Photochemical Reactions of the Natural Furocoumarin, Imperatorin

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Photochemical behavior of imperatorin was investigated including photolysis and sigmatropic effects in different solvents and photodimerization. The structures of the photoproducts obtained were determined by chemical and spectral methods.

Natural and synthetic coumarins are important due to their biological activities, e.g. photosensitizing effect of xanthotoxin and trimethylpsorolene.[1] Behavior of coumarins and furocoumarins (xanthotoxin only) under irradiation with ultraviolet light has been studied previously.[2-9]

Imperatorin (**1**), known also as ammidin is a natural furocoumarin and occurs in the fruits of *Ammi majus* (Umbelliferea).[10] No previous studies on the photolysis of imperatorin are reported. This paper deals with the behaviour of imperatorin towards:

a) Photolysis and sigmatropic reactions in different solvents. b) Photodimerization.

Results and Discussion

Photolysis and Sigmatropic Reactions in Different Solvents. Irradiation of **1** in different solvents (cf. Experimental) at room temperature resulted in the formation of two furocoumarins (R_f 0.28 and 0.36) in all the tried solvents, but with different yields (Table 1). IR spectrum of the first product, R_f 0.28, $C_{11}H_6O_4$, M^+ 202, showed bands at 1720 and 3340 cm^{-1} characteristics for δ-lactone and associated OH groups (phenolic, from iron(III) chloride test) respectively. It was thought to be xanthotoxol (**2**) from MS (Chart 1). The ^1H NMR of its acetate derivative in $CDCl_3$ solution showed two singlet peaks at δ 2.50 and 7.53 for -OCOC<u>H</u>$_3$ and aromatic proton at C-5 respectively, two doublets at δ 6.35 and 7.76 (J=10 Hz) for two α-pyrone protons, and other two furan protons. The mass spectrum showed molecular ion at m/z 202, and only one mode of fragmentation (Chart 1). Final confirmation was obtained by mixed melting point with an authentic sample (mp and mixed mp 240 °C) and also by its transformation to xanthotoxin, a natural furocoumarin, mp and mixed mp 145 °C (cf. Experimental).

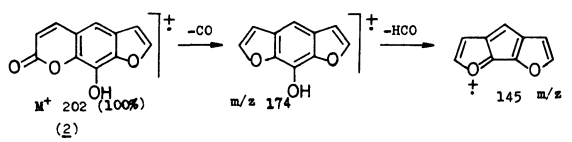


Chart 1.

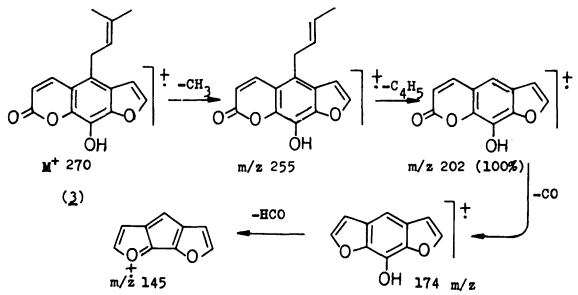


Chart 2.

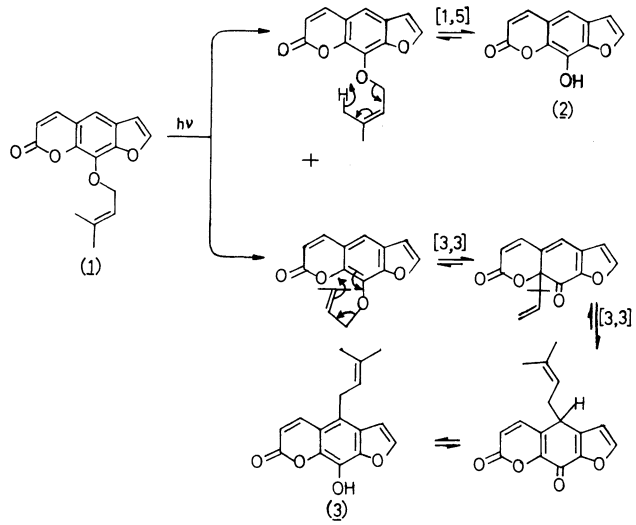
IR spectrum of the second product, R_f 0.36, $C_{16}H_{14}O_4$, M^+ 270, mp 228 °C indicated the presence of a hydroxyl group and δ-lactone. It was thought to be *allo*-imperatorin (**3**) from its fragmentation behavior (Chart 2) in the mass spectrum.

The ^1H NMR spectrum of its acetate derivative supported the above identification as *allo*-imperatorin where it displayed a singlet at δ 2.5 for -OCOC<u>H</u>$_3$. The isoprenyl group attached at C-5 showed signals at δ 4.15 and 4.29 due to C<u>H</u>$_2$, H-9 (both doublet of doublets J=12.5) 4.22 due to H-10 (doublet of doublets J=5), and 2.2 singlet for 2C<u>H</u>$_3$. Final confirmation was achieved by preparing *allo*-imperatorin followed by mixed mp where no depression occurred. (cf. Experimental).

Table 1. Yields with Different Solvents

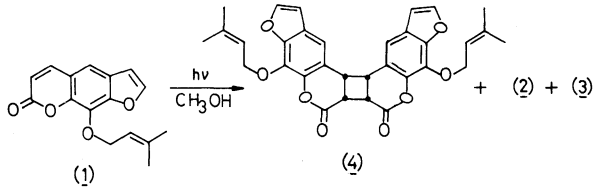
Solvent	Xanthotoxol (**2**)	*allo*-Imperatorin (**3**)	Imperatorin dimer (**4**)
	mg	mg	mg
Benzene	25	16	—
1,4-Dioxane	18	19	—
Tetrahydrofuran	13	16	—
Ethyl acetate	4	4	—
Acetone	26	25	—
Acetonitrile	15	5	—
Dimethyl sulfoxide	46	17	—
Acetic acid	246	23	—
Methanol	73	22	11

The mechanism of photolysis of imperatorin (**1**) to produce these products **2** and **3** may be illustrated as in Scheme 1 where xanthotoxol (**2**) is produced via antrafacial [1,5] hydrogen shift, whereas, *allo*-imperatorin (**3**) is most likely formed through aromatic Claisen rearrangement, where the isoprenyl group underwent one inversion to give an ortho-isomer and another to give the para-isomer via [3,3] sigmatropic rearrangement.



Scheme 1.

Photodimerization Reaction. Imperatorin (**1**) was irradiated in methanolic solution where the dimeric product head-to-head syn (**4**) was formed via [2+2] photo-cycloaddition in addition to xanthotoxol (**2**) and *allo*-imperatorin (**3**).



Formulation of the photo-dimer (**4**) was based on analytical and spectral data. IR spectrum showed a band at 1750 cm^{-1} characteristic of δ-lactone. The mass spectrum showed the expected molecular ion at

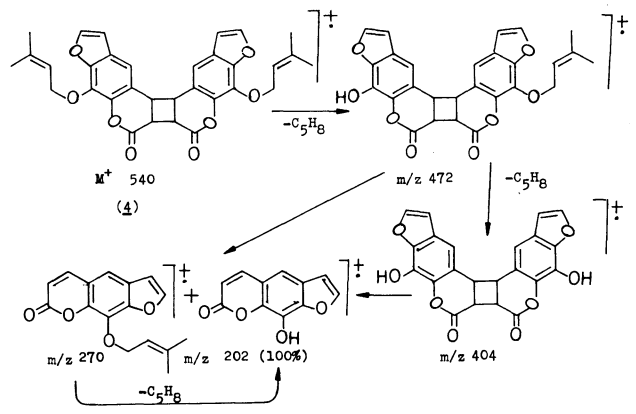
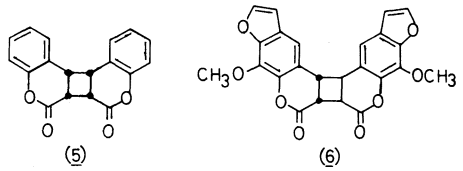


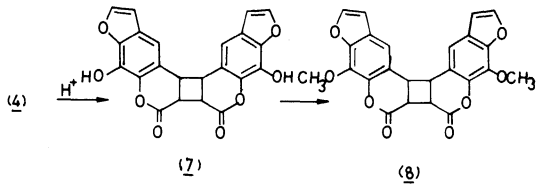
Chart 3.

m/z 540, and only one mode of fragmentation (Chart 3).

This result is in agreement with the work of Anet[8] who reported that photo-irradiation of coumarin in ethanol solution produced a dimer **5**, having the head-to-head syn structure. In contrast, Kruch and Farid[7] found that irradiation of xanthotoxin in non-polar solvents led to formation of the dimer **6**, having the head-to-head anti structure.



The weight loss due to the acid hydrolysis of the dimer **4** afforded other support to the structure, where it was found that the calculated value (12.6 mg) is in good agreement with the observed value (12.1 mg). The acid hydrolysis of the dimer **4** gave a gray dimer **7**, containing hydroxyl groups as shown from IR spectrum (3500 cm^{-1}). The dimer **7** was methylated with methyl iodide in the presence of anhydrous potassium carbonate to give the dimer **8**. The IR spectrum showed absence of any OH group.



The difference in melting points and solubilities of xanthotoxin dimer (**8**) and that of Krauch and Farid[7] showed that the configuration of the two dimers is different, i.e. the dimer is not head-to-head anti **8**. The abnormally high melting point of the dimer **8** will not be surprising when we know that the melting point of the head-to-head syn coumarin dimer **5** is 100 °C higher than the head-to-head anti dimer.[11]

Experimental

Imperatorin was supplied by Memphis Chemical Co., Cairo, Egypt. All melting points (°C) are uncorrected and were taken in a Fischer electric melting point apparatus. Infrared spectra were recorded on a Unicam SP 2000 infrared Spectrophotometer using KBr pellet technique. ^1H NMR spectra were obtained in $CDCl_3$ on a Brucker 400 MHz apparatus. Mass spectra were measured on a Varian Mat 711, direct inlet at 70 eV. The photolysis apparatus used is a 500 W medium pressure wide spectrum mercury lamp (Hanovia TQ 718) supported in a water cooled quartz tube.

Irradiation of Imperatorin (1): A solution of imperatorin (**1**) (675 mg, 0.0025 mole) in different solvents (10 ml) (except methanol) (Table 1), was irradiated in the corning glass test tubes which were degassed, sealed in vacuo. The irradiation was carried out without filter at 25—30 °C, for 100 h. The tubes were opened and the solution was evaporated to dryness to give gummy material, which was further separated by

TLC (silica gel, benzene-ethyl acetate 9:1) to give xanthotoxol (**2**) (R_f 0.28, mp 240 °C) and *allo*-imperatorin (**3**) (R_f 0.36, mp 228 °C) (cf. Table 1).

Xanthotoxol (2): IR 3340 (OH), 3000 (CH, CH_2 str.), 1720 (δ-lactone), and 1600 (C=C) cm^{-1}. MS *m/z* (rel intensity) 202 (M^+, 100) ($C_{11}H_6O_4$), 174 (48, M-CO), 145 (10, $M-C_2HO_2$), 118 (10), 90 (16), 75 (22), and 61 (52).

***allo*-Imperatorin (3)** IR: 3330 (OH), 3000 (CH_2, CH_3 str.), 1720 (δ-lactone), and 1600 (C=C) cm^{-1}. MS *m/z* (rel intensity) 270 (M^+, 0.6, $C_{16}H_{14}O_4$), 255 (0.8, $M-CH_3$), 202 (100, $M-C_5H_8$), 174 (48, $M-C_6H_8O$), 144 (5, $M-C_7H_9O_2$), 118 (4), 90 (18), 75 (8), and 61 (52).

Acetylation of Xanthotoxol (2): A solution of xanthotoxol (**2**) (0.5 g) in acetic anhydride (10 ml) was refluxed for 2 h. The reaction mixture was diluted with water (10 ml). The solvent was evaporated under reduced pressure to dryness and the residue was washed with toluene, then petroleum ether 40—60 °C, to give a solid material which was recrystallized from ethanol to give *O*-acetylxanthotoxol as pale yellow crystals; mp 175 °C (lit,[12] 175 °C). IR 1750 ($OCOCH_3$), 1720 (δ-lactone), 1630 and 1600 (C=C) cm^{-1}. ^1H NMR δ=2.5 (s, 3H, $OCOCH_3$), 6.35 (d, 1H, H-3, *J*=10 Hz), 7.77 (d, 1H, H-4, *J*=10 Hz), 7.53 (s, 1H, H-5), 6.83 (d, 1H, H-6, *J*=2.5 Hz), and 7.67 (d, 1H, H-7, *J*=2.5 Hz).

Methylation of Xanthotoxol (2): A solution of xanthotoxol (**2**) (0.5 g), methyl iodide (1 ml) in acetone (10 ml) in the presence of potassium carbonate (2 g) as base catalyst was refluxed on water bath for 6 h. Potassium iodide was separated and filtered off. The acetone solution was evaporated under reduced pressure to give xanthotoxin which was recrystallized from ethanol to give colourless crystals; mp 145 °C (lit,[13] 146 °C). IR 3120 (CH_2, CH_3 str.), 1730 (δ-lactone), and 1600 (C=C) cm^{-1}. ^1H NMR δ=4.3 (s, 3H, OCH_3), 6.37 (d, 1H, H-3, *J*=10 Hz), 7.77 (d, 1H, H-4, *J*=10 Hz), 7.34 (s, 1H, H-5), 6.8 (d, 1H, H-6, *J*=2.5 Hz), and 7.69 (d, 1H, H-7, *J*=2.5 Hz). MS *m/z* (rel intensity) 216 (M^+, 100, $C_{12}H_8O_4$), 201 (23, $M-CH_3$), 173 (32, $M-C_2H_3O$), 145 (10, $M-C_3H_3O_2$), 117 (2), 89 (12) and 63 (10).

Acetylation of *allo*-Imperatorin (3): *allo*-Imperatorin (**3**) (0.5 g) was acetylated according to method used for xanthotoxol acetate to give *allo*-imperatorin acetate, colourless crystals, mp 126 °C. (lit,[15] 108 °C) IR 1750 ($OCOCH_3$), 1720 (δ-lactone), 1630, and 1600 (C=C) cm^{-1}. ^1H NMR δ=2.5 (s, 3H, $OCOCH_3$), 6.38 (d, 1H, H-3, *J*=10 Hz), 7.77 (d, 1H, H-4, *J*=10 Hz), 6.83 (d, 1H, H-6, *J*=2.5 Hz), 7.79 (d, 1H, H-7, *J*=2.5 Hz), 4.15 (d, 1H, CH_2, H-9, *J*=12.5 Hz), 4.29 (d, 1H, CH_2, H-9, *J*=12.5 Hz), 4.22 (dd, 1H, H-10, *J*=5 Hz), and 2.2 (s, 6H, $2CH_3$, H-12 and H-13).

Rearrangement of Imperatorin (1) to *allo*-Imperatorin (3): Imperatorin (**1**) (1 g) was fused at 200 °C, for 25 min. under reduced pressure. The melted product changes to solid. The solid product was washed with CH_2Cl_2, and then recrystallized from ethanol to give the colourless crystals of *allo*-imperatorin (**3**); mp 228 °C (lit,[14,15] 228 °C).

Irradiation of Imperatorin (1) in Methanol Solution: Irradiation of imperatorin (**1**) (675 mg, 0.0025 mol) in methanol for 100 h gave a solid material which was washed with hot methanol to give 11 mg of the dimeric product (**4**) (mp above 360 °C). Evaporation of the filtrate afforded a mixture of two compounds. Further separation with TLC (silica gel, benzene-ethyl acetate 9:1) afforded xanthotoxol (**2**) (R_f 0.28, mp 240 °C) and *allo*-imperatorin (**3**) (R_f 0.36, mp 228 °C).

Imperatorin Dimer (4): IR: 3000 (CH_2, CH_3 str.), 1750 (δ-lactone), and 1610 (C=C) cm^{-1}. MS *m/z* (rel intensity) 540 (M^+, 3, $C_{32}H_{24}O_8$), 472 (6, $M-C_5H_8$), 404 (0.8, $M-C_{10}H_{16}$), 270 (20, ½M), 202 (100, ½M$-C_5H_8$), 174 (20, ½M$-C_6H_8O$), 149 (20), 89 (10), and 69 (20).

Acid Hydrolysis of Imperatorin Dimer (4) into Xanthotoxol Dimer (7); A mixture of imperatorin dimer (**4**) (0.05 g), ethanol (10 ml) and a mixture of concentrated sulfuric acid and ethanol (1.5 ml: 12.5 ml), was refluxed with stirring for 6 h. The initial white precipitate was converted into a gray precipitate (0.0379 g) which was filtered off and washed with ethanol mp>360 °C. IR (Nujol) 3500 (OH), 1750 (α-pyrone) and 1610 (C=C) cm^{-1}.

Methylation of Xanthotoxol Dimer (7) into Xanthotoxin Dimer (8): A mixture of xanthotoxol dimer (**7**) (0.026 g), methyl iodide (1 ml), anhydrous potassium carbonate (2 g) and acetone (10 ml) was refluxed on a water bath for 6 h. The inorganic salt with the insoluble faint brown product were filtered off, washed with diluted hydrochloric acid, distilled water then methanol to give the methylated dimer (**8**), mp>360 °C. IR(Nujole) 3000 (CH_3 str.), 1730 (α-pyrone), and 1600 (C=C) cm^{-1}.

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