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Photochemical Reaction of Furocoumarin (Psoralen). The Reactive Site in Its Photoexcited State

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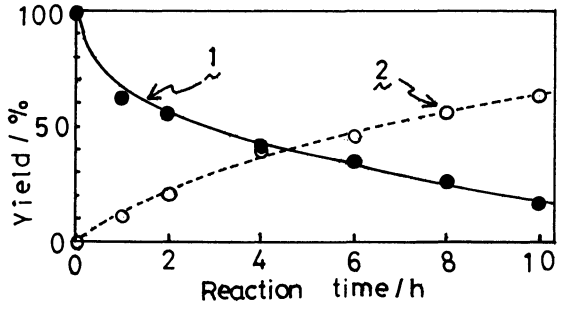
The 3,4-double bond of photoexcited furocoumarin shows a higher reactivity than the 4',5'-double bond toward simple olefins, leading to the formation of cyclobutane derivatives.

Furocoumarins (psoralens) have been used for treatment of psoriasis and/or vitiligo under the exposure to the ultraviolet light. Their biological activity is correlated to the photochemical reactivity of furocoumarin with DNA, resulting in the modification of DNA.[2)] The modification of DNA by furocoumarins is believed to involve three steps; (1)intercalation of furocoumarin between adjacent base pairs including thymine in DNA, (2)formation of monoadduct of furocoumarin with thymine residue of DNA by the photochemical reaction, (3)subsequent photochemical reaction of the monoadduct with another thymine residue, resulting in the formation of di-adduct, thus, the cross-linking of DNA by furocoumarin. Judging from the so far reported results, the 4',5'-double bond, rather than the 3,4-double bond, of the photoexcited furocoumarin in DNA is more reactive with the thymine residue forming a cyclobutane ring.[3)] However, the similar reactivity is not always observed in the photochemical reaction of furocoumarin with thymine derivatives free from DNA.[4)] These results are hardly explained on a reasonable basis.

In order to get a better understanding of the biological activity, the photochemical reactivity of furocoumarin with a variety of olefins is systematically studied here.

When a benzene solution(80.0 mL) of furocoumarin(ca. 0.3 mmol) is irradiated in the presence of 2,3-dimethyl-2-butene(ca. 1.8 mmol), a smooth reaction undergoes as shown in Fig. 1. After the complete consumption of furocoumarin, white crystals as a reaction product were isolated in 77% yield by purifying the reaction mixture with chromatography on silica gel; mp 141.0-142.0 °C. All the spectroscopic data satisfy the structure 2, which is formed by [2+2] cycloaddition reaction of the 3,4-double bond of the photoexcited furocoumarin 1 with 2,3-dimethyl-2-butene.[5)]



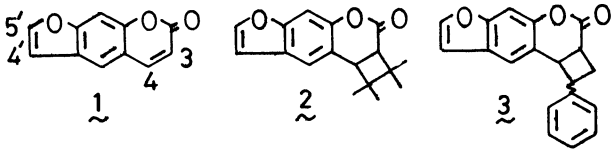


Fig. 1. Photochemical reaction of furocoumarin(4.10×10^{-3}M) with 2,3-dimethyl-2-butene(2.28×10^{-2}M).

The similar cyclobutane-adducts are isolated, starting with a variety of olefins. They include mono-, di-, tri-, and tetrasubstituted ethylenes;1-hexene (the yield of the corresponding cyclobutane:47%), 1-heptene(24%), 1-octene(16%), styrene(29%), *p*-methylstyrene(34%), 2-methyl-1-butene(47%), 2-ethyl-1-butene(31%), methylenecyclopentane(71%), cyclohexene(37%), cyclooctene(60%), *trans*-3-hexene(47%), 2-methyl-2-butene(74%), and 2-methyl-2-pentene(53%). All the cyclobutane derivatives here isolated are formed through the reaction of 3,4-double bond of 1.[6] The unsymmetrically substituted ethylene such as styrene yields one isomer as the major product. Based on the analysis of the NMR spectrum, the regiochemistry of the addition product could be deduced as shown in 3.[7]

As above described, the 3,4-double bond of photoexcited furocoumarin shows a higher reactivity than the 4',5'-double bond toward a variety of olefins in solution. Thus, the present result shows a remarkable contrast with the photochemical reactivity of furocoumarin in DNA, where the 4',5'-double bond reacts first with an unsaturated compound. The difference in reactivity in different environments would be explained by assuming an important contribution of non-bonded interaction of furocoumarin with DNA preceding the photochemical events in the biological environment.

References

1)Part of this work has been done at the Pennsylvania State University-The Schuylkill Campus and has been presented at the 192nd ACS Meeting(Organic #267), Anaheim, CA, September, 1986.

2)For example, see C.D.Cimino, H.B.Gamper, S.T.Isaacs, and J.E.Hearst, Ann.Rev.Biochem., 54, 1151 (1985) and the references cited therein.

3)a)K.Straub, D.Kanne, J.E.Hearst, and H.Rapoport, J.Am.Chem.Soc., 103, 2347 (1981); b)D.Kanne, K.Straub, H.Rapoport, and J.E.Hearst, Biochem., 21, 861 (1982); c)D.Kanne, K.Straub, J.E.Hearst, and H.Rapoport, J.Am.Chem.Soc., 104, 6754 (1982); d)D.Kanne, H.Rapoport, and J.E.Hearst, J.Med.Chem., 27, 531 (1984).

4)a)B.S.Hahn, P.C.Joshi, L.S.Kan, and S.Y.Wang, Photobiochem. Photobiophys., 3, 113 (1981); b)E.J. Land, F.A.A.Rushton, R.L.Beddoes, J.M.Bruce, R.J.Cernik, S.C.Dawson, and O.S.Mills, J.Chem.Soc., Chem.Commun., 1982, 22; c)S.G.Shim and Y.Z.Kim, Photochem.Photobiol., 38, 265 (1983).

5)MS:m/e;270.1242(M^+ for $C_{17}H_{18}O_3$). IR(KBr):2960, 2940, 1740, 1460, 1300, 1220, 1180, 1160, 1130, 1090, 1030, 930, 860, 845, 770, 730 cm^{-1}. ^{1}H-NMR($CDCl_3$):δ;7.58ppm(1H, $H_{5'}$, d, J=2.2 Hz), 7.18(2H, H_5 and H_8, br s), 6.69(1H, $H_{4'}$, dd, J=2.2, 0.9 Hz), 3.49(1H, H_4, d, J=9.8 Hz), 3.19(1H, H_3, d, J=9.8 Hz), 1.29(3H, CH_3, s), 1.21(3H, CH_3, s), 1.02(3H, CH_3, s), 0.73(3H, CH_3, s). ^{13}C-NMR($CDCl_3$):δ;167.3 ppm, 154.0, 149.6, 145.7, 124.1, 120.4, 116.0, 106.0, 100.0, 45.0, 44.6, 42.9, 41.7, 26.4, 25.7, 21.2, 20.8. UV max($CHCl_3$):299 nm(logε:3.54), 288(3.58), 257(4.03), 241(3.97). The UV spectrum gives a clear indication whether the 3,4-double bond has reacted or the 4',5'-double bond has. If the 4',5'-double bond has been saturated, the intact 3,4-double bond as a part of conjugated system gives rise to a strong absorption around 330 nm. Cf., Refs. 3a, 3b, and 4a.

6)Indene, ethyl vinyl ether, and 1,4-dioxene were once reported to afford the similar cyclobutanes in the photochemical reaction with 8-methoxyfurocoumarin. C.Heinrich and S.Farid, Chem.Ber., 100, 1685 (1967).

7)Although the detailed analysis of the NMR spectrum would suggest the *trans*-stereochemistry of the cyclobutane ring, the X-ray analysis is planned to confirm the stereochemistry unequivocally.

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