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Photocycloaddition of khellin and oleic acid methyl ester

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ABSTRACT

In the present study, photoreaction of khellin with oleic acid methyl ester (OAME) was investigated to seek information parallel to the photobiologically relevant 8-MOP-fatty acid Photocycloaddition. Khellin and oleic acid methyl ester were dissolved in methanol and the solution was deaerated by bubbling with nitrogen gas for about 1 hr and irradiated for 72 hr in a photochemical reactor. Progress of the reaction was monitored by thin layer chromatography (chloroform-methanol, 98:2). At the end of the reaction formation of a number of products was indicated on TLC. The two major photoproducts were isolated by eluting with dichloromethane-ethyl ether (1:1, v/v) on a silica column. The products were identified as 3 and 4 from their spectral properties.

Key words: Khellin, Oleic acid methyl ester, Furochromones, Photocycloaddition.

INTRODUCTION

The naturally occurring furochromones khellin has received considerable attention largely because of its vasodilatory properties and of its ability to induce skin pigmentation upon ultraviolet light treatment of patient suffering from vitiligo [1]. Unlike psoralens, khellin does not photo induce cross-links in DNA in vitro or Chinese hamster cells in vivo. This behaviour was associated to explain the low photogenotoxicity in yeast and the lack of phototoxic erythemal response when treating vitiligo with khellin [2]. It's very low DNA-photo binding, and consequently poor antiproliferative and antipsoriasic activity, was attributed to the hindering effect of the two bulky methoxy groups which prevent interaction in to the double helix. The furan side C4-cycloadduct between khellin and thymine was in fact produced by irradiation in a frozen state [3] when steric effect should be less important. A comparison of photo physical and photochemical properties of khellin with those of 8-methoxypsoralen (8-MOP) indicated that quantum yields of fluorescence and triplet formation decreases as solvent polarity increases, which is opposite to that of 8-MOP. Moreover the photocycloadditivity of khellin to olefins is

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much lower than that of 8-MOP. Khellin<>dimethylfumarate 4’, 5’-monoadduct (KDF) did not form adducts with various olefins and thus it was thought that 2,3- double bond of chromone moiety in khellin is hardly reactive in contrast with 3,4-double bond of coumarin moiety in 8-MOP. Thus different behaviour is shown by the γ- pyrone ring of khellin with respect to the α-pyrone ring of furocoumarins: when the later compounds are irradiated with UV-A in solution, they mainly undergo C4-cyclodimerization at that level [4]. When irradiation is carried out in the presence of suitable substrate (e.g.pyrimidine base, unsaturated fatty acids) the pyrone ring is still involved. No evidence for such behavior was found with khellin, probably because the 6, 7-olefinic double bond not conjugated with the benzofuran moiety, and therefore should not be involved in the excited states of the molecule.

In the present study, photoreaction of khellin with oleic acid methyl ester (OAME) was investigated to give further insight into the reactive excited state and selectivity in photoaddition reaction of khellin and also to seek information parallel to the photobiologically relevant 8-MOP-fatty acid photo cycloaddition [5].

MATERIALS AND METHODS

Apparatus and Chemicals

All chemicals used were of analytical grade. Khellin was purchased from Sigma Chemical Company and recrystallized from methanol. UV spectra were recorded on a Shimadzu 160 A instrument. IR spectra were recorded as KBr discs on a Perkin Elmer model spectrum RX1. ^{1}H –NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance DRX-300 spectrometer using TMS as internal standard and $(CD_3)_2CO$ as solvent. High-resolution mass spectra were determined with a VG-ZAB-BEQ9 spectrometer at 70 eV ionization voltage. Merck silica gel 60 F_{254} plates were used for analytical TLC ; column choromatography was performed on Merck silica gel 60 (70- 230 mesh).

Photoirradiation procedure

Khelin (100 mg , 0.385) and oleic acid methyl ester (516 mg, 1.93 mM) (molar ratio 1:5) were dissolved in methanol and the solution was deaerated by bubbling with nitrogen gas for about 1 hr and irradiated for 72 hr in a Rayonet photochemical reactor (The Southern New England Ultraviolet Co; Model RPR-208 equipped with four RUL-350 nm fluorescence lamps) for the complete conversion of the reactants. Progress of the reaction was monitored by thin layer chromatography (chloroform-methanol,98:2).At the end of reaction the formation of a number of products was indicated on TLC .The two major photoproducts were isolated by eluting with dichloromethane-ethyl ether(1:1,v/v) on a silica column. The products were identified as **3** and **4** from their spectral properties.

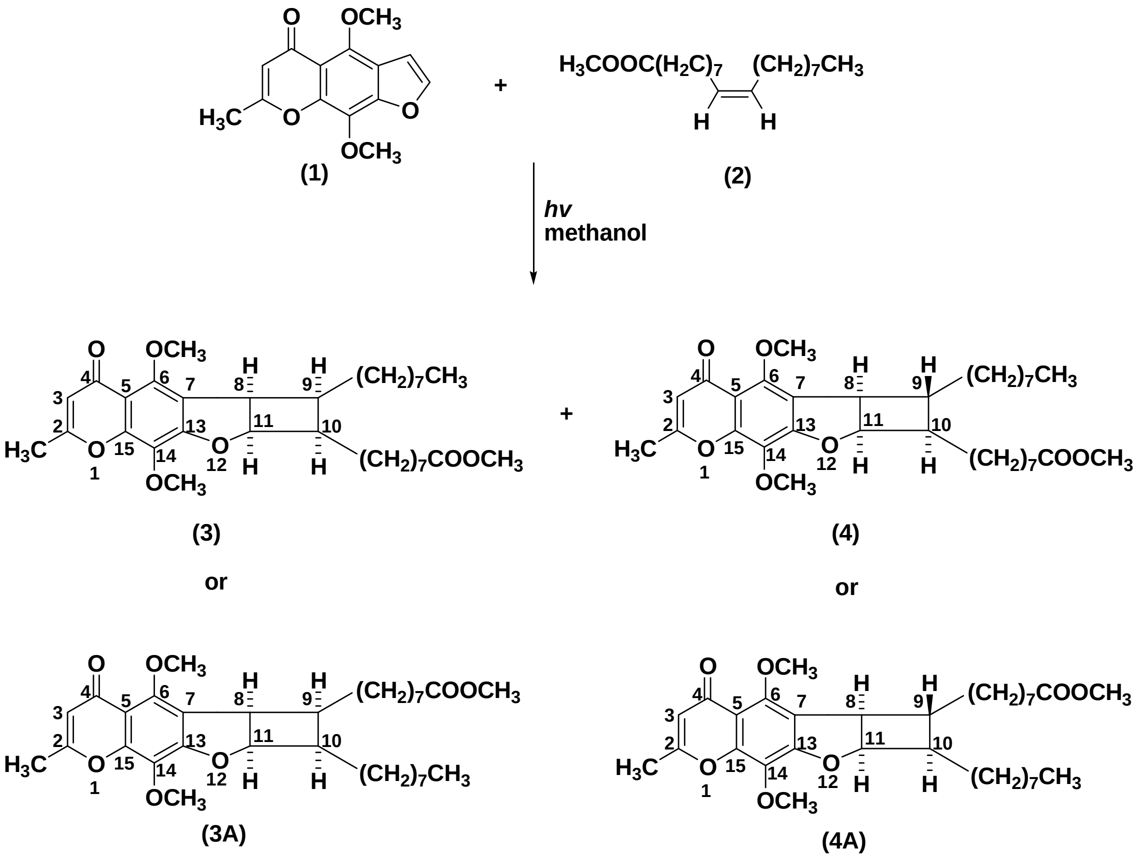
Compound **3:** Yield: 26 mg; mp 178° C; UV λ_{max} (MeOH) 251, 348 sh. nm; IR (KBr): 830, 1655, 1741, 1240, 1205, 2962; HRMS calcd. for $C_{33}H_{48}O_7$ 556.3400 found 556.3410; ^{1}H-NMR ($(CD_3)_2CO$): δ 6.12 (s, 1H, H-3), 4.51 (dd, 1H, J=6.5, 6.1 Hz, H-11), 3.83 (s, 3H, $COOCH_3$), 3.75 (s, 3H, $-OCH_3$), 3.69 (dd, J=6.5, 6.2 Hz, 1H, H-8), 3.61 (s, 3H, $-OCH_3$), 2.46 (m, 1H, H-10), 2.35 (m, 1H, H-9), 2.25-1.25 (m, $(CH_2)_n$-OAME, CH_3-pyrone), 0.98 (t, 3H, CH_3); ^{13}C-NMR $(CD_3)_2CO$): 180.2 (C-4), 175.1 ($COOCH_3$), 162.7 (C-2), 159.4 (C-6), 153.2 (C-13), 148.2 (C-15), 134.2 (C-14), 119.7 (C-7), 111.8 (C-3), 103.5 (C-5), 73.9 (C-11), 56.4 (C-10), 50.2

(COOCH$_3$), 40.5 (OCH$_3$), 38.3 (C-8), 37.2 (OCH$_3$), 33.1 (C-9), 32.5-25.1 ((CH$_2$)$_n$-OAME), 21.7 (CH$_3$), 17.1 (CH$_3$); MS m/z: 556, 525, 541, 494, 485, 392, 260, 232, 231.

Compound **4**: Yield: 21 mg; mp 162° C; UV λ_{max} (MeOH) 251, 348 sh. nm; IR (KBr): 830, 1656, 1745, 1238, 1205, 2960; HRMS calcd. for $C_{33}H_{48}O_7$ 556.3400 found 556.3395; ^{1}H-NMR ((CD$_3$)$_2$CO): δ 6.11 (s, 1H, H-3), 4.51 (dd, 1H, J=6.5, 6.1 Hz, H-11), 3.82 (s, 3H, COOCH$_3$), 3.76 (s, 3H, -OCH$_3$), 3.69 (dd, J=6.5, 2.1 Hz, 1H, H-8), 3.61 (s, 3H, -OCH$_3$), 2.46 (m, 1H, H-10), 2.35 (m, 1H, H-9), 2.25-1.25 (m, (CH$_2$)$_n$-OAME, CH$_3$-pyrone), 0.97 (t, 3H, CH$_3$); ^{13}C-NMR (CD$_3$)$_2$CO): 181.2 (C-4), 175.7 (COOCH$_3$), 162.1 (C-2), 159.6 (C-6), 153.9 (C-13), 147.2 (C-15), 134.5 (C-14), 119.4 (C-7), 112.2 (C-3), 102.9 (C-5), 74.1 (C-11), 56.6 (C-10), 51.2 (COOCH$_3$), 40.7 (OCH$_3$), 39.3 (C-8), 37.7 (OCH$_3$), 34.5 (C-9), 32.5-25.1 ((CH$_2$)$_n$-OAME), 21.7 (CH$_3$), 17.5 (CH$_3$); MS m/z: 556, 525, 541, 494, 485, 392, 260, 232, 231.

RESULTS AND DISCUSSION

Irradiation of a deareated, nitrogen saturated, methanolic solution of khellin **(1)** and oleic acid methyl ester **(2, OAME)** with a light of 350 nm for 72 hr, and purification of the crude product by silica gel column chromatography afforded two major products **3** and **4** in isolable yields (scheme.1)



Scheme-1

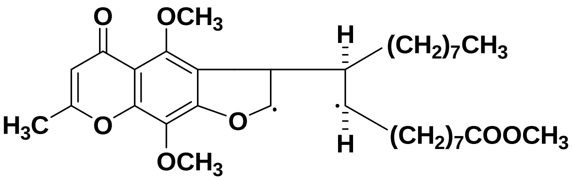
Photocycloaddition of Khellin and Oleic acid methyl ester

The structures of the photoproducts were characterized by the spectroscopic methods as described below. The UV absorption spectra of photoproducts, λ_{max} (MeOH) 251, 348 Sh. nm are very similar to each other and resemble to that of 4', 5'-dihydrokhellin, indicating that 4',5'-double bond of khellin is saturated in the photoproducts. IR spectra also indicated the saturation of 4', 5'-double bond on photoproduct formation. The olefinic C-H stretching bands of furan ring o khellin at 3060 and 3100cm^{-1} disappear in the photoproduct and a characteristic cyclobutane ring deformation band appeared at 830cm^{-1}. Moreover, the carbonyl stretching band of khellin at 1655 cm^{-1} was intact; indicating that pyrone double bond of khellin was not affected on photo reaction. Mass spectra of the photoproducts showed molecular ion peaks of 1:1 adduct of khellin and OAME at m/z 556 and its fragments, corresponding to the adducts. These data suggested that the photoadduct is composed of khellin and OAME (1:1), formed by [2π+2π] cycloaddition of 4, 5-fury bond of khellin to C=C double bond of OAME. Both the adducts gave similar ^{1}H-NMR spectra with various small shift differences. The spectra showed that there is a upfield shift of the olefinic proton in the parent khellin and OAME: C-4'and C-5' olefinic proton at δ 6.66 and 7.52 shifted to δ 3.69 and 4.51;and 9,10 olefinic protons at δ5.5 shifted to δ 2.46 and 2.35 ppm, indicating that the adducts are formed on furan side of khellin. Assignment of the stereochemical configuration on the cyclobutane ring of the photoproducts was done by considering the observed values of coupling constants .Generally J_{cis} is greater than J_{trans} in cyclobutane systems [6]. The coupling constant $J_{8,9}$ of the doublet in the photoproduct **3** is 6.1Hz which is greater than the corresponding coupling constant $J_{8,9}$ 2.1 Hz in the photoproduct **4** . Thus **3** and **4** were assigned *cis –cis* and *cis – trans* configuration, respectively. The photoadducts could not be decided as head to head (HH) or head to tail (HT) from the present data , because the position of fatty acid side chains on the cyclobutane ring only have subtle , uninterpretable effects on the ^{1}H-NMR spectra . Hence, alternative structures **3A** and **4 A** for **3** and **4** could not be decided. HH is defined as shown in structure **3** and **4** in which 'O' of the furan and fatty acid ester side chain are bonded to adjacent corners of the cyclobutane. In HT stereochemistry these are bonded to diagonal corners as in **3A** and **4A**. *cis* and *trans* refer to position of 'H' relative to plane of cyclobutane.

The probable mechanism for the formation of **3** and **4** could be through the intermediacy of the 1, 4-diradicals (**5** or **6**), which arises from triplet excited state of the khellin and ground state OAME via an exciplex (scheme2). Starting with OAME, which is *cis* the 1, 4-diradical may proceed to ring closure, forming cyclobutane adducts with *cis*- stereochemistry. Alternatively, twisting around the 9, 10-bond of OAME in the diradical intermediate before ring closure gives cyclobutane adduct with *trans* configuration.

Mechanistic pathway of Photocycloaddition of Khellin and Oleic acid methyl ester

The photocycloadducts are formed regioselectively on furanyl 4', 5'-double bond of khellin probably due to the localization of excitation energy on the furanyl 4', 5'-double bond in the reactive excited state. Geometric and steric considerations are important in determining the orientation of the excited triplet and khellin and alkenes ground state, which in turn determines the stereochemical structures of the initial bond formed to make the diradical. Hence, the lack of formation of the other isomers in isolable yields may be due to the geometric requirements of exciplex formation. Oleic acid methyl ester is found in abundance in lipids of many living organisms; hence, the present study may be of biological significance. Further extensive research will be undertaken to explore a detailed aspect of the khellin-fatty acid photochemistry.



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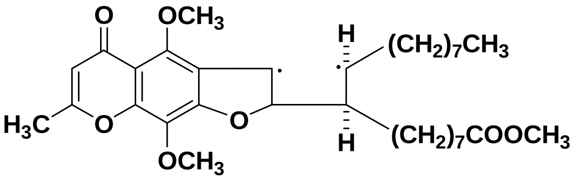

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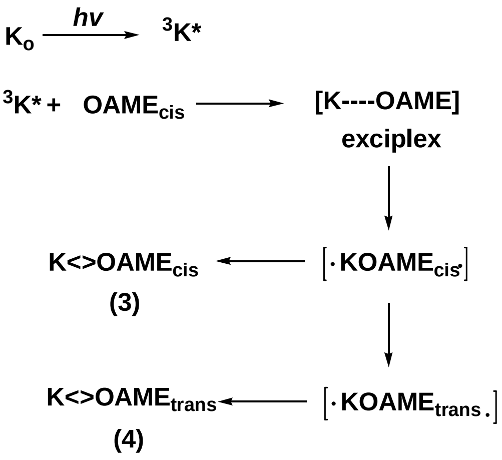

scheme-2

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