Monatshefte für Chemie 113, 197—200 (1982)

Monatshefte für Chemie
Chemical Monthly

Synthesis of Obtusinin and 7-(3′-Hydroxymethylbut-2′-enyloxy)-6-methoxy-2*H*-1-benzopyran-2-one

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(Received 23 April 1981. Accepted 15 May 1981)

Obtusinin (**1**) has been synthesised by the reaction of 6-methoxy-7-(3′-methylbut-2′-enyloxy)-2*H*-1-benzopyran-2-one (**3**) with OsO_4. Synthesis of 7-(3′-hydroxymethylbut-2′-enyloxy)-6-methoxy-2*H*-1-benzopyran-2-one (**2**) has been achieved by the regiospecific oxidation of **3** with SeO_2 followed by reduction of the formed aldehyde with KBH_4.

(Keywords: Osmium tetraoxide; Potassium borohydride; Regiospecific oxidation; Selenium dioxide)

Synthese von Obtusinin und 7-(3′-Hydroxymethylbut-2′-enyloxy)-6-methoxy-2H-1-benzopyran-2-on

Obtusinin (**1**) wurde über 6-Methoxy-7-(3′-methylbut-2′-enyloxy)-2*H*-1-benzopyran-2-on (**3**) mit OsO_4 synthetisiert. Die Darstellung von 7-(3′-Hydroxymethylbut-2′-enyloxy)-6-methoxy-2*H*-1-benzopyran-2-on (**2**) wurde mittels regioselektiver Oxidation von **3** mit SeO_2, gefolgt von Reduktion des gebildeten Aldehyds mit KBH_4, bewerkstelligt.

Introduction

Obtusinin, isolated[1] from *Haplophyllum obtusifolium* was assigned the structure of 7-(2′,3′-dihydroxy-3′-methylbutyloxy)-6-methoxy-2*H*-1-benzopyran-2-one (**1**). Another coumarin, 7-(3′-hydroxymethylbut-2′-enyloxy)-6-methoxy-2*H*-1-benzopyran-2-one (**2**) was also isolated[2] from the same species. The structures of these compounds were elucidated on the basis of their spectral data; no chemical evidence was given. The present communication describes the unambiguous synthesis of **1** and **2** in view to provide synthetic evidence to their structures.

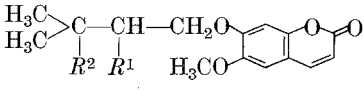
0026-9247/82/0113/0197/$ 01.00

Results and Discussion

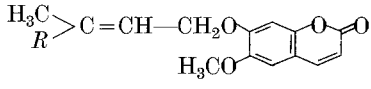
2 was synthesised starting from 6-methoxy-7-(3′-methylbut-2′-enyloxy)-2*H*-1-benzopyran-2-one[3] (**3**). The regiospecific oxidation of **3** with selenium dioxide (1 mol equiv.) in dimethylsulphoxide furnished an aldehyde (**4**) as the major product. The structure of **4** was assigned as 7-(3′-formylbut-2′-enyloxy)-6-methoxy-2*H*-1-benzopyran-2-one on the basis of its ^{1}H-NMR spectral data, which showed besides the normal signals, a singlet at δ 9.47 integrating for one proton (characteristic of the aldehyde group) and another singlet at δ 1.84 for a terminal methyl group. Reduction of **4** with potassium borohydride in ethanol afforded the alcohol **2**, which was assigned the structure of 7-(3′-hydroxymethylbut-2′-enyloxy)-6-methoxy-2*H*-1-benzopyran-2-one on the basis of its spectral characteristics and ^{1}H-NMR spectral data of its acetate **5**.

The synthesis of obtusinin (**1**) was also effected from the isopentenyloxy-2*H*-1-benzopyran-2-one **3**. Treatment of **3** with osmium tetraoxide in benzene yielded the intermediate osmate which was decomposed with sodium bisulphite to give the required **1**. The structure of **1** was established on the basis of its spectral studies and ^{1}H-NMR spectral data of its acetate **6**.

Compounds **1** and **2** were found identical with the description of the natural samples. However, a direct comparison of the natural and synthetic samples could not be made due to the non-availability of the natural samples.



1 $R^1 = R^2 = OH$
6 $R^1 = OCOCH_3$, $R^2 = OH$



2 $R = CH_2OH$
3 CH_3
4 CHO
5 CH_2OCOCH_3

Experimental

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 621 spectrophotometer and ^{1}H-NMR spectra were recorded on a Perkin-Elmer R-32 spectrometer with $SiMe_4$ as internal standard.

7-(3′-Formylbut-2′-enyloxy)-6-methoxy-2H-1-benzopyran-2-one (**4**)

6-Methoxy-7-(3′-methylbut-2′-enyloxy)-2*H*-1-benzopyran-2-one[3] (**3**) (0.5 g) was dissolved in *DMSO* (10 ml) and SeO_2 (0.24 g, 1.1 mol equiv.) added during 2 h with constant stirring at 20–22°. The reaction was TLC monitored and after the completion of reaction ($\sim$ 20 h), the mixture was poured into crushed ice

and solid separated was filtered. The reaction product was column chromatographed over silica gel to give **4** (0.2 g) from chloroform as colourless needles, m.p. 174–175°.

^{1}H-NMR ($CDCl_3$) δ: 1.85 (s, 3 H, 3′-CH_3), 3.89 (s, 3 H, OCH_3), 4.95 (d, 2 H, J = 6.5 Hz, —OC**H**$_2$—CH=), 6.25 and 7.60 (each d, each 1 H, J = 9.5 Hz, H 3 and H 4), 6.59 (m, 1 H, —OCH_2—C**H**=), 6.77 and 6.86 (each s, each 1 H, H 8 and H 5), 9.45 (s, 1 H, —CHO).

7-(3′-Hydroxymethylbut-2′-enyloxy)-6-methoxy-2 H-1-benzopyran-2-one (**2**)

To the above aldehyde (**4**, 200 mg) in absolute ethanol (50 ml), potassium borohydride (20 mg) was added and the contents were stirred for 2.5 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated. The residue crystallised from acetone—petroleum ether as colourless needles of **2** (175 mg), m.p. 98–99° (Lit.[2] m.p. 97–98°).

^{1}H-NMR ($CDCl_3$) δ: 1.77 (s, 3 H, 3′-CH_3), 2.29 (bs, 1 H, —OH, exchangeable with D_2O), 3.87 (s, 3 H, —OCH_3), 4.05 (s, 2 H, —C**H**$_2$OH), 4.70 (d, 2 H J = 6.5 Hz, —OC**H**$_2$—CH=), 5.75 (1 H, t, —OCH_2—C**H**=), 6.23 and 7.63 (each d, each 1 H, J = 9.5 Hz, H 3 and H 4), 6.76 and 6.82 (each s, each 1 H, H 8 and H 5).

IR (KBr): 3470 (OH), 1710 (C=O), 1620, 1570, 1520 cm^{-1} (C=C).

Treatment of the alcohol, **2** with Ac_2O—C_5H_5N yielded the acetate **5**, m.p. 136–137°. ^{1}H-NMR ($CDCl_3$) δ: 1.80 (s, 3 H, 3′-CH_3), 2.08 (s, 3 H, —O*Ac*), 3.88 (s, 3 H, OCH_3), 4.50 (s, 2 H, —C**H**$_2$O*Ac*), 4.69 (d, 2 H, J = 6.5 Hz, —OC**H**$_2$—CH=), 5.72 (m, 1 H, —OCH_2—C**H**=), 6.22 and 7.55 (each d, each 1 H, J = 9.5 Hz, H 3 and H 4), 6.76 and 6.82 (each s, each 1 H, H 8 and H 5).

7-(2′,3′-Dihydroxy-3′-methylbutyloxy)-6-methoxy-2 H-1-benzopyran-2-one (obtusinin) (**1**)

Compound **3** (300 mg) was dissolved in thiophene free dry benzene (20 ml) and to this solution OsO_4 (300 mg) was added. After leaving the mixture for 18 h, benzene was removed in vacuo at room temp. The black osmate ester was suspended in aq. ethanol (30 ml) and decomposed by refluxing with $NaHSO_3$ (1 g) for 30 min. It was cooled, filtered and the residue washed with ethanol. The combined filtrate was diluted with water (30 ml), ethanol removed in vacuo and the residue taken up in ethylacetate. Evaporation of the solvent gave a solid, which crystallised from acetone—petroleum ether to give the diol **1** (240 mg), m.p. 136–138° (Lit.[1] m.p. 135–137°).

^{1}H-NMR (*DMSO-d_6*) δ: 1.13 and 1.18 (each s, each 3 H, =CMe_2), 3.35 (s, 1 H, 3′-OH, exchangeable with D_2O), 3.82 (s, 3 H, OCH_3), 3.95 [m, 1 H, —OCH_2—C**H**(OH)—], 4.34 [d, 2 H, J = 6.5 Hz, —OC**H**$_2$—CH(OH)—], 5.20 (d, 1 H, J = 5.5 Hz, 2′-OH, exchangeable with D_2O), 6.25 and 7.88 (each d, each 1 H, J = 10 Hz, H 3 and H-4), 7.06 and 7.18 (each s, each 1 H, H 8 and H 5).

IR (KBr): 3495 (OH), 3315-2290 (OH), 1720 (C=O), 1615, 1565, 1525 cm^{-1} (C=C).

1, on treatment with Ac_2O—C_5H_5N gave the monoacetate **6**, m.p. 97–98° (Lit.[1] m.p. 98–99°). ^{1}H-NMR ($CDCl_3$) δ: 1.23 and 1.27 (each s, each 3 H, =CMe_2), 2.07 (s, 3 H, —O*Ac*), 2.11 (s, 1 H, OH), 3.83 (s, 3 H, —OCH_3), 4.32 [d, 2 H, J = 6.5 Hz, —OC**H**$_2$—CH(O*Ac*)—], 5.16 [m, 1 H, —OCH_2—C**H**(O*Ac*)—], 6.24

and 7.16 (each d, each 1 H, $J = 10$ Hz, H 3 and H 4), 6.84 and 7.38 (each s, each 1 H, H 8 and H 5).

All compounds gave satisfactory analyses of carbon and hydrogen (within $\pm$ 0.4%).

Acknowledgement

We are grateful to the Council of Scientific and Industrial Research, New Delhi for financial assistance to one of us (*M.K.*).

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