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Structure of 2-Methoxy-6-nonyl-1,4-benzoquinone, C₁₆H₂₄O₃, a Synthetic Contact Allergen Related to the Naturally Occurring Primin

BY GERD ULRICH, KARL HEINZ KLASKA AND OTTO H. JARCHOW

Mineralogisch-Petrographisches Institut der Universität Hamburg, Grindelallee 48, D-2000 Hamburg 13, Federal Republic of Germany

HELMUT W. SCHMALLE*

Anorganisch-Chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

WILFRIED A. KÖNIG, HOLGER HEITSCH AND RALPH RATHMANN

Institut für Organische Chemie der Universität Hamburg, Martin-Luther-King-Platz 6, D-2000 Hamburg 13, Federal Republic of Germany

AND BJÖRN M. HAUSEN AND KARL-HEINZ SCHULZ

Universitäts-Hautklinik Hamburg-Eppendorf, Martinistrasse 52, D-2000 Hamburg 20, Federal Republic of Germany

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Abstract. C₁₆H₂₄O₃, *M_r* = 264.36, triclinic, *P* $\bar{1}$, *a* = 4.167 (1), *b* = 9.658 (1), *c* = 19.093 (1) Å, α = 89.66 (1), β = 87.27 (1), γ = 79.07 (1)°, *V* = 753.65 (1) Å³, *Z* = 2, *D_x* = 1.165 Mg m⁻³, $\lambda(\text{Cu K}\alpha)$ = 1.5418 Å, μ = 0.595 mm⁻¹, *F*(000) = 288, *T* = 295 K, *R* is 0.047 for 1682 observed unique reflections. The angle between the quinone ring plane and

the mean plane defined by the aliphatic nonyl chain atoms is 17.4 (3)°. The average C_{sp²}—C_{sp³} bond distance and corresponding angle of the side chain are 1.522 (3) Å and 113.2 (2)°. The average dimensions of the quinone ring are C—C 1.485 (3), C=C 1.337 (3), C=O 1.209 (3) Å, C—C—C 118.4 (2), C=C—C 120.8 (2), O=C—C 120.8 (2)°. Neighboring molecules form dimers across centres of symmetry which are linked by C—H···O hydrogen

* Author to whom correspondence should be addressed.

bonds, with H(3)⋯O(4ⁱ) 2.42 (4), C(3)⋯O(4ⁱ) 3.299 (2) Å, and angle C(3)—H(3)⋯O(4ⁱ) 164 (3)°. The dimers are held together by van der Waals forces between the nonyl side chains, and by C(16)—H⋯O(2ⁱⁱ) hydrogen bonds, with H(163)⋯O(2ⁱⁱ) 2.56 (4), C(16)⋯O(2ⁱⁱ) 3.357 (3) Å, and angle C(16)—H(163)⋯O(2ⁱⁱ) 140 (3)° [(i) $-x, 1-y, -z$; (ii) $-1-x, -y, -z$].

Introduction. The toxic and irritant principle of *Primula obconica* ssp. was discovered by Nestler (1904). The pure compound was isolated by Bloch & Karrer (1927) and named primin; the chemical structure was finally elucidated by Schildknecht, Bayer & Schmidt (1967) as 2-methoxy-6-pentyl-1,4-benzoquinone. Cross-sensitization tests in primin-sensitive patients with primin and related quinones were carried out by Hjorth, Fregert & Schildknecht (1969) where primin was found to be the strongest sensitizer among the 2-methoxy-6-alkyl-1,4-benzoquinones tested.

Kurtz & Dawson (1971) synthesized analogues of of poison ivy and poison oak allergens (3-*n*-alkylcatechols, alkyl: C₁ to C₁₉) and found the maximum of allergenic power with undecylcatechol in guinea-pig sensitization tests. It was interesting to compare these results with primin analogues (alkyl: C₁ to C₁₅), which were tested for their sensitizing potency (Hausen, Schmalle, Schulz, Faasch, Heitsch, Rathmann & König, 1990); the most potent sensitizer was 2-methoxy-6-undecyl-1,4-benzoquinone.

Experimental. The preparation of the title compound was carried out in analogy to that of 6-dodecyl-2-methoxy-1,4-benzoquinone; further details about this class of compounds are given in by Schmalle, Jarchow, Adiwidjaja, König, Heitsch, Rathmann, Hausen & Schulz (1988). Thin yellow platelets were obtained by slow evaporation of a propanone solution after two weeks of crystallization. A crystal of dimensions 0.67 × 0.18 × 0.04 mm was selected for the X-ray experiments. Weissenberg photographs exhibited triclinic symmetry with possible space groups *P1* or *P1̄*. Lattice parameters were determined on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromatized Cu Kα radiation. θ values of 24 reflections in the range 14.3 < θ < 41.0° were used for the refinement of cell dimensions.

Intensities of 2866 reflections (excluding 128 standards) up to $(\sin\theta)/\lambda = 0.588 \text{ \AA}^{-1}$ were collected using the ω - 2θ scan technique, zigzag mode, and variable scan speeds between 0.24 and 20° min⁻¹. Miller indices ranges: 0 < *h* < 4, -11 < *k* < 11, -22 < *l* < 22. Two standard reflections monitored every 2 h of measuring time showed 1.3% loss of intensities. Four orientation control reflections were measured every

Table 1. Positional coordinates and equivalent isotropic displacement parameters for 2-methoxy-6-nonyl-1,4-benzoquinone

$$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* a_j$$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{eq} (Å ²)
O(1)	-0.2317 (5)	0.0386 (2)	0.1619 (1)	0.067 (1)
O(2)	-0.3178 (4)	0.1244 (1)	0.0323 (1)	0.062 (1)
O(4)	0.0271 (6)	0.5398 (2)	0.1000 (1)	0.086 (1)
C(1)	-0.1572 (5)	0.1502 (2)	0.1473 (1)	0.047 (1)
C(2)	-0.2071 (5)	0.2116 (2)	0.0751 (1)	0.049 (1)
C(3)	0.1468 (6)	0.3401 (2)	0.0594 (1)	0.055 (1)
C(4)	-0.0256 (6)	0.4226 (2)	0.1123 (1)	0.057 (1)
C(5)	0.0369 (5)	0.3606 (2)	0.1826 (1)	0.054 (1)
C(6)	-0.0190 (5)	0.2332 (2)	0.2002 (1)	0.046 (1)
C(7)	0.0491 (6)	0.1633 (2)	0.2701 (1)	0.052 (1)
C(8)	0.1202 (6)	0.2606 (2)	0.3272 (1)	0.054 (1)
C(9)	0.1962 (6)	0.1840 (2)	0.3965 (1)	0.055 (1)
C(10)	0.2469 (7)	0.2833 (2)	0.4549 (1)	0.058 (1)
C(11)	0.3434 (6)	0.2084 (2)	0.5235 (1)	0.057 (1)
C(12)	0.3838 (6)	0.3088 (2)	0.5822 (1)	0.059 (1)
C(13)	0.4847 (6)	0.2343 (2)	0.6504 (1)	0.055 (1)
C(14)	0.5216 (7)	0.3337 (2)	0.7094 (1)	0.064 (1)
C(15)	0.6188 (8)	0.2585 (3)	0.7775 (1)	0.075 (1)
C(16)	-0.3640 (8)	0.1700 (2)	-0.0392 (1)	0.067 (1)

300 recorded data. Data reduction led to 2082 unique reflections, $R_{int} = 0.023$. Lp and analytical absorption corrections were applied, ψ -scan technique, min. and max. transmission factors were 0.7997 and 0.9983. 1682 reflections were considered observed with $I > 3\sigma(I)$, 400 reflections were unobserved.

Data statistics showed a tendency to hypercentricity for this structure, which could be solved by direct methods with *SHELXS84* (Sheldrick, 1984). Refinements and subsequent difference Fourier syntheses with the program *GX* (Mallinson & Muir, 1985) revealed all H atoms, which were refined with variable positional and isotropic displacement parameters. The structure was finally refined by full-matrix least squares minimizing $\sum w(|F_o| - |F_c|)^2$ with $w = [15(\sin^2\theta)/\lambda^2]/\sigma^2(F_o)$, on F_{hkl} with anisotropic displacement parameters for the C and O atoms using 268 variables and 1682 reflections; $R = 0.047$, $wR = 0.049$. The final maximum shift to e.s.d. ratio was 0.160. The maximum height in final difference Fourier synthesis was 0.24 e Å⁻³. Scattering factors were used as in the *GX* program system. The refined atomic and equivalent isotropic displacement parameters are listed in Table 1.* Intermolecular distances were calculated with *GX*, intermolecular angles obtained by *ORFFE* (Busing, Martin, Levy, Brown, Johnson & Thiesen, 1971).

* Lists of structure factors, anisotropic thermal parameters, torsion angles and H-atom parameters, and figures showing side-chain packing and interchain distances have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52898 (21 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

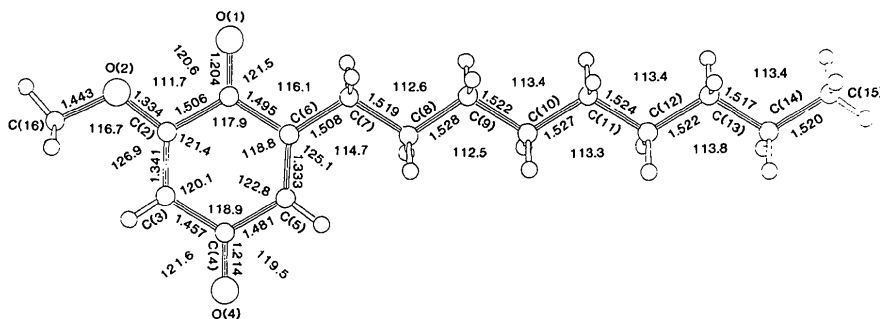


Fig. 1. Atom numbering and molecular conformation of 2-methoxy-6-nonyl-1,4-benzoquinone with bond distances (Å) and angles ($^{\circ}$); σ 's for all distances and angles are 0.003 Å and 0.2° for non-H atoms.

Discussion. The atom-labelling scheme of the molecule and interatomic distances and angles for the non-H atoms are shown in Fig. 1. The chain packing of the molecules is presented in Fig. 2, drawn with *ORTEP* (Johnson, 1971). The molecules are linked together *via* C—H \cdots O contacts across centres of symmetry with dimensions H(3) \cdots O(4ⁱ) 2.42 (4) and C(3) \cdots O(4ⁱ) 3.299 (2) Å, the angle around H(3) is $164 (3)^{\circ}$ [symmetry operation: (i) $-x, 1-y, -z$]. The packing of these dimers is caused by C(16)—H(163) \cdots O(2ⁱⁱ) interactions with distances H(163) \cdots O(2ⁱⁱ) 2.56 (4) and C(16) \cdots O(2ⁱⁱ) 3.357 (3) Å, the angle around H(163) being $140 (3)^{\circ}$ [symmetry operation: (ii) $-1-x, -y, -z$].

The preparation of crystals suitable for X-ray structure analysis was successful for primin (Schmalle, Jarchow, Hausen & Schulz, 1984), for the title compound and for 2-methoxy-6-dodecyl-1,4-benzoquinone (Schmalle *et al.*, 1988). Crystals were grown by slow evaporation from solutions in acetone and propanone. Primin analogues with odd numbers of side-chain C atoms crystallized easier and revealed crystals of better quality than those with even numbers of C atoms. These differences in crystallization may be explained by different packing types of the side chains. In the crystal structures of primin (Schmalle *et al.*, 1984) and of the title compound ($D_x = 1.230$ and 1.165 Mg m^{-3}), the molecules form dimers related by a centre of symmetry, which are held together by attractive van der Waals interactions between the side chains (Fig. 2). In contrast the side chains for the dodecyl analogue (Schmalle *et al.*, 1988) exhibit end-to-end (CH₃ \cdots CH₃) constellations of the side chains *via* centres of symmetry, which results in a less-dense packing of the dimers in the crystal ($D_x = 1.116 \text{ Mg m}^{-3}$). In all these structures the side chain is slightly rotated from the quinone ring; the angle between the quinone ring plane and the alkyl chain plane is $13.4 (4)^{\circ}$ in primin, $17.4 (3)^{\circ}$ in the title compound and $20.8 (2)^{\circ}$ in the dodecyl analogue. In the allergen perezone (Hausen & Soriano-García, 1987), a sesquiterpene-1,4-benzoquinone bearing a 1,5-dimethyl-4-hexenyl side chain, the angle between the quinone ring and the side

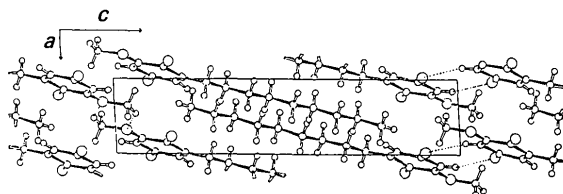


Fig. 2. The *ac* projection of the unit cell. C—H \cdots O interactions between the quinonoid ring systems are marked with dotted lines.

chain is $102.6 (6)^{\circ}$ (Soriano-García, Toscano, Flores-Valverde, Montoya-Vega & López-Celis, 1986).

According to a hypothesis on the structure-sensitizing relationship of allergens bearing an aliphatic side chain, the latter is anchored in the lipid layer of the cell membrane of a stimulator cell. In this position its ring system with the moiety O=C—C=C—R is available for nucleophilic attack of —SH and ϵ -amino groups of the binding sites of surface proteins of epidermal Langerhans cells (Hausen, 1981). With respect to their different sensitizing capacities the chemical correlations of the primin analogues have been compared with other related naturally occurring allergenic benzoquinones (Cremer, Hausen & Schmalle, 1987). Further structure-activity relationships of contact allergens are discussed by Dupuis & Benezra (1982), Benezra, Ducombs, Sell & Fousserau (1985) and Hausen (1988).

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Structure of 4-(D-galacto-Pentaacetoxy-pentyl)-1-phenylpyrazole

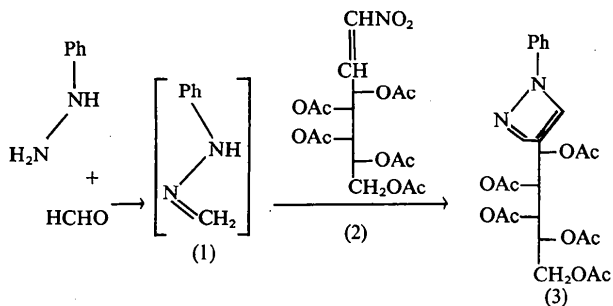
BY M. J. DIANEZ AND A. LOPEZ-CASTRO

Instituto de Ciencia de Materiales, Centro Mixto Universidad de Sevilla, CSIC, Sevilla, Spain

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Abstract. 1,2,3,4,5-Penta-*O*-acetyl-5-(1-phenyl-4-pyrazolyl)-D-arabinitol, C₂₄H₂₈N₂O₁₀, *M_r* = 504.49, monoclinic, *P*2₁, *a* = 21.663 (7), *b* = 5.644 (8), *c* = 10.884 (3) Å, β = 102.06 (5)°, *V* = 1301 (2) Å³, *Z* = 2, *D_m* = 1.29, *D_x* = 1.28 Mg m⁻³, λ(Mo Kα) = 0.7107 Å, μ = 0.095 mm⁻¹, *F*(000) = 532, *T* = 300 K, final *R* = 0.072 for 1639 observed reflections. The dihedral angle between the pyrazole and phenyl rings is 25.9 (4)° and between the pyrazole ring and galacto chain 57.5 (7)°. The molecules are linked by van der Waals forces.

Introduction. Gomez-Guillen, Hans, Lassaletta & Martin Zamora (1989) reported the synthesis of 4-(D-galacto-pentaacetoxy-pentyl)-1-phenylpyrazole (3) by the reaction of formaldehyde phenylhydrazone (1), generated *in situ*, with 3,4,5,6,7-penta-*O*-acetyl-1-nitro-1,2-dideoxy-D-galacto-hept-1-enitol (2).



The compound (3) is a substance of considerable interest as a precursor of *C*-nucleosides of pyrazole and has a structure very similar to the natural ones, such as pyrazomycin. To elucidate the geometric and conformational details of this compound we undertook its structure analysis.

Experimental. Colourless needle-shaped crystal. *D_m* measured by flotation, crystal size: 0.18 × 0.32 × 0.52 mm; Enraf-Nonius CAD-4 diffractometer, graphite-monochromated Mo Kα; accurate cell parameters from 25 strong reflections with 4 < θ < 13°; 2283 independent reflections with θ < 22° in the range (0 ≤ *h* ≤ 22, 0 ≤ *k* ≤ 5, -11 ≤ *l* ≤ 11) of which 1639 were considered observed [*I* < 2σ(*I*)]. Intensities corrected for Lp effects, but absorption and extinction corrections ignored. Two standard reflections (413 and 213) monitored after every 100 reflections showed no significant variation in intensity. Structure solved by direct methods using *MULTAN80* (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980); full-matrix least-squares refinement based on *F* of the positional and isotropic thermal parameters for non-H atoms; then positional and anisotropic thermal parameters; all H atoms located from difference syntheses; further refinement with anisotropic thermal parameters for non-H atoms and fixed H atoms with isotropic temperature factors corresponding to those of carrier atoms. Final *R* =