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OXIDATIVE CYCLIZATION OF MORUSIN WITH MANGANESE DIOXIDE

Taro Nomura,* Toshio Fukai, and Masa Katayanagi
Faculty of Pharmaceutical Science, Toho University,
542, Miyama-cho, Funabashi-shi, Chiba, 274, Japan

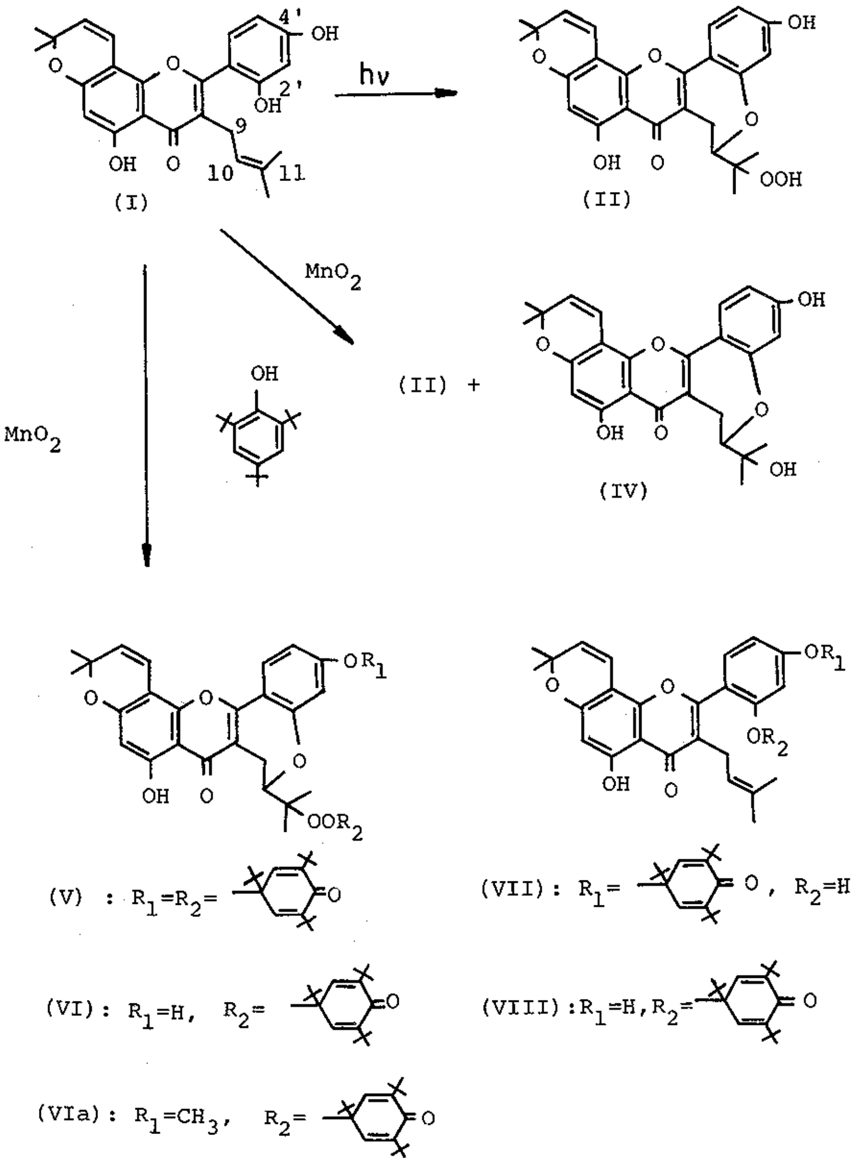
Oxidative cyclization of morusin (I) by using one-electron transfer oxidizing agents (manganese dioxide, silver oxide) afforded morusin hydroperoxide (II). A similar reaction was carried out in the presence of 2,4,6-tri-tert-butylphenol, a radical quencher, to give compounds (V-VIII) coupled with the 2,4,6-tri-tert-butylphenoxy radical. On the basis of above results, the possible mechanism of this oxidative cyclization was discussed. In addition, cyclomorusin (III) and XI were obtained from I with manganese dioxide in a nitrogen atmosphere.

In the previous communications,[1-3] the authors reported the structure determination of a series of prenylflavones including morusin (I), cyclomorusin (III), and compound A (IV), obtained from the root bark of Morus alba L. and described the photo-oxidative cyclization of I and other prenylflavones.

When a solution of I in $CHCl_3$ was irradiated with a high-pressure mercury lamp, morusin hydroperoxide (II) was obtained in ca 80% yield.$^{3)}$ In this connection, we attempted the oxidative cyclization of I with manganese dioxide and obtained II in 35% yield. In this communication, we report the reaction mechanism of the oxidative cyclization and the formation of III from I by manganese dioxide.

A solution of I (25 mg) in dry benzene (20 ml) containing manganese dioxide$^{4)}$ (400 mg) was allowed to stand at room temperature in the dark for 12 hr. The products were purified by preparative TLC to give II and IV in 35% and 2% yield, respectively. When silver oxide$^{4)}$ was used as an oxidizing agents instead of manganese dioxide, II was obtained in 85% yield. To elucidate the mechanism of this oxidative cyclization by the one-electron transfer oxidizing agents, we tried the reaction in the presence of a radical quencher, such as 2,4,6-tri-*tert*-butylphenol, as follows. A solution of I (200 mg) and 2,4,6-tri-*tert*-butylphenol (200 mg) in dry benzene (40 ml) containing manganese dioxide (2 g) was allowed to stand for 3 days in the dark. After the purification by preparative TLC, four crystalline substances, V (16%), VI (4%), VII (1%), and VIII (1.5%) were obtained. These four compounds gave characteristic color reactions for flavones and exhibited a green color with methanolic-$FeCl_3$. The structural elucidations of these four compounds were accomplished on the basis of the following spectral data.

Compound (V),$^{5)}$ $C_{61}H_{80}O_{10}$, mp 152-154°, pale yellow needles from


4'
OH
2'
OH
9
10
11
OH
O
O
(I)
hν
(II)
OOH
MnO2
MnO2
OH
(II) +
(IV)
OR1
OOR2
OR2
(V) : R1=R2=
(VI): R1=H, R2=
(VIa): R1=CH3, R2=
(VII): R1= , R2=H
(VIII): R1=H, R2=

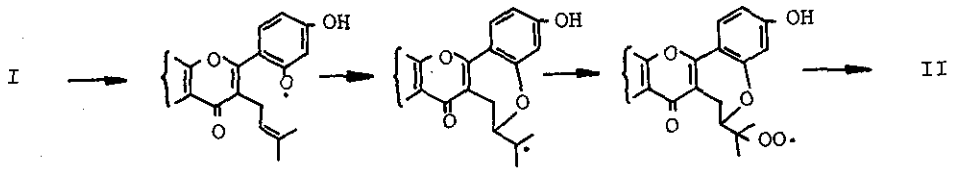
methanol, negative on Gibbs test, uv[λ_{Max}^{MeOH} nm(log ε): 238(4.69), 280(4.59), 334(4.07); $\lambda_{Max}^{MeOH+AlCl_3}$: 283.5(4.83), 358(4.61), 420(4.07); $\lambda_{Max}^{MeOH+NaOMe}$: 283.5(4.59), 380(sh 3.90)]. The uv spectra exhibited the absorption patterns similar to those of 4'-O-methyl ether of II.[3,6] The nmr spectrum(δ in $CDCl_3$) shows the protons of six tertiary butyl groups, such as 0.86(9H, s), 1.08(9H, s), 1.24(27H, s), 1.48(9H, s), and shows the AMX pattern, such as 2.28(1H, dd, J = 9 and 15 Hz, C_9 - H), 3.70(1H, dd, J = 2 and 15 Hz, C_9 - H), 4.28(1H, dd, J = 2 and 9 Hz, C_{10} - H). These results suggest that V can be regarded as a flavone[3,7,8] containing a dihydrooxepin ring and coupling with two tri- tert-butylphenoxy radicals. From these data, the structure of compound (V) is represented by the formula V.

Compound (VI),[5] $C_{43}H_{52}O_9$, mp 123-125°, pale yellow needles from methanol, negative on Gibbs test, ir [ν_{Max}^{Nujol} 3320 cm^{-1}], uv[λ_{Max}^{MeOH} nm(log ε): 236.5(4.64), 279(4.55), 335(4.25); $\lambda_{Max}^{MeOH+AlCl_3}$: 229(4.63), 282.5(4.56), 361(4.30), 417.5(4.04); $\lambda_{Max}^{MeOH+NaOMe}$: 267.5(4.62), 392.5(4.44)]. The uv spectra were similar to those of II.[3] The nmr spectrum(δ in $CDCl_3$) shows the protons of three tertiary butyl groups and the AMX pattern, such as 0.88(9H, s), 1.24 (9H, s), 1.48(9H, s), 2.46(1H, dd, J = 10 and 16 Hz, C_9 - H), 3.64(1H, dd, J = 2 and 16 Hz, C_9 - H), 4.32(1H, dd, J = 2 and 10 Hz, C_{10} - H), ms m/e: 436, 421,377.[3] By treating with ethereal CH_2N_2, VI forms a monomethyl ether (VIa), $C_{44}H_{54}O_9$ (M^+ 726), mp 155-160°, which shows a green coloration with methanolic-$FeCl_3$. From these data, compound (VI) is represented by the formula VI.

Compound (VII)[5], $C_{43}H_{52}O_7$, mp 185°, pale yellow prisms from methanol, positive on Gibbs test, ir[ν_{Max}^{Nujol} 3400 cm^{-1}], uv [λ_{Max}^{MeOH} nm(log ε): 242(4.68), 270(4.75), 300(sh 4.19), 350(sh 3.94); $\lambda_{Max}^{MeOH+AlCl_3}$: 278(4.75), 337(4.07), 415(3.90); $\lambda_{Max}^{MeOH+NaOMe}$ 245(4.72), 269(4.75), 362(4.07), nmr(δ in $CDCl_3$) [1.09(9H, s), 1.24(18H, s), 3.07(2H, br d, J = 6 Hz, C_9 - H), 5.08(1H, m, C_{10} - H)], ms m/e: 680(M^+), 625(M^+ - C_4H_7).[9] From these results, compound (VII) is represented by the formula VII.[10]

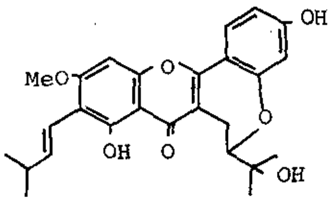
Compound (VIII)[5], $C_{43}H_{52}O_7$, mp 120-122°, pale yellow prisms from methanol, negative on Gibbs test, ir[ν_{Max}^{Nujol} 3400 cm^{-1}], uv [λ_{Max}^{MeOH} nm(log ε): 240(4.80), 269.5(4.83), 300(sh 4.17), 348(3.95); $\lambda_{Max}^{MeOH+AlCl_3}$: 242.5(4.74), 277.5(4.89), 300(sh 4.07), 410(sh 3.90); $\lambda_{Max}^{MeOH+NaOMe}$:269(4.85), 363(4.25)], nmr(δ in $CDCl_3$) [0.76(9H,s), 1.24(21H, s, protons of two tertiary butyl groups and C_{11} - CH_3), 3.15(2H, br d, J = 6 Hz, C_9 - H), 5.18(1H, m,C_{10} - H), ms m/e: 680(M^+), 625(M^+ - C_4H_7).[9] From these data, compound (VIII) is represented by the formula VIII.[10]

Considering the results of the oxidative cyclization carried out in the presence of radical quencher, the possible mechanism of the formation of II from I using one-electron transfer oxidizing agents in the dark was postulated as drawn in Scheme 1. Furthermore, the present results suggest the possible models for the biosynthesis of certain uncommon flavonoids, for example, chaplashin (IX)[7] and oxyisocyclointegrin (X)[8], which are supposed

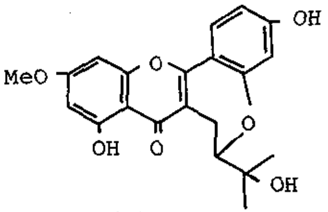


Scheme 1

to be derived *in vivo* from 3-prenyl-2'-hydroxyflavone precursor.



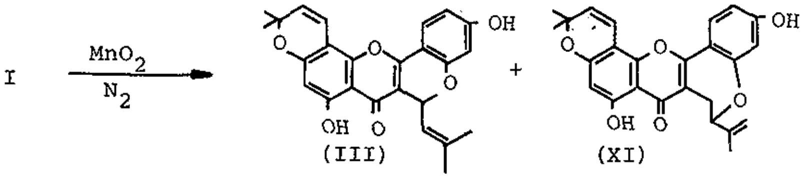
(IX)



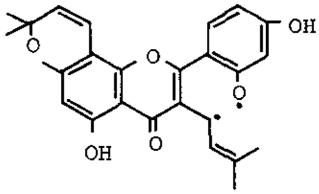
(X)

In addition, we tried this oxidative cyclization in a nitrogen atmosphere, as follows. The solution of I (90 mg) in dry benzene (60 ml) containing manganese dioxide4) (1.5 g) was allowed to stand in a nitrogen atmosphere in the dark for 5 days. The product was purified by preparative TLC and yellow needles were obtained in 40% yield. This product was, however, found by nmr spectroscopy to be a mixture of III and XI in a ratio of 3 : 2. After repeated recrystallization, III and XI were obtained in a pure form and were identical with authentic specimens.1)

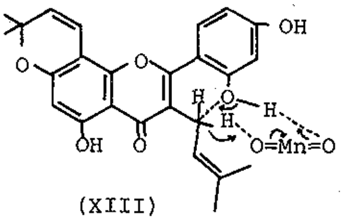
As reported so far, oxidative cyclization of 3-prenyl-2'-hydroxyflavone using 2,3-dichloro-5,6-dicyanobenzoquinone,1,11,12) and photo-oxidative cyclization3) did not give the flavone containing



pyran ring, but gave the flavone containing dihydrooxepin ring. Therefore the formation of III from I is particularly interesting. Although the mechanism of the formation of III has not been clear, it is likely that the formation of III proceeds *via* the biradical (XII), or the concerted process (XIII)[13] occurring on the surface of the manganese dioxide.



(XII)



(XIII)

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4 The commercially available manganese dioxide and silver oxide were used for this reaction.

5 Elemental analysis of this compound gave satisfactory result.

6 The uv spectrum of 4'- O - methyl ether of II [$\lambda_{\text{Max}}^{\text{MeOH}}$ nm(log ε): 236.5(4.25), 279(4.27), 337(3.99); $\lambda_{\text{Max}}^{\text{MeOH+AlCl}_3}$: 283.5(4.29), 359(4.07), 423.5(3.72); $\lambda_{\text{Max}}^{\text{MeOH+NaOMe}}$: 286(4.34), 387(3.55)].

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10 The discrimination between VII and VIII was supported from the following data. By comparig the nmr spectra of V and VI, the signals of the *t* -butyl group of the 1,3,5-tri-*t*-butyl-2,5-cyclohexadiene-4-one group coupled to the hydroxyl group at C_4, of V were observed at 1.08 and 1.24. The signals of the *t*-butyl group of VII were in good agreement with those of V, but not the signals of the *t*-butyl group of VIII. Further, the results of Gibbs test supported these structures (VII and VIII).

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