4) to 110.5(3)°. The five-membered γ-lactone ring is in an envelope conformation with C(5) representing the flap. The conjugated double bonds in the seven-membered ring B are not coplanar as indicated by the torsion angle C(6)–C(7)–C(8)–C(9) (−24.7°). The C(7)–C(8) bond is shortened slightly.

TABLE 1

Atomic ($\times$ 10^4) parameters

Atom	x/a	y/b	z/c
C(1)	4 668(2)	7 663(4)	3 313(6)
C(2)	5 379(2)	7 623(5)	3 719(7)
C(3)	5 524(2)	7 468(5)	5 606(7)
C(4)	5 087(2)	6 474(4)	6 526(6)
C(5)	4 391(2)	6 923(3)	6 313(5)
C(6)	3 944(2)	6 260(4)	7 502(5)
C(7)	3 524(2)	5 308(4)	7 287(5)
C(8)	3 328(2)	4 654(4)	5 714(5)
C(9)	3 366(2)	5 178(3)	4 131(4)
C(10)	4 310(2)	6 658(3)	4 376(5)
C(11)	3 167(2)	4 416(4)	2 631(5)
C(12)	2 947(2)	3 065(4)	2 881(5)
C(13)	2 890(2)	2 524(4)	4 448(5)
C(14)	3 039(2)	3 331(4)	5 960(5)
C(15)	2 672(2)	1 158(4)	4 735(5)
C(16)	3 125(2)	0 201(4)	3 927(7)
C(17)	1 993(2)	0 944(4)	4 132(7)
C(18)	5 315(2)	6 225(5)	8 348(7)
C(19)	5 078(2)	5 266(4)	5 429(5)
C(20)	3 619(2)	6 492(3)	3 796(5)
O(21)	5 386(1)	4 306(3)	5 549(5)
O(22)	3 183(1)	4 838(3)	1 161(3)
O(23)	2 811(1)	2 437(3)	1 399(3)
O(24)	2 940(1)	2 948(3)	7 424(3)
O(25)	4 637(1)	5 144(2)	4 149(3)
H(1a) *	447	859	361
H(1b)	455	757	198
H(2a)	556	832	306
H(2b)	553	658	303
H(3a)	549	820	639
H(3b)	595	724	599
H(5)	436	780	641
H(6)	399	647	860
H(7)	330	500	837
H(15)	264	102	590
H(16a)	305	−046	463
H(16b)	309	007	272
H(16c)	358	035	409
H(17a)	176	152	475
H(17b)	194	109	302
H(17c)	184	017	440
H(18a)	571	587	847
H(18b)	502	573	893
H(18c)	542	693	895
H(20a)	342	720	424
H(20b)	359	670	267
H(23)	289	296	058

* B 3.0 Å^2.

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

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

[6] J. R. Hansen, 'Chemistry of Terpenes and Terpenoids,' ed. A. A. Newman, Academic Press, New York, 1972, p. 8.

[7] J. R. Hanson, in ref. 6, pp. 170—182.

[8] R. Bucourt, *Topics in Stereochem.*, 1974, **8**, 159.

All internal and external angles associated with the quinone moieties of icetexone and conacytone agree within 3σ; however, internal torsion angles differ by as much as 13°. In both compounds O(22) and O(23) are pulled together, owing to interaction with H(23). This is reflected in the angles about C(11)–O(22) and C(12)–O(23). The methyl groups of the isopropyl moiety attached to C(13) are symmetrically disposed above and below the quinone ring. This is reflected in the torsion angles C(12)–C(13)–C(15)–C(17) −63.7 and C(12)–C(13)–C(15)–C(16) 62.4°. A least-squares plane fitted through the six carbon atoms of the quinone ring indicate deviations of up to 0.05 Å. A least-squares plane through the quinone ring and all attached atoms show the two oxygen atoms are bent above the plane while the other four substituents lie below the plane.

TABLE 2

Bond distances (Å) and bond angles (°)

(*a*) Distances			
C(1)–C(2)	1.526(6)	C(7)–C(8)	1.453(5)
C(2)–C(3)	1.499(8)	C(8)–C(9)	1.342(5)
C(3)–C(4)	1.552(6)	C(9)–C(20)	1.484(5)
C(4)–C(5)	1.542(5)	C(20)–C(10)	1.528(5)
C(5)–C(10)	1.533(5)	C(9)–C(11)	1.464(5)
C(10)–C(1)	1.525(5)	C(11)–C(12)	1.486(5)
C(4)–C(18)	1.511(7)	C(12)–C(13)	1.342(5)
C(4)–C(19)	1.512(6)	C(13)–C(14)	1.472(5)
C(19)–O(21)	1.190(5)	C(14)–C(8)	1.510(5)
C(14)–O(24)	1.218(5)	C(11)–O(22)	1.219(4)
C(19)–O(25)	1.365(5)	C(12)–O(23)	1.349(4)
O(25)–C(10)	1.471(4)	C(13)–C(15)	1.503(5)
C(5)–C(6)	1.483(5)	C(15)–C(16)	1.509(6)
C(6)–C(7)	1.333(5)	C(15)–C(17)	1.518(6)
(*b*) Angles			
C(1)–C(2)–C(3)	113.6(4)	C(10)–C(5)–C(6)	117.0(3)
C(2)–C(3)–C(4)	113.5(4)	C(9)–C(8)–C(14)	120.4(3)
C(3)–C(4)–C(5)	108.1(3)	C(8)–C(14)–C(13)	120.0(3)
C(4)–C(5)–C(10)	98.9(3)	C(14)–C(13)–C(12)	117.5(3)
C(5)–C(10)–C(1)	110.5(3)	C(13)–C(12)–C(11)	122.6(3)
C(10)–C(1)–C(2)	110.7(3)	C(12)–C(11)–C(9)	119.6(3)
C(3)–C(4)–C(18)	110.8(4)	C(11)–C(9)–C(8)	119.2(3)
C(5)–C(4)–C(18)	116.8(4)	C(9)–C(11)–O(22)	122.6(3)
C(18)–C(4)–C(19)	112.7(4)	C(12)–C(11)–O(22)	117.8(3)
C(3)–C(4)–C(19)	107.4(4)	C(11)–C(12)–O(23)	114.2(3)
C(5)–C(4)–C(19)	100.3(3)	C(13)–C(12)–O(23)	123.2(3)
C(4)–C(19)–O(25)	108.8(3)	C(12)–C(13)–C(15)	123.6(4)
C(4)–C(19)–O(21)	129.9(4)	C(13)–C(15)–C(16)	111.5(3)
O(21)–C(19)–O(25)	121.3(4)	C(13)–C(15)–C(17)	112.2(3)
C(19)–O(25)–C(10)	109.2(3)	C(16)–C(15)–C(17)	111.6(4)
C(1)–C(10)–O(25)	107.7(3)	C(14)–C(13)–C(15)	118.8(3)
O(20)–C(10)–O(25)	108.0(2)	C(13)–C(14)–O(24)	121.2(4)
C(5)–C(6)–C(7)	133.1(4)	C(8)–C(14)–O(24)	118.8(3)
C(6)–C(7)–C(8)	129.6(4)	C(7)–C(8)–C(14)	115.5(3)
C(7)–C(8)–C(9)	124.0(3)	C(11)–C(9)–C(20)	117.3(3)
C(8)–C(9)–C(20)	123.4(3)	C(1)–C(10)–C(20)	112.7(3)
C(9)–C(20)–C(10)	113.1(3)	C(4)–C(5)–C(6)	113.1(3)
C(20)–C(10)–C(5)	114.4(3)		

TABLE 3

Torsion angles (°)

(*a*) Internal			
Ring A			
C(1)–C(2)	−41.7	C(4)–C(5)	70.6
C(2)–C(3)	41.9	C(5)–C(10)	−73.8
C(3)–C(4)	−58.8	C(10)–C(1)	60.7
Ring A′			
C(5)–C(10)	40.0	C(19)–C(4)	29.3
C(10)–O(25)	−24.6	C(4)–C(5)	−41.7
O(25)–C(19)	−3.2		
Ring B			
C(5)–C(6)	11.3	C(9)–C(20)	60.1
C(6)–C(7)	−5.4	C(20)–C(10)	−81.2
C(7)–C(8)	−24.7	C(10)–C(5)	36.0
C(8)–C(9)	0.6		
Ring C			
C(8)–C(9)	−4.5	C(12)–C(13)	1.5
C(9)–C(11)	−1.9	C(13)–C(14)	−7.8
C(11)–C(12)	3.6	C(14)–C(8)	9.6
(*b*) External			
O(23)–C(12)–C(13)–C(15)	0.4		
C(12)–C(13)–C(15)–C(17)	−63.7		
C(12)–C(13)–C(15)–C(16)	62.4		
C(20)–C(9)–C(11)–O(22)	−2.6		
O(23)–C(12)–C(11)–O(22)	2.4		
C(7)–C(8)–C(14)–O(24)	6.1		
C(15)–C(13)–C(14)–O(24)	−6.0		

Icetexone appears to have a unique structural type.

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