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Photodegradation of Natural Substances: Photooxygenation and Ozonolysis of 4-Methoxy-7-methyl-5 H-furo [3,2-g][1]benzopyran-5-one (Visnagin)

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Abstract. The photooxygenation of 4-methoxy-7-methyl-5 H-furo[3,2-g][1]benzopyran-5-one (Visnagin, **1**) in methanol in absence and in presence of a sensitizer (methylene blue) has been studied. 6-Formyl-7-hydroxy-5-methoxy-2-methylchromone (**4a**), methyl 7-hydroxy-5-methoxy-2-methylchromone-6-carboxylate (**4b**) and 7-hydroxy-5-methoxy-2-methylchromone-6-carboxylic acid (**4c**) could be isolated and identified in each case. The formation can be interpreted in terms of intermediate production of a 1.2-dioxetane like **2**.

A comparative study on the ozonolysis of Visnagin (**1**) in ethyl acetate both in absence and in presence of dimethyl sulfide, was also undertaken. Ozone attacks **1** either at the furan ring (to give **4a, c**) or at both the furan and γ-pyrone site (to afford **10**). Possible reaction mechanisms are considered and the structures of the new products are based upon compatible and spectroscopic evidences.

Introduction

4-Methoxy-7-methyl-5 H-furo[3,2-g][1]benzopyran-5-one (Visnagin **1**) is one of the main active constituents of *Ammi visnaga L.* which grow in Egypt. Visnagin has been isolated and characterized by Späth and Gruber 1938/41 [1], and several total syntheses have been reported [2]. Members of this family are well-recognized as vasodilators, and they are applied in the treatment of angina pectoris, as well as of bronchial asthma [3], and as suntanning agents [4]. Visnagin has been found to be a photoactive compound, especially in the photoinduction of DNA-cross links [5], e. g. in viral DNA [6]. By virtue of the sensitivity of the furan ring to oxidizing agents [7], the potential of drugs which contain this heterocycle may be seriously affected during manufacturing processes, applications and/or storage. This together with the continued widespread interest in the chemistry of singlet oxygen and its possible roles in biological processes [8], as well as the expanding utilities in organic syntheses [9], has prompted us to study the photooxygenation of Visnagin (**1**). A comparative study on the effect of ozone on **1** also motivated our interest in the present investigation. Some scattered work has appeared on oxidative ring cleavage of the furo[3,2-g][1]benzopyran systems in order to obtain biologically active derivatives [10]; however, photodegradation and ozonolysis of Visnagin have not been studied so far.

Results and Discussion

A solution of **1** in absolute methanol containing methylene blue was irradiated at 25 °C in a Pyrex reactor ($\lambda > 300$ nm) while a stream of oxygen being circulated in a moderate rate within the solution. After 48 h, **1** had disappeared in the reaction medium. Working-up of the photolysate mixture by column chromatography resulted in isolation of 6-formyl-7-hydroxy-5-methoxy-2-methylchromone (**4a**), methyl 7-hydroxy-5-methoxy-2-methylchromone-6-carboxylate (**4b**), and 7-hydroxy-5-methoxy-2-methylchromone-6-carboxylic acid (**4c**), in sequence. When the

photolysis of **1** in methanol was performed at 25 °C for 48 h in absence of the sensitizer, **1** was recovered in ca. 40 % yield, and **4a – c** were isolated, however in comparatively smaller amounts. When the photo-oxidation of **1** was carried out at 25 °C in dry toluene, the reaction was completed after ca. 120 h to give **4a** and **4c** as major photo products.

The identy of **4a** was established by comparing its m. p. and spectroscopic data with those of a reference sample, prepared by oxidizing **1** with potassium dichromate in an acidic medium [11]. Analytical and spectroscopic data for **4c** were also in good accord with the assigned structure (cf. Table 1).

A mechanism that accounts for the formation of **4a** is depicted in Scheme 1. It involves addition of singlet oxygen to the furan ring in **1** to afford the 1,2-dioxetane (path A), in the usual manner [13]. Rearrangement of **2** and solvolysis of the resulting intermediate **3** yields **4a**. On this basis, addition of $^1O_2$ to the furan ring in **1** to give endoperoxide **5** (path B) is, thus, discarded [4, 8c]. Further oxidation of **4a** produced **4c**, which is smoothly esterified in the presence of methanol [4, 8c] to give **4b**.

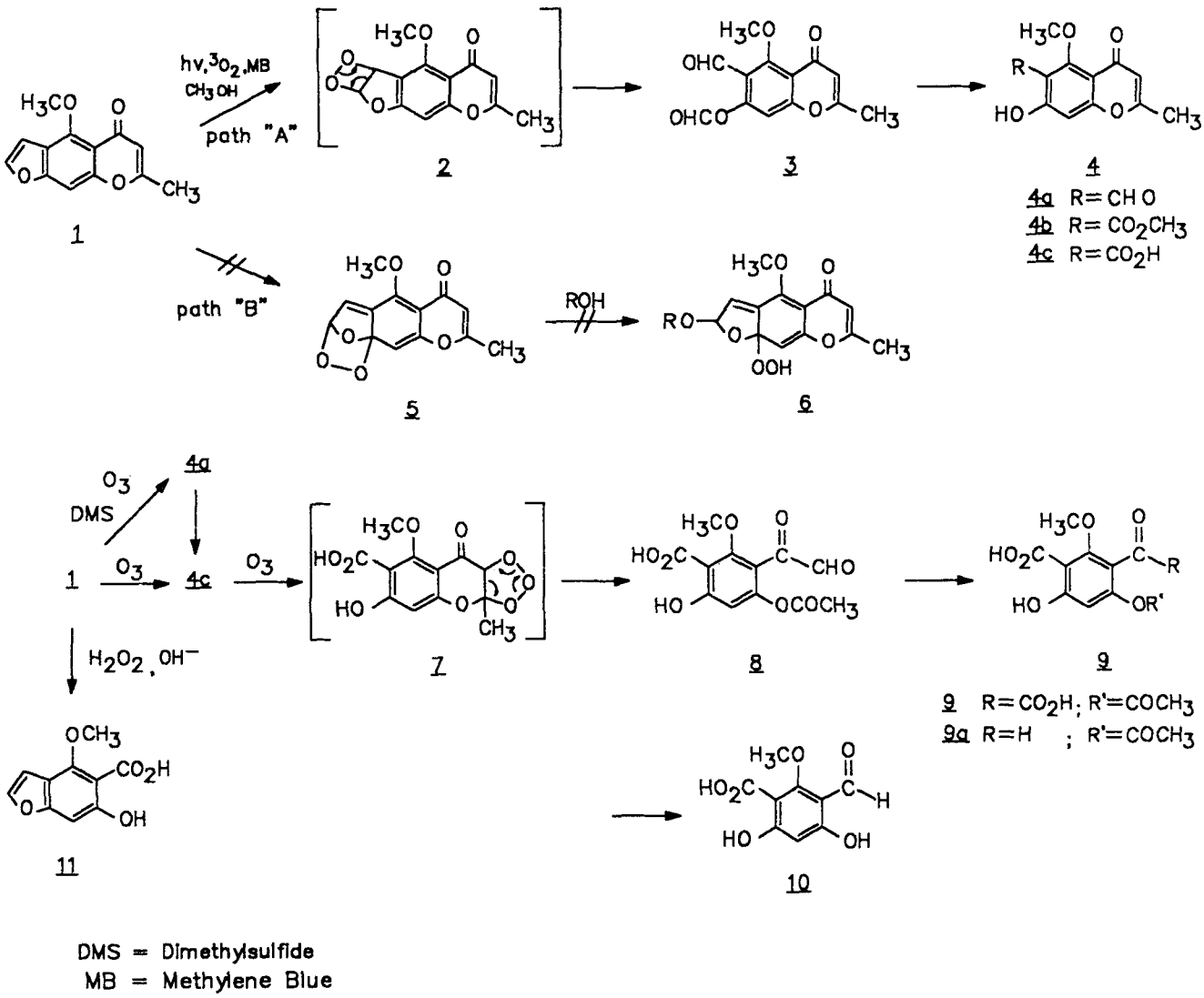
Similar to these results, a recent paper on the photoreaction of 4′-methyl- or 5′,4,8-trimethylpsoralen in the presence of flavin-mononucleotide (FMN) has shown, that the furan moiety is predominantly degradated oxidatively, as with $^1O_2$, while the coumarin moiety remains intact [14].

Ozonolysis of **1** in dry ethyl acetate was performed at −40 °C for 30 min in the presence of dimethyl sulfide, and **4a** was obtained in ca. 95 % yield. This selective oxidation of **1** to give **4a** provides an important and convenient route for producing salicyl aldehyde derivatives from furan-containing precursors. When the ozonolysis of **1** was carried out in absence of dimethyl sulfide, a mixture of **4a** (20 %) and **4c** (35 %) were recovered. In addition, a pale-yellow crys-

Table 1 Analytical, IR- and ^{1}H NMR data of **4a – c** and **10**

Compound M. p. (type of [°C] crystals/ solvent)	Yield [%] [a] experiments No.	M. formula (M. weight) M^+ [m/z %]	Analysis calcd./found [%] C	H	IR in KBr in [cm^{-1}]	^{1}H NMR δ [ppm] in $CDCl_3$
4a 189 – 191 [c] (colourless leaflets/aq. methanol)	1 [b]: 64 2 [b]: 30 3 [b]: 60 4 : 90 5 : 30	$C_{12}H_{10}O_5$ (234.2) 234 (48)			3090 (C – H_{ar}), 1660 (C = O), 1630 (C = O, γ-pyrone), 1585 (C = C), 1350 (C – O)	2.22 (d, J_{HH} = 2.5 Hz, 3 H, CH_3), 4.00(s, 3 H, OCH_3), 5.90 (qu, 1 H, H – 3 pyrone), 6.35 (s, 1 H, H_{ar}), 10.28 (s, 1 H, CHO), 11.95 (br. s, OH) [d]
4b [f] 192 – 194 (colourless needles/ ethanol)	1 [b]: 19 2 [b]: 17	$C_{13}H_{12}O_6$ (264.2) 264 (< 5)	59.10 59.27	4.57 4.68	3300 (O – H), 1670 (C = O, ester), 1630 (C = O, γ-pyrone), 1600, 1590 (C = C), 1360 (C – O)	2.22 (d, J_{HH} = 2.5 Hz, 3 H, CH_3), 3.51 (s, 3 H, OCH_3), 4.13 (s, 3 H, $COOCH_3$), 5.11 (qu, 1 H, H – 3 pyrone), 5.84 (s, OH) [d], 6.13 (s, 1 H, H_{ar})
4c 210 – 212 (yellow needles/ aq. ethanol)	1 [b]: 8 2 [b]: 5 3 [b]: 18 5 : 5	$C_{12}H_{10}O_6$ (250.2) 250 (< 5)	57.60 57.85	4.31 4.02	3505, 3400 (O – H), 1670 (C – O, acid), 1650 (C – O, γ-pyrone), 1600 – 1540 (C = C), 1340 (C – O)	
10 178 – 180 [e] (light yellow needles/ n-hexane)	5 : 65	$C_9H_8O_6$ (212.1) 212 (100)	50.95 50.82	3.80 3.77	3300 – 2600 (broad O – H, C – H_{ar}, C – $H_{aliph.}$), 1680 – 1610 (C – O, broad), 1600 (C = C_{ar}), 1260 – 1220 (C – O)	4.13 (s, 3 H, OCH_3), 6.33 (s, 1 H, H_{ar}), 10.08 (s, 1 H, CHO), 12.17 (br. s, OH) [d], 12.50 (br. s, OH) [d]

[a] based on Visnagin (**1**); [b] the photolysis was carried out at 25 °C; [c] reported in loc. cit. [11]: 189 °C; [d] exchangeable with D_2O; [e] melts with green colour; [f] compare cit. [12].



talline material was isolated (ca. 40 %) and identified as 5-formyl-4-hydroxy-6-methoxysalicylic acid (**10**). The structure rests on the following data, (a): its elemental analysis and molecular weight determination (MS) corresponds to $C_9H_8O_6$, (b): the ^1H NMR spectrum of **10** lacks the principal features of the γ-pyrone ring (cf. **4a – c**), namely, a doublet for the CH_3 protons, and a quadrouplet for the vinyl proton constituting the allylic system; however, the spectrum showed singlets at δ 4.13 (3 H, OCH_3), 6.33 (1 H_{ar}) and 10.08 (1 H, CHO). The OH protons gave two singlets (exchangeable with D_2O) at δ 12.17 and 12.50 ppm, (c): the mass spectrum of **10** showed the molecular ion peak at m/z 212 (100 %). Loss of a neutral CO_2 molecule from $M^{+}\bullet$, frequently observed in the mass spectra of aromatic carboxylic acids [15], yielded a radical cation at m/z 168 (70 %).

The mechanism for formation of **10** is also shown in Scheme 1. The γ-pyrone ring in the carboxylic acid **4c**, the latter initially formed by ozonolysis of the furan ring adds ozone to afford the ketoaldehyde **8** via the ozonide **7**. Oxidation of **8** followed by loss of CO_2 from the resulting carboxylic acid **9** yields **9a** which upon solvolysis produces **10**. A similar cleavage of the γ-pyrone ring by ozone was observed in the controlled oxidation of **1** with alkine hydrogen peroxide solution which produces 6-hydroxybenzofuran-4-methoxy-5-carboxylic acid (**11**) [11]. Furthermore this mechanism is similar to the nonenzymatic pathway encountered in the biological oxidation of certain chromone derivatives [16].

Experimental

All melting points are uncorrected. Ozonolysis of **1** was carried out using an 'Ozongenerator' (Fischer Labor- und Verfahrenstechnik, Germany). Visnagin (**1**) was available from Memphis Co., Cairo, Egypt. IR ([cm^{-1}], in KBr): Perkin-Elmer 157 G. ^1H NMR (δ [ppm], in $CDCl_3$): Bruker WH-90 (TMS as internal reference). MS (70 eV): MS 50 of Kratos

(A.E.I.). TLC: DC-Alufolien (E. Merck, Darmstadt) and toluene-ethyl acetate (6:4, v/v) as solvent system. Column chromatography: Silica gel (E. Merck, Darmstadt) using chloroform or chloroform-ethyl acetate (1:1, v/v) as eluents.

1) Photodegradation of Visnagin (**1**) *in the Presence of Methylene Blue*

A solution of **1** (2.3 g, 10 mmol) in absol. methanol (230 ml) containing methylene blue (30 mg) was irradiated in a Pyrex vessel ($\lambda > 313$ nm) with a Hg-high pressure lamp (Philips HPK 125). The temperature was maintained at 25 °C by cooling. Oxygen gas was steadily allowed to pass through the mixture at a moderate rate. The reaction was monitored at regular intervals by TLC until disappearance of **1** after 48 h. The photolysates were adsorbed on 10 g of silica gel by evaporating the solvent under reduced pressure, then subjected to column chromatography on silica gel. Careful elution with chloroform yielded **4a** and **4b** while elution with chloroform/ethyl acetate afforded **4c** ([1] see Table 1).

2) Photolysis of **1** *without Methylene Blue in Methanol*

Similarly to procedure[1] photolysis of **1** (1 g, 4,3 mmol) was performed in absolute methanol (230 ml) in a Pyrex reactor ($\lambda > 313$ nm) for 48 h but in the absence of methylene blue. **1** act itself as an self-sensitizer.

Working up as described before has resulted in recovery of **1** (400 mg, 40 %) along with isolation of **4a** (300 mg, 30 %), **4b** (200 mg, 17 %), and **4c** (50 mg, 5 %).

3) Photolysis of **1** *without Methylene Blue in Toluene*

In a similar manner, photolysis of **1** (1 g, 4,4 mmol) was done in dry toluene (230 ml) in a Pyrex reactor ($\lambda > 313$ nm) for 120 h in absence of methylene blue. Working up as described before, yielded **4a** and **4c**.

4) Ozonolysis of **1** *in the Presence of Dimethyl Sulfide*

Ozone was lead in a steady stream through the solution of **1** (1 g, 4,3 mmol) in dry ethyl acetate (100 ml) containing dimethyl sulfide (1 ml), at −40 °C (dry ice/acetone) for 30 min. Excess of ozone and volatile materials were expelled from the mixture under a stream of argon. The residual material was collected and proved to be **4a**.

5) Ozonolysis of **1** *without Dimethyl Sulfide*

Similarly, ozonolysis of **1** (1 g, 4,3 mmol) was performed in dry ethyl acetate (100 ml) at −40 °C for 30 min but in absence of dimethyl sulfide. After removal of the volatile materials under a stream of argon, the residue was subjected to column chromatography on silica gel. Working up resulted in yielding **4a**, **10**, and **4c** after elution with chloroform/ethyl acetate (1:2, v/v), and chloroform/ethyl acetate (1:2, v/v), respectively (see Table 1).

During working up in the formentioned experiments 1–5, minor constituents of varying polarities, so far unidentified, were also isolated.

Esterification of **4c**

A solution of **4c** (200 mg, 0,8 mmol) in absol. methanol (40 ml) containing 0.2 ml cc. H_2SO_4 was refluxed for 4 h. After evaporation of the volatile material in vacuo, the residue was treated with 5 % aq. $NaHCO_3$ The undissolved material was collected (130 mg, 70 %) and recrystallized from ethanol and proved to be **4b** (m.p., mixed m.p. and comparative IR spectra).

[1] Yields are based on **1** and approximate.

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