Crystal Structure of 8-(3-Methyl-3-benzoylamino-butyl)-7-methoxycoumarin

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The title compound, C₂₂H₂₃NO₄, is a derivative of osthol isolated from *Imperatoria Osthuthium*, known to possess an anti-inflammatory activity in rats,¹ and is used in various medicinal preparations in India and also in the traditional Chinese system of medicine.² Synthetic derivatives of osthol are used for hepatitis prevention,³ since osthol specifically increases the glycosylation of the hepatitis antigen and secretion of hepatitis B virus *in vitro*.⁴ In this paper we report on the synthesis and crystal structure of a semi-synthetic derivative of osthol. It was prepared by a Ritter reaction⁵ and in the resulting derivative a double bond in the isoprenyl unit of osthol is modified to a single bond, and the final product also contains a benzamide group. The packing is also stabilized by a C-H...O interaction.

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Osthol, isolated from *Imperatoria Osthuthium*, exhibits anti-inflammatory activity in rats,¹ and is used in various medicinal preparations in India and also in the traditional Chinese system of medicine.² Synthetic derivatives of osthol are used for hepatitis prevention,³ since osthol specifically increases the glycosylation of the hepatitis antigen and secretion of hepatitis B virus *in vitro*.⁴ In this paper we report on the synthesis and crystal structure of a semi-synthetic derivative of osthol. It was prepared by a Ritter reaction⁵ and in the resulting derivative a double bond in the isoprenyl unit of osthol is modified to a single bond, and the final product also contains a benzamide group.

Benzonitrile was added to a solution of Osthol (100 mg / 0.41 mmol) dissolved in benzene, and the reaction mixture was cooled at 0°C, followed by slow addition of sulfuric acid. The reaction mixture was stirred at room temperature for 2–3 h and was quenched after a complete disappearance of Osthol with a saturated solution of sodium bicarbonate. The final compound (Fig. 1) was extracted with ethyl acetate and dried over sodium sulfate. The compound was purified using column chromatography with 10% ethyl acetate in hexane as a mobile phase. Rod-shaped crystals were obtained using a slow-evaporation technique from a mixture of ethyl acetate and hexane.

The crystal and experimental details are given in Table 1. The

structure was solved using direct methods, using SHELXS, and refined with SHELXL. Anisotropic refinement on all non-hydrogen atoms, with the hydrogen atoms included only in the structure factor calculations, gave a final *R*-factor of 0.0629. The final atomic coordinates and temperature factors for all of the nonhydrogen atoms are given in Table 2. An ORTEP plot of the molecule at the 30% probability level is shown in Fig. 2.

In the above reaction, osthol is modified in such a way that a benzamide moiety becomes attached to the isoprenyl end, and the sp² carbon atoms at C7 and C8 are converted to sp³ carbon atoms with C7–C8 = 1.541(3) Å, C9–C8–C7 = 116.0(2)° and the torsion angles of [C9–C8–C7–C14] = –70.2(3)° and [C9–C8–C7–C13] = 52.8(3)°, respectively. The corresponding values in osthol⁶ are 1.327(3) Å, 127.2(2)°, –1.61° and 177.8(2)°, respectively. The relative orientation of the peptide unit

Fig. 1 Schematic diagram of the title compound.

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Table 1 Crystal and experimental data

Formula: C ₂₂ H ₂₃ NO ₄	
Formula weight = 365.41	
Crystal system: monoclinic	
Space group: <i>P</i> 2 ₁ / <i>c</i>	<i>Z</i> = 4
<i>a</i> = 11.383(3) Å	
<i>b</i> = 17.831(4) Å	<i>β</i> = 94.127(5)°
<i>c</i> = 9.802(2) Å	
<i>V</i> = 1984.4(8) Å ³	
<i>D_x</i> = 1.223 g/cm ³	
No. of reflections used = 3499	
2 θ _{max} = 50.00° with Mo <i>K</i> α	
<i>R</i> = 0.0629	
(Δ / σ) _{max} = 0.000	
($\Delta\rho$) _{max} = 0.294 e/Å ^{–3}	
($\Delta\rho$) _{min} = –0.151 e/Å ^{–3}	
Measurement: Siemens SMART CCD	
Program system: SAINT	
Structure determination: SHELXS 97	
Refinement: full matrix	
CCDC No: 663291	

Table 2 Fractional coordinates ($\times 10^4$) and equivalent isotropic thermal parameters ($10^3 \times \text{\AA}^2$) for non-hydrogen atoms

Atom	x	y	z	U_{eq}
C(1)	3890(2)	1136(2)	1209(3)	53(1)
C(2)	2912(2)	1299(2)	1912(3)	55(1)
C(3)	3775(3)	1234(2)	-205(3)	64(1)
C(4)	1832(2)	1535(2)	1291(3)	58(1)
C(5)	2708(3)	1464(2)	-870(3)	74(1)
C(6)	1759(3)	1600(2)	-124(3)	71(1)
C(7)	6880(2)	1436(1)	3334(2)	44(1)
C(8)	5784(2)	1583(2)	2355(3)	51(1)
C(9)	5039(2)	902(2)	1951(3)	55(1)
C(10)	4745(4)	1188(2)	-2293(3)	96(1)
C(11)	881(3)	1660(2)	2136(4)	73(1)
C(12)	2124(3)	1346(2)	4150(4)	81(1)
C(13)	7677(2)	823(2)	2836(3)	64(1)
C(14)	6499(3)	1235(2)	4752(3)	72(1)
C(15)	1021(3)	1576(2)	3481(4)	85(1)
C(16)	7994(2)	2528(1)	2471(2)	40(1)
C(17)	8512(2)	3287(1)	2789(2)	40(1)
C(18)	9418(2)	3532(2)	2029(3)	53(1)
C(19)	9905(3)	4233(2)	2226(3)	67(1)
C(20)	9478(3)	4701(2)	3180(3)	72(1)
C(21)	8561(3)	4478(2)	3920(3)	70(1)
C(22)	8078(3)	3768(2)	3739(3)	53(1)
N(1)	7535(2)	2155(1)	3484(2)	44(1)
O(1)	3033(2)	1213(1)	3316(2)	69(1)
O(3)	2331(2)	1253(2)	5354(3)	125(1)
O(2)	4772(2)	1083(2)	-855(2)	85(1)
O(4)	8003(2)	2276(1)	1299(2)	52(1)

$$U_{\text{eq}} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* (\mathbf{a}_i \cdot \mathbf{a}_j).$$

Fig. 2 Perspective view of the molecule, showing thermal ellipsoids at the 30% probability level.

(C7-N1-C16-O4-C17) with respect to the benzene ring (C17...C22) is $31.4(1)^\circ$. The methoxy group at C3 is coplanar

Fig. 3 View of the packing showing the C-H... π interactions.

with the fused benzene rings, as seen in osthol. The change in the conformation may be attributed to a bulky substitution at atom C7.

The angle between the benzopyran ring formed by the A & B rings and the C ring is $83.8(1)^\circ$. The atoms of the functional group show higher thermal parameters compared to those of the coumarin ring. Two such chains run in opposite directions. The molecular packing in the crystal structure is further stabilized by C-H... π interactions (Fig. 3). The molecules in the crystal lattice are packed together via C-H...O ($-1+x, y, z$), and N-H...O ($x, -y+1/2, z+1/2$) hydrogen bonds with a head-to-tail fashion. A ring set motif, $R^1_2(8)$, is formed through these hydrogen bonds.

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References

1. J. Liu, W. Zhang, L. Zhou, X. Wang, and Q. Lian, *Zhong yao cai.*, **2005**, 28, 1002.
2. R. Liu, S. Zschocke, E. B. Reininger, and R. Bauer, *Planta Med.*, **1998**, 64, 525.
3. T. Okamoto, T. Kobayashi, and S. Yoshida, *Med. Chem.*, **2007**, 3, 35.
4. R. L. Huang, C. C. Chen, Y. L. Huang, D. J. Hsieh, C. P. Hu, C. F. Chen, and C. Chang, *Hepatology*, **1996**, 24, 508.
5. J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, **1948**, 70, 4045.
6. T. Borowiak and I. Wolska, *Acta Cryst.*, **1989**, C45, 620.