Synthesis and crystal structure of 2-acetoxy-3-(3,4-diacetoxyphenyl) propanoic acid

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2-Acetoxy-3-(3,4-diacetoxyphenyl)propanoic acid has been synthesised as a derivative of 2-hydroxy-3-(3,4-dihydroxyphenyl)propanoic acid (danshensu) to improve its chemical stability and liposolubility. It was readily hydrolysed to release the bioactive danshensu. Its crystal structure and stereochemistry were determined by X-ray single crystal diffraction analysis.

Keywords: 2-acetoxy-3-(3,4-diacetoxyphenyl)propanoic acid, crystal structure, X-ray diffraction analysis

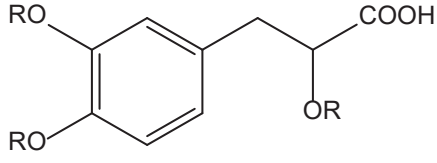
2-Hydroxy-3-(3,4-dihydroxyphenyl)propanoic acid, also called danshensu, is an active component of the root of *Salvia miltiorrhiza* used as a traditional herb in China and other Asian countries. Danshensu exhibits well-known pharmacological activities, such as dilating coronary arteries, inhibiting platelet aggregation, improvement of microcirculation and protection of myocardium from reperfusion injury.[1–4] Although danshensu is widely used, it does not easily enter into cells by crossing the cell membranes due to its phenolic hydroxyl group and so is poorly soluble in lipidic matrices.[5] Thus, there is a great need to find new danshensu derivatives with potent biological activity, good stability and liposolubility.

Over the past several decades, many danshensu derivatives have been designed and synthesised to increase their stability and liposolubility.[6–8] These derivatives were expected to exhibit similar biological activity to danshensu due to both the ester and ether linkages, which are easily hydrolysed to release bioactive danshensu.

X-ray crystallography has been increasingly used to determine the molecular structure of organic compounds. However, the crystal structure of danshensu derivatives is rarely reported. Here, we have synthesised successfully an important danshensu derivative, 2-acetoxy-3-(3,4-diacetoxyphenyl) propanoic acid, named triacetyl danshensu (Fig. 1). The structure and stereochemistry were determined by X-ray single crystal diffraction analysis for the first time.

Results and discussion

Triacetyl danshensu was synthesised by reaction of danshensu and acetic anhydride in the presence of a catalytic amount of perchloric acid.



Danshensu : R = H
Triacetyl danshensu : R =Ac

Fig. 1 Structures of danshensu and triacetyl danshensu.

Suitable crystals of triacetyl danshensu were selected after examination under a polarising microscope. Diffraction data were collected at 296(2) K on a Bruker Smart CCD diffractometer with Mo-Kα radiation (λ = 0.71073 Å). The data integration and reduction were processed with SAINT software.[9] The structures were solved by the direct method using SHELXTL and subject to a full-matrix least-squares refinement on F^2 with the SHELXL-97 program.[10] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were determined *via* difference Fourier maps and refined with isotropic atomic displacement parameters. The X-ray crystal structure of triacetyl danshensu showing the atom numbering and molecular packing in the crystal is shown in Figs 2 and 3 respectively.

The crystal of triacetyl danshensu is monoclinic, with space group *P* 2(1) and unit cell parameters: a = 11.428(3) Å, b = 6.1995(17) Å, c = 12.737(4) Å, α = *90*°, β = 105.794(6)°, γ = *90*° and V = 868.3(4) Å^3. Two molecules (one triacetyl danshensu, one water of crystallisation) form the asymmetric unit. A total of 4401 reflections had their intensities integrated and scaled (1.85 ≤ θ ≤ 25.09), of which 2914 were considered significant [R_{int} = 0.05]. Completeness to theta (25.09°) = 99.5%.

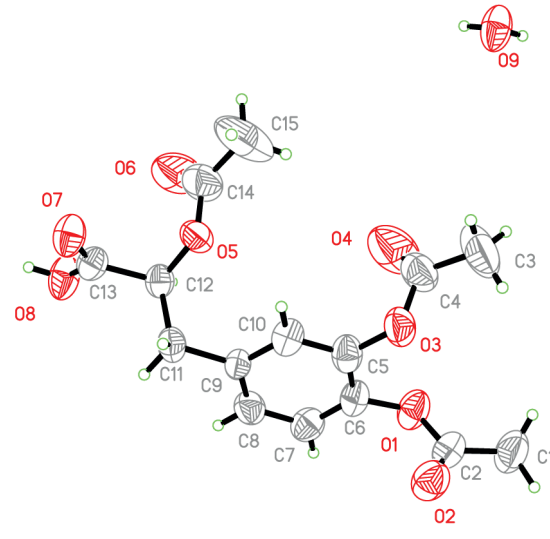


Fig. 2 Molecular structure and ORTEP drawing of triacetyl danshensu, showing the atomic numbering. Thermal ellipsoids are drawn at 50% probability.

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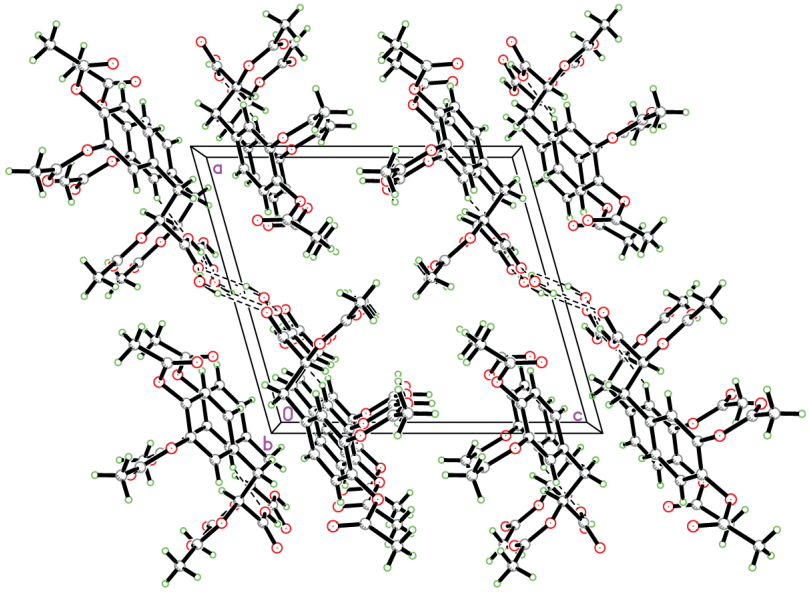

Fig. 3 Molecular packing of triacetyl danshensu, viewed along the b-axis. The dashed lines represent hydrogen bonds.

Table 1 Hydrogen bond data for triacetyl danshensu

D–H..A	d(D–H)/Å	d(H..A)/Å	d(D..A)/Å	∠DHA/°
O(8)-H(8B)...O(9)[a]	0.82	1.78	2.558(6)	156.9
O(9)-H(9A)...O(7)[b]	0.83(2)	2.05(2)	2.870(6)	171(8)
O(9)-H(9B)...O(7)[c]	0.83(2)	2.03(3)	2.847(6)	168(8)

Symmetry transformations used to generate equivalent atoms:

[a]: –x + 1, y–3/2, –z + 1.

[b]: –x + 1, y + 1/2, –z + 1.

[c]: x, y + 1, z – 1.

The goodness-of-fit on F^2 is 0.908. Final indices were R_1 = 0.0577, wR_2 = 0.1357 [I > 2 σ (I)]. The largest difference between peak and hole was 0.189 and –0.177 e Å^{-3}. The bond lengths and bond angles of triacetyl danshensu were found to be quite normal: C–C lengths range from 1.341(8) Å [C(6)–C(7)] to 1.533(7) Å [C(11)–C(12)] and C–O lengths range from 1.168(8) Å [O(4)–C(4)] to 1.438(6) Å [O(5)–C(12)] while angles range from 106.6(4)° [O(5)–C(12)–C(11)] to 128.8(7)° [O(4)–C(4)–C(3)].

The crystal packing of triacetyl danshensu is ensured through a complex network of hydrogen bonds occurring between neighbouring molecules. The carboxyl group is engaged in the hydrogen bonds with hydroxyl groups of lattice water. The water molecule is serving as a hydrogen bonding hub by a bifurcated donor hydrogen bond to two hydroxyl groups, as represented by O(9)–H(9A)...O(7) and O(9)–H(9B)...O(7) and by a bifurcated acceptor hydrogen bond from one hydroxyl group as represented by O(8)–H(8B)...O(9) (Table 1). These intermolecular interactions result in the formation of chains of molecules and the adjacent chains interact as shown in the lattice structure. CCDC1433400 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.cam.ac.uk/data_request.cif.

Experimental

The elemental analysis was performed by on an Elementar Vario EL III elemental analyser. Optical rotations were measured with a PerkinElmer 343 polarimeter. IR spectra were recorded on a FTIR-8400S spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 500 MHz spectrometer. Mass spectra were obtained using a Bruker micro TOF-Q II spectrometer. X-ray single crystal diffraction was carried out on a Bruker Smart CCD diffractometer. All the reagents were of analytical grade.

Synthesis of triacetyl danshensu; general procedure

A catalytic amount (0.2 g) of perchloric acid was added to a mixture of danshensu (10.0 g, 50.0 mmol) in acetic anhydride (20 mL). The reaction mixture was stirred at 60 °C for 6 h. After the reaction was finished, the mixture was cooled to room temperature, poured into icy water and extracted with ethyl acetate. The organic layer was shaken with brine, dried over Na_2SO_4 and then evaporated to leave a crude material, which was purified by chromatography on a silica gel column yielding the compound as a white solid (8.9 g). Then the solid was purified by crystallisation from acetic acid.

2-Acetoxy-3-(3,4-diacetoxyphenyl)propanoic acid: White solid; yield 55%; $[\alpha]_D^{22}$ = +81.67 (c = 1,CH_3OH). IR (KBr, cm^{-1}): 3504 (–OH), 3061–3085 (ArH), 2855–2929 (C–H), 1774 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.20 (s, 1H, –COOH), 7.15–7.18 (m, 3H, ArH), 5.07–5.09 (m, 1H, –CH), 3.02–3.16 (m, 2H, $-CH_2$), 2.02– 2.50 (m, 9H, $-CH_3$); ^{13}C NMR (125 MHz, DMSO-d_6): δ 170.38, 169.82, 168.24, 168.18, 141.62, 140.74, 135.26, 127.34, 124.33, 124.30, 72.16, 39.61, 20.39, 20.40; MS (ESI) *m/z*: 347.0741 [M + Na]$^+$. Anal. calcd for $C_{15}H_{16}O_8 \cdot H_2O$: C, 52.63; H, 5.30; found: C, 52.62; H, 5.19%.

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