Tetrahedron. Vol. 24, pp. 6615 to 6618. Pergamon Press 1968. Printed in Great Britain

PHOTOINDUCED REACTIONS—XXII

PHOTOOXIDATIVE CYCLIZATION OF 3-METHOXYFLAVONES[1]

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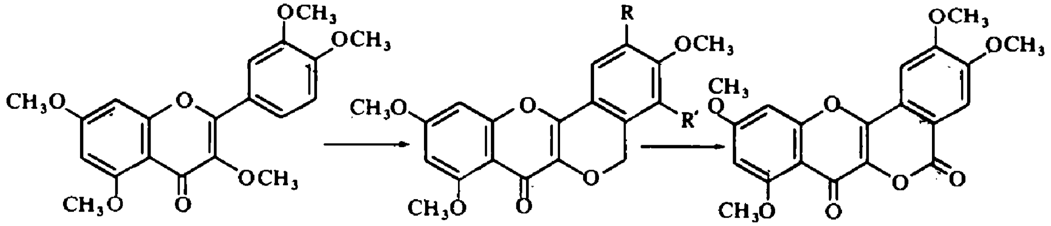
(*Received in Japan* 1 *May* 1968; *Received in the UK for publication* 9 *July* 1968)

Abstract—In the photooxidation of two 3-methoxyflavones with oxygen using a high-pressure mercury lamp (Pyrex), 3,7-dimethoxyflavone (VII) undergoes oxidative photocyclization to VIII, analogous to photomethylquercetins reported by Waiss *et al.*, and a further oxidized compound, 7'-methoxychromono-(3':2–3:4)isocoumarin (IX). 3-Methoxyflavone (X) yields chromono(3':2–3:4)isocoumarin (XII). On the other hand, 3-methoxy-5-hydroxyflavones are unreactive under these conditions.

IN connection with the photochemistry of flavonoids[2,3] Waiss *et al.*[2] observed that irradiation of quercetin pentamethyl ether (I) with UV light under nitrogen results in photocyclization to α- and β-photomethylquercetins (II and III), lumimethylquercetin, and methoxy-β-photomethylquercetin. They also showed that oxidation of β-photomethylquercetin (III) with permanganate affords a corresponding lactone IV. These results represent possible models for the biosynthesis of certain uncommon flavonoids, for example peltogynol[4] (V) and distemonanthin[5] (VI) which are supposed to be derived *in vivo* from a 3-methoxyflavonoid precursor. In the course of our investigation on the photosensitized oxygenation of 3-hydroxyflavones,[3] we have observed that other 3-methoxyflavones also undergo similar photocyclization. Although the transformation of I to II and III was carried out under nitrogen,[2] it is obvious that this reaction must involve a dehydrogenation step. Since we expected that this photocyclization may be facilitated by the presence of a hydrogen acceptor, irradiation was carried out under oxygen.

A soln of 3,7-dimethoxyflavone (VII) in pyridine was irradiated with a high-pressure mercury lamp (Pyrex filter) under bubbling oxygen. A TLC analysis revealed that the products consisted of at least seven compounds, from which two crystalline products $C_{17}H_{12}O_4$ (VIII, 4%) and $C_{17}H_{10}O_5$ (IX, 11%) could be isolated. Compound VIII exhibits signals at τ 1·86–3·25 (7H, multiplet), 4·82 (2H, singlet), and 6·15 (3H, singlet) in its NMR spectrum, which clearly indicates that one of the two OMe groups in VII is converted to a methylene group with equivalent protons and that one aromatic proton in VII disappears. From the NMR data and by considering the analogous transformation of I to II and III, structure VIII was assigned to this compound. The molecular formula of IX was confirmed by the appearance of a parent peak at *m/e* 294 in its mass spectrum. An IR band at 1738 cm^{-1} suggests the presence of a lactone group. Structure IX, which was assigned for this compound from the above data, was firmly established by its synthesis.[5]

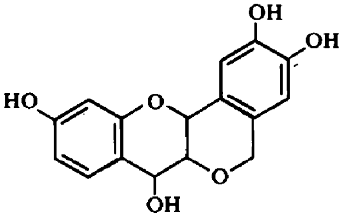
Photooxidation of 3-methoxyflavone (X) under similar conditions afforded salicylic acid (17%) and a lactonic compound $C_{16}H_8O_4$ (XII, 11%) which exhibits spectral



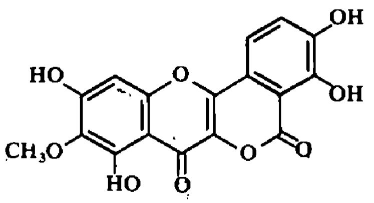
I

II: R = H, R' = OCH_3
III: R = OCH_3, R' = H

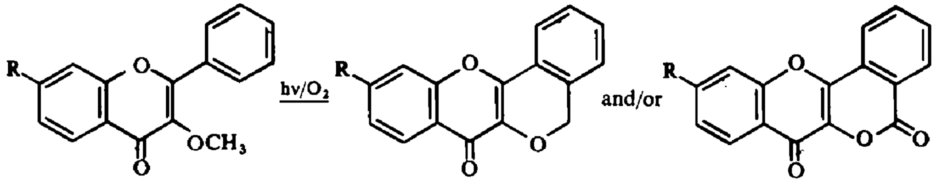
IV



V



VI



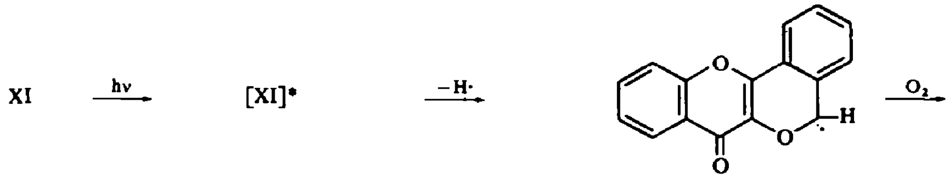
VII: R = OCH_3
X: R = H

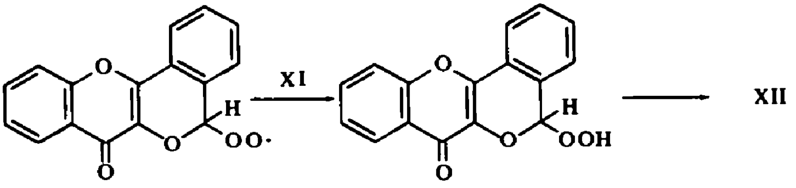
VIII: R = OCH_3
XI: R = H (not isolated)

IX: R = OCH_3
XII: R = H

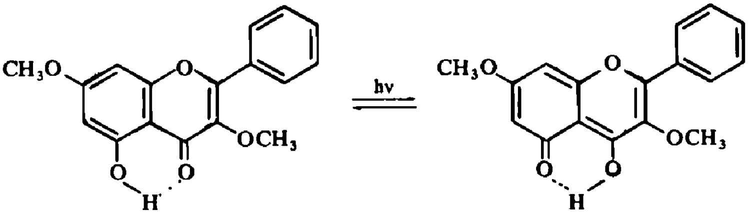
properties (Experimental) similar to those of IX. Structure XII was assigned for this compound.

Although in the photoxidation of X we were unable to isolate XI analogous to VIII, it is quite reasonable that the lactones IX and XI could be formed by photochemical autoxidation of VIII and IX, respectively. In fact, it has been reported[6] that isochromanes are photochemically autoxidized to form peroxides or their decomposition products, involving a radical chain mechanism. In our case, the formation of XII from XI can be achieved by sequences as follows.





It should be mentioned that 3-methoxyflavones bearing a 5-hydroxy group, e.g. 3,7-dimethoxy-5-hydroxyflavone (XIII) and quercetin 3,7,3',4'-tetramethyl ether, did not undergo similar photocyclization but were recovered unchanged. Considering their structural features, stability towards photooxidation could be due to hydrogen bonding of the 5-hydroxyl to the 4-carbonyl group. Such an interaction would cause an intramolecular hydrogen abstraction in the excited state to yield a tautomer, e.g. XIV. A similar hydrogen abstraction has been proposed for *o*-hydroxybenzophenone,[7] which is not photoreduced and is known to be a photostabilizer.



XIII XIV

EXPERIMENTAL

Materials. 3-Methoxyflavone,[8] 3,7-dimethoxyflavone,[9] and quercetin 5,7,3',4'-tetramethyl ether[10] were prepared by reported procedures.

3,7-*Dimethoxy-5-hydroxyflavone* (XIII). 3,5,7-Trimethoxyflavone[11] was partially demethylated according to the procedure by Dean *et al.*[12] To a soln of 3,5,7-trimethoxyflavone (1·4 g) in CH_2Cl_2 (150 ml) was added under ice-cooling BCl_3 (3 ml) cooled at −70°. After standing for 3 hr, the mixture was washed with NaOAcaq and then dried. Crystallization of the product gave 0·56 g (42%) of XIII, m.p. 144–146° (lit.[13] m.p. 145–146°).

Photooxidation

(a) 3,7-*Dimethoxyflavone* (VII). A soln of VII (1·20 g) in pyridine (120 ml) was irradiated using a 100 W high-pressure mercury lamp (Ushio, UM100) with a water-cooled Pyrex jacket under bubbling O_2 (8·5 hr). A mixture was evaporated under red press to give a residue which was shown by TLC to consist of 7 compounds. The residue was chromatographed on silica gel (30 g). Elution with C_6H_6 yielded crystals (0·42 g, 35% recovery), which were recrystallized from EtOH, m.p. 122–125°, identified as the starting material (by IR). Elution with C_6H_6–$CHCl_3$ (4:2 to 2:3) yielded VIII (32 mg, 4% based on the reacted VII) which was recrystallized from C_6H_6, m.p. 222–225°; ν_{max}^{KBr} 1600–1630 cm^{-1}; λ_{max}^{EtOH} 233 (log ε 4·23), 255 (4·13), 315–350 mμ (4·23). (Found: C, 72·87; H, 4·23. $C_{17}H_{14}O_4$ requires: C, 72·85; H, 4·32%).

Further elution with C_6H_6–$CHCl_3$ (1:4), then with $CHCl_3$ yielded IX (89 mg, 11%) which was recrystallized from EtOH–pyridine, m.p. 271–272°; ν_{max}^{KBr} 1738, 1640, 1613 cm^{-1}; λ_{max}^{EtOH} 235 (log ε 4·15), 252 (4·15), 321 (4·24), 332 (4·25), 347 mμ (4·09). (Found: C, 69·29; H, 3·49. $C_{17}H_{10}O_5$ requires: C, 69·39; H, 3·43%). The compound was identical with an authentic sample, m.p. 271–272°, which was synthesized by reported method[5] (by IR and TLC).

(b) 3-*Methoxyflavone* (X). A soln of X (1·2 g) in pyridine (130 ml) was irradiated as described above. The products were chromatographed on silica gel (30 g). Elution with C_6H_6–$CHCl_3$ (1:4) yielded XII (134 mg, 11%), which was recrystallized from $CHCl_3$, m.p. 294° (lit.[14] m.p. 287°); ν_{max}^{KBr} 1760 (weak), 1742, 1655, 1610 cm^{-1}; λ_{max}^{EtOH} 254·5 (log ε 4·16), 265·5 (3·85), 307 (4·03), 318 (4·02), 336 (3·99), 352 mμ (3·89); mass spectrum, *m/e* 264 (parent peak). (Found: C, 72·48; H, 3·34. $C_{16}H_8O_4$ requires: C, 72·73; H, 3·05%).

Elution with $CHCl_3$ yielded salicyclic acid (110 mg, 17%) which was purified by sublimation, m.p. 158–160°, and was identical with an authentic sample (by IR).

Photooxidation of X in the presence of rose bengal in a similar manner was carried out. In this case, the starting material was recovered (8%) and XII (14% based on the reacted X) was obtained.

(c) 3,7-*Dimethoxy-5-hydroxyflavone* (XIII). A soln of XIII (0·51 g) in pyridine (90 ml) was irradiated as described in (a). Evaporation of the reaction mixture gave pure XIII (by IR and TLC).

(d) *Quercetin* 3,7,3′,4′-*tetramethyl ether*. A soln of the tetramethylquercetin (716 mg) in pyridine (150 ml) was irradiated in the presence of rose bengal (20 mg) in a similar manner for 16·5 hr. TLC showed only a very weak spot other than that of the starting material which was recovered (88%) from the reaction mixture.

(e) *Quercetin pentamethyl ether* (I). A soln of I (1·20 g) in pyridine (300 ml) was irradiated in a similar manner to that described in (a) using 10% $CuSO_4$aq and window glass as filters. After 7 hr, TLC showed that the products consisted of at least 10 compounds. The products were not further investigated.

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