Crystal Structure of 6 α ,7 α :24 α ,25 α -Diepoxy-5 α ,12 α -dihydroxy-1-oxo-20S,22R-witha-2-enolide Isolated from *Datura quercifolia* Leaves

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Phytochemical investigations of the *Datura quercifolia* (Solanaceae) plant yielded a minor withanolide. The structure of the withanolide was established by spectral analysis and X-ray diffraction studies as 6 α ,7 α :24 α ,25 α -diepoxy-5 α ,12 α -dihydroxy-1-oxo-20S,22R-witha-2-enolide (C₂₈H₃₈O₇ · CH₃OH). The withanolide crystallizes in the orthorhombic space group *P*2₁2₁2₁ with unit cell parameters *a* = 6.916(4), *b* = 19.199(2), *c* = 20.138(5) Å, *Z* = 4, *D*_{cal} = 1.288 Mg m⁻³. The crystal structure was solved by direct methods and refined to *R* = 0.0462 for 1628 observed reflections. The ring conformations are: A and B, *half-chair*; C, *chair*; D, intermediate between *half-chair* and *envelope*; E, *dipplanar*. The geometry of the rings is *trans* at the A/B, B/C and C/D ring junctions. The twist along the length of the steroid nucleus is negligible [C19–C10...C13–C18 = 3.3°]. The crystal structure is stabilized by intra- and intermolecular O–H...O and C–H...O hydrogen bonds.

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Phytochemical investigations of the *Datura quercifolia* plant led to the isolation and characterization of several datura lactones, which are of a withanolide skeleton.¹ Datura lactones differ from other withanolides in having a rare epoxide functionality in the lactone ring. Keeping in view the structural features of datura lactones and an increase in demand for withanolides on account of their multifaceted pharmacological and medicinal applications, we re-investigated the chemical constituents of *Datura quercifolia* agents, which are used to treat various conditions, such as infections, organ transplantation, cancer and rheumatoid arthritis.²

Leaves of *Datura quercifolia* were collected from experimental fields of RRL, Srinagar, India, in the month of July, 2004. A voucher specimen (No. RRL DL0010) was deposited in the Herbarium. Powdered leaves of *Datura quercifolia* were extracted with toluene while stirring. The extract was concentrated to dryness under reduced pressure and subjected to column chromatography over silica gel on a glass column of 0.04 m dia. The column was eluted with solvents by gradually increasing the percentage of MeOH in CHCl₃. In all,

Fig. 1 Chemical structure of the title compound.

Table 1 Crystal and experimental data

Crystal description	light green rectangular
Crystal size	0.3 × 0.2 × 0.2 mm
Empirical formula	C ₂₈ H ₃₈ O ₇ · CH ₃ OH
Formula weight	518.63
Wavelength	0.71073 Å, Mo K α
Crystal system	orthorhombic
Space group, <i>Z</i>	<i>P</i> 2 ₁ 2 ₁ 2 ₁ , 4
Unit cell dimensions	
<i>a</i>	6.916(4) Å
<i>b</i>	19.199(2) Å
<i>c</i>	20.138(5) Å
Volume (<i>V</i>)	2674(2) Å ³
<i>D</i> _{cal}	1.288 Mg m ⁻³
Absorption coefficient	0.093 mm ⁻¹
Absorption correction	ψ -scan (<i>T</i> _{min} = 0.9666 and <i>T</i> _{max} = 0.9872)
Extinction coefficient	0.0025(9)
Reflections collected / unique	2691/2690 [<i>R</i> _{int} = 0.0060]
Reflections observed (<i>I</i> > 2 σ (<i>I</i>))	1628
2 θ range for entire data collection	2.12 < θ < 24.97°
No. of parameters refined	350
Final <i>R</i>	0.0462
<i>wR</i> (<i>F</i> ²)	0.1203
Goodness-of-fit	1.005
(Δ / σ) _{max}	−0.001 (for y C12)
($\Delta\rho$) _{max}	0.217 e Å ⁻³
($\Delta\rho$) _{min}	−0.194 e Å ⁻³
Measurement	Enraf-Nonius CAD4
Program system	SHELX
Structure determination	direct methods
Refinement	full-matrix least-squares on <i>F</i> ²
Structure drawing	ORTEP-3 for Windows

CCDC-293742 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Fig. 2 ORTEP view of the molecule with displacement ellipsoids drawn at the 40% probability level.

105 fractions of 100 ml each were collected and pooled on the bases of TLC patterns using CHCl_3 :MeOH = 9:1 as a developing solvent. Spots were visualized by spraying with freshly prepared cerium(III)-ammonium sulfate. Fractions 23–29, showing same TLC pattern, were pooled, dried and subjected to rechromatography using 100–200 mesh SiO_2 gel columns (1:20 ratio) and eluted with CHCl_3 :MeOH mixtures of increasing polarity. In all, 60 fractions of 200 ml each were collected. Fractions 37–44 were pooled on the bases of TLC (CHCl_3 :MeOH = 9:1) and again subjected to column chromatography; 30 fractions of 100 ml each were collected. Fractions 23–28 were concentrated under reduced pressure. The residue upon crystallization from MeOH yielded the title compound as fine needles (Fig. 1), m.p. 261–262°C. The isolated compound was characterized by physical and spectroscopic methods, followed by X-ray diffraction studies. The molecular formula was established as $\text{C}_{28}\text{H}_{38}\text{O}_7$ by positive high resolution fast atom bombardment mass spectrometry (HRFAB-MS). The other physical and spectroscopy data are in good agreement with the literature. Because of the absence of any significant anomalous scatterers in the compound, the absolute configuration of the molecule has not been determined from the X-ray diffraction experiment, and the assumed chirality of the molecule was determined from the synthesis route.³ The crystal structure of the title compound with water as the solvent molecules was reported earlier by Padha *et al.*⁴

During an anisotropic refinement of all non-hydrogen atoms, atom O29 of the methanol solvent was found to be disordered to three positions (O291, O292, O293), with the refinable occupancy constrained to add up to 1. The refined occupancy converged to 0.36(1), 0.24(1) and 0.40(1), respectively, with a significant decrease in the *R* factor compared with the refinement with the atom position un-split. All of the three disordered components were set to have equal temperature factors during the refinement. All H atoms (except C29 and O29 H atoms) were geometrically fixed and allowed to ride on the corresponding non-H atoms with C–H = 0.93–0.98 Å, and $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$ for the methyl groups and $1.2U_{\text{eq}}(\text{C})$ for other H atoms. The crystal and experimental data are listed in Table 1.

The bond distances and bond angles of the title compound show a fair amount of agreement with those of some analogous withanolides.^{5,6} The mean bond lengths are: $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3) = 1.523(7)$; $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^2) = 1.501(7)$; $\text{C}(\text{sp}^3)\text{--O} = 1.446(6)$; $\text{C}(\text{sp}^2)\text{=O} = 1.207(6)$ Å. The shortest $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3)$ bond lengths are observed in rings B and E, to which epoxide is fused at C6, C7 and C24, C25 atoms [$\text{C6--C7} = 1.456(7)$ and $\text{C24--C25} =$

$1.478(7)$ Å]. For similar withanolides having epoxide at the same position in ring B, variations of the $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3)$ bond lengths have been observed.⁶ Significant asymmetry between the two C–O epoxy bond lengths [$\text{C24--O4} = 1.463(6)$, $\text{C25--O4} = 1.450(7)$ Å] is observed. The bond angles (C12--C13--C17 , C14--C13--C17 , C8--C14--C15 , C8--C14--C13 , C13--C14--C15) show significant deviations from the ideal tetrahedral value of 109.4° . Deviations of this kind are a consequence of a strain caused by the fusion of five- and six-membered rings.

Ring A is highly distorted from the normal *chair* conformation, assuming instead an $5\alpha,10\beta$ -half-chair conformation due to localization of a double bond at the C2=C3 position [$\text{C2=C3} = 1.335(8)$ Å] with the asymmetry parameter [$\Delta\text{C}_2(\text{C2--C3}) = 4.88$]. Atoms C5 and C10 are displaced to opposite sides by 0.352(5) and 0.491(5) Å, respectively, from the mean C1/C2/C3/C4 plane. Ring B assumes a $9\alpha,10\beta$ -half chair conformation instead of a *chair* conformation due to epoxide fused at C6 and C7. The rotational axis for this ring passes through the C6--C7 and C9--C10 bonds with the asymmetry parameter $\Delta\text{C}_2(\text{C9--C10}) = 3.08$. Ring C has a *chair* conformation. The rotational symmetry is dominant; a pseudo- C_2 axis intercepts the C8--C9 and C12--C13 bonds with the asymmetry parameter [$\Delta\text{C}_2(\text{C8--C9}) = 2.20$]. The best mirror plane for this ring passes through the C8 and C12 atoms with asymmetry parameter [$\Delta\text{C}_s(\text{C8}) = 3.47$]. The five-membered ring D adopts a conformation approximately halfway between that of a $13\beta,14\alpha$ -half chair [$\Delta\text{C}_2(\text{C13--C14}) = 7.50$] and a 13β -envelope [$\Delta\text{C}_s(\text{C13}) = 12.74$] with a phase angle of pseudorotation $\Delta = 10.87^\circ$ and a maximum torsion angle of $\phi_m = 48.01^\circ$. Atom C13 is 0.502(5) Å on one side and C14 is $-0.252(5)$ Å on the other side with respect to the plane through C15, C16, and C17. The conformation of ring E is C25, O3 diplanar [$\Delta\text{C}_2(\text{C22--C23}) = 7.25$]. Ring E makes a dihedral angle of $73.1(1)^\circ$ with the plane of the steroid nucleus.

The $\text{C3}\cdots\text{C16}$ distance, which is a measure of the length of the steroid nucleus, is 8.987 Å. The distance between terminal atoms C3 and C27 is 15.256 Å. The twist of the molecule about its length when viewed from head to tail is determined by the $\text{C19--C10}\cdots\text{C13--C18}$ pseudo-torsion angle. This has a value of -3.3° , which implies that the tail of the molecule is twisted slightly anticlockwise by that angle. The crystal structure is stabilized by the presence of O–H $\cdots$ O and C–H $\cdots$ O intra- and intermolecular hydrogen bonds. The molecules related by a two-fold screw are packed in the unit cell in interpenetrating layers.

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