SYNTHESIS OF 8-AZA-2,3-DIOXABICYCLO[4.4.0]DECAN-7-ONES USING MANGANESE(III)-CATALYZED AEROBIC OXIDATION

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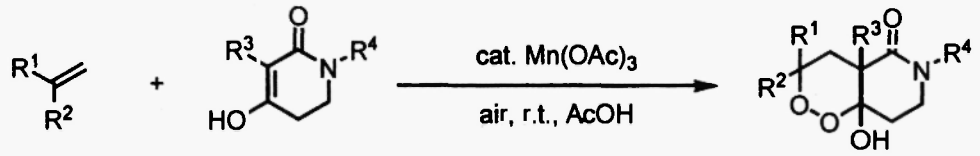
Abstract: The reaction of 1,1-disubstituted ethenes with 2,4-piperidinediones in the presence of a catalytic amount of manganese(III) acetate was carried out in acetic acid at room temperature in air, producing 1-hydroxy-8-aza-2,3-dioxa-bicyclo[4.4.0]decan-7-ones in excellent yields. The structures of the azadioxabicyclo[4.4.0]decanones and the catalytic reaction mechanism were discussed.

The 1,2-dioxane scaffold is very important in nature as a metabolite and biologically active substance.[1] In general, biogenetic compounds involving unsaturated chemical bonds are oxidized by molecular oxygen *in vivo* to produce hydroperoxy and/or peroxy materials during the first reaction stage *via* respiration, digestion, and detoxification.[2] These peroxides are labile and further oxidized to finally transform into carbon dioxide and water with energy. However, since some biogenetic peroxides have potent activities toward cells,[3] the synthesis of the peroxide framework *in vitro* has attracted considerable attention from the point of the development of new antibiotics in spite of its instability.

Recently, we developed the aerobic peroxidation of a mixture of alkenes and nitrogen heterocycles using a catalytic amount of manganese(III) acetate. The reaction of 2,3-pyrrolidinediones,[4] 2,4-pyrrolidinediones,[5] and 4-piperidone-3-carboxylates[6] in the presence of alkenes gave the corresponding azadioxabicyclic compounds. On the other hand, hydroperoxides were obtained by a similar reaction of barbituric acid,[7] pyrazolidine-3,5-diones,[8] and 4-hydroxyquinolin-2-ones.[9] In connection with our peroxide synthesis study, we investigated the manganese(III)-catalyzed aerobic oxidation using 2,4-piperidinedione derivatives in the hope of developing a new azadioxabicyclic framework such as an antimalarial analogue.[10]

We first synthesized the 2,4-piperidinedione-3-carboxylates **2** as the *enol* form from the Dieckmann condensation of 4-aza-3-oxoheptanedioates which were prepared by the reaction of the corresponding 3-aminopropanoates with ethyl malonyl chloride.[11] The obtained 2,4-piperidinedione-3-carboxylates **2** were also converted by decarboxylation into 2,4-piperidinediones **4**. With a preparative amount of the 2,4-piperidinediones **2** and **4** in hand, we then examined the manganese(III)-based reaction of 1,1-disubstituted ethenes **1** with 2,4-piperidinedione-3-carboxylates **2**. 1,1-Diphenylethene (**1**: R^1 = R^2 = Ph) (0.5 mmol) and **2** (R^3 = CO_2Et, R^4 = Bn) (1 mmol) were dissolved in glacial acetic acid (20 mL) and a catalytic amount of manganese(III) acetate (0.15 mmol) was added to the mixture. The mixture was then stirred at room temperature in air until the ethene **1** was completely consumed. After chromatographic separation, only one product was isolated.[12] The ^{13}C NMR spectral peaks of the product at δ 96.6 (C-1) and 85.1 ppm (C-4) were assigned to the characteristic peak of the 1,2-dioxan-3-ol ring system[13] together with an ester carbonyl, amide carbonyl (δ 168.9 and 166.6 ppm), and quaternary carbon (C-6) at the ring junction (δ 55.9 ppm).[14] The ^1H NMR spectrum indicated the presence of two sets of an AB quartet of benzyl protons and H-5 methylene protons at δ 4.78 (1H, d, J = 15.03 Hz), 2,94 (1H, d, J = 15.03Hz), 3.80 (1H, d, J = 14.72 Hz), and 3.43 ppm (1H, d, J = 14.72 Hz),



1 2 3

Table-1: Mn(III)-Catalyzed Aerobic Oxidation of a Mixture of Alkenes **1** and 2,4-Piperidinedioene-3-carboxylates **2**[a]

Entry	Alkene 1		Piperidinedione 2		1:2:Mn(OAc)$_3$	Time	3
	R^1	R^2	R^3	R^4		h	Yield/%[b]
1	Ph	Ph	CO_2Et	Bn	1:2:0.3	9	88
2	4-ClC_6H_4	4-ClC_6H_4	CO_2Et	Bn	1:2:0.3	9	74
3	4-FC_6H_4	4-FC_6H_4	CO_2Et	Bn	1:2:0.5	10	71
4	4-MeC_6H_4	4-MeC_6H_4	CO_2Et	Bn	1:2:0.3	9	85
5	4-$MeOC_6H_4$	4-$MeOC_6H_4$	CO_2Et	Bn	1:2:1	15	81[c]
6	Ph	Me	CO_2Et	Bn	1:2:0.3	9	93
7	4-MeC_6H_4	Me	CO_2Et	Bn	1:2:0.3	9	82
8	4-ClC_6H_4	Me	CO_2Et	Bn	1:2:0.3	10	95
9	Et	Et	CO_2Et	Bn	10:1:0.3	13.5	66
10	Me	Me	CO_2Et	Bn	Excess:2:0.3	9	77
11	Ph	H	CO_2Et	Bn	1:2:0.3	9	75
12	n-C_7H_{15}	H	CO_2Et	Bn	1:2:0.3	9	17
13	Ph	Ph	CO_2Et	Me	1:2:0.3	9	90
14	Ph	Ph	CO_2Et	Et	1:2:0.3	9	82[d]
15	Ph	Ph	CO_2Et	Pr	1:2:0.3	9	88[d]
16	Ph	Ph	CO_2Et	i-Pr	1:2:0.3	9	78[d]
17	Ph	Ph	CO_2Et	Ph	1:2:0.3	15	50
18	Ph	Ph	CO_2Pr-i	Bn	1:2:0.3	12	93

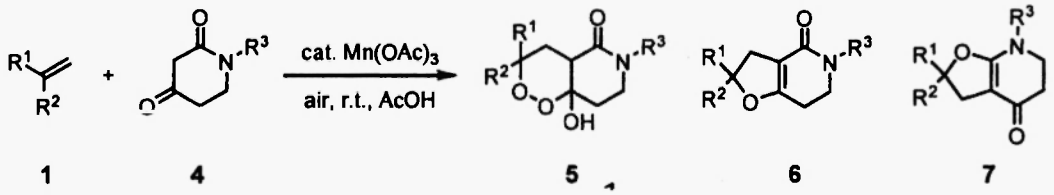
[a] The reaction of the alkenes **1** (0.5 mmol) with 2,4-piperidinediones **2** was carried out in glacial acetic acid (20 mL) in the presence of manganese(III) acetate dihydrate in air at room temperature. [b] Isolated yield based on the amount of the alkene **1** used. [c] Ethyl 6-acetoxy-3-benzyl-8,8-bis(4-methoxyphenyl)-3-aza-7-oxabicyclo[4.3.0] nonan-2-one-1-
carboxylate (11%) was also isolated as a minor product. [d] A small amount of the corresponding decarboxylated azadioxabicyclo[4.4.0]decanone (4-6%) was also isolated under the conditions.

respectively. The methylene protons of H-9 and H-10 appeared as a broad doublet at 2.86 (2H, J = 9.62 Hz, H-9), a triplet of doublets at 2.61 (1H, J = 13.52 and 9.62 Hz), and broad doublet at 1.85 (1H, J = 13.52 Hz). All the peaks in the NMR spectrum were also correlated by H-H COSY and H-C COSY. In addition, the absorption band of the hydroxyl group appeared at 3400-3100 cm^{-1} together with two carbonyls at 1751 and 1639 cm^{-1} in the IR spectrum. Accordingly, the product was determined to be ethyl 8-benzyl-1-hydroxy-4,4-diphenyl-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylate (**3**), and the combustion analysis also supported the structure. The exact structure was finally confirmed by X-ray crystallography (Figure 1).[15] The X-

ray crystallographic data for **3** ($R^1 = R^2 = Ph$, $R^3 = CO_2Et$, $R^4 = Bn$) illustrate that the hydroxyl group at C-1 is in an axial-like orientation due to the anomer effect, and the relationship between the hydroxyl group and the ethoxycarbonyl group at C-6 is the *syn* configuration.[5b,6]

In order to apply the catalytic oxidation to other alkenes **1** with 2,4-piperidinediones **2**, the reactions of various alkenes **1** with 2,4-piperidinediones **2** were carried out under similar conditions (Table-1, Entries 2-18). All of the reactions gave the desired 1-hydroxy-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one-6-carboxylates **3** in good to excellent yields except for the reaction using 1-nonene (**1**: $R^1 = n\text{-}C_7H_{15}$, $R^2 = H$) (Table-1, Entry 12).

We next examined a similar reaction using the 2,4-piperidinediones **4**. Although it needed longer reaction times and slightly excess amounts of catalyst to consume alkenes **1** in comparison with the reaction using **2**, the desired 4,4-diaryl-1-hydroxy-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-ones **5** were obtained in good to excellent yields (Table-2). Surprisingly, a small amount of 2,3,6,7-tetrahydrofuro[3,2-*c*]pyridin-4(5*H*)-ones **6** and/or 2,3,6,7-tetrahydrofuro[2,3-*b*]-pyridin-4(5*H*)-ones **7** was also isolated (Entries 2-8). The tetrahydrofuropyridinones **6** and **7** were probably formed due to the reversibility of the endoperoxidation and use of an excess amount of catalyst.



1 **4** **5** **6** **7**

Table-2: Reaction of 1,1-Disubstituted Alkenes **1** with 2,4-Piperidinedioenes **4** in the Presence of Manganese(III) Acetate[a]

Entry	Alkene 1		Piperidinedione 4	1:2:$Mn(OAc)_3$	Time	Product (Yield/%)[b]		
	R^1	R^2	R^3		h	**5**	**6**	**7**
1	Ph	Ph	Bn	1:2:0.3	18	99		
2	4-ClC_6H_4	4-ClC_6H_4	Bn	1:2:1	16	77	10	8
3	4-MeC_6H_4	4-MeC_6H_4	Bn	1:2:1	16	87	12	
4	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Bn	1:2:1	14	66	16	
5	Ph	Ph	Me	1:1.1:1	14	60[c]	16	
6	Ph	Ph	Et	1:2:1	14	81	5	
7	Ph	Ph	Pr	1:2:1	9	72	8	
8	Ph	Ph	*i*-Pr	1:2:1	18	77	11	12
9	Ph	Ph	Ph	1:2:1	30	70		

[a] The reaction of the alkenes **1** (0.5 mmol) with 2,4-piperidinediones **4** was carried out in glacial acetic acid (20 mL) in the presence of manganese(III) acetate dihydrate in air at room temperature. [b] Isolated yield based on the amount of the alkene **1** used. [c] The alkene **1** (18%) was recovered after the usual workup.

The manganese(III)-catalyzed aerobic oxidation could be explained by a similar mechanism for the reaction using 2,3-pyrrolidinediones,[4] 2,4-pyrrolidinediones,[5] and 4-piperidone-3-carboxylates.[6] The manganese(III)-piperidinedione enolate complex **A** would be formed by the reaction of 2,4-piperidinediones **2** or **4** with manganese(III) acetate during the first stage. The enolate complex formation is the key to the catalytic reaction. The enolate complex easily led to oxidize the alkenes **1** to produce the corresponding carbon radicals **B**, which take up dissolved molecular oxygen in the solvent to form peroxy radicals **C**. The peroxy radicals **C** could be reduced by manganese(II) species followed by cyclization to finally produce the corresponding 1-hydroxy-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-ones **3** or **5**. The manganese(III) species should be reproduced in the reaction system, and the catalytic cycle must be continued until the added alkenes **1** are completely consumed. The 2,4-piperidinedione-3-carboxylates **2** exist in the solvent as the *enol* form so that the manganese(III)–enolate complex should be easily formed *in situ* using the hydroxyl and carboxylate moieties. However, the 2,4-piperidinediones **4** are present as the *keto* form and the rate of the enolization would be slow in a protic solvent. Since the formation of the manganese(III)-2,4-piperidinedione enolate complex would be the rate-determining step,[16] it could be understood that it took a longer reaction time using the 2,4-piperidinediones **4** than that using the 2,4-piperidinedione-3-carboxylates **2**.

In summary, the convenient synthesis of 1-hydroxy-8-aza-2,3-dioxabicyclo[4.4.0]decan-7-one derivatives **3** and **5** was demonstrated by the reaction of alkenes **1** with the 2,4-piperidinediones **2** and **4** in the presence of a catalytic amount of manganese(III) acetate in air. The azadioxabicyclo[4.4.0]decanone scaffold is interesting from the viewpoint of biological activity. For example, naturally occurring artemisinin is a well-known strong antimalarial agent,[9] and the activity of azaartemisinin as an analogue of 7-aza-2,3,5-trioxabicyclo[4.4.0]decan-8-one is stronger than that of natural artemisinin.[17] Therefore, the present azadioxabicyclic compounds are also expected to have some biological activities, and the bioassay for RNA is currently underway in our department.

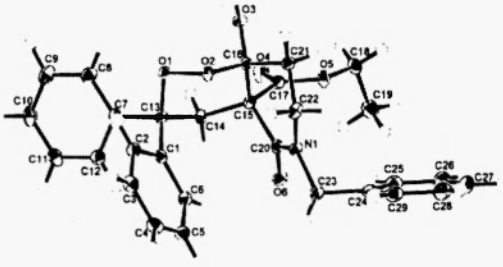
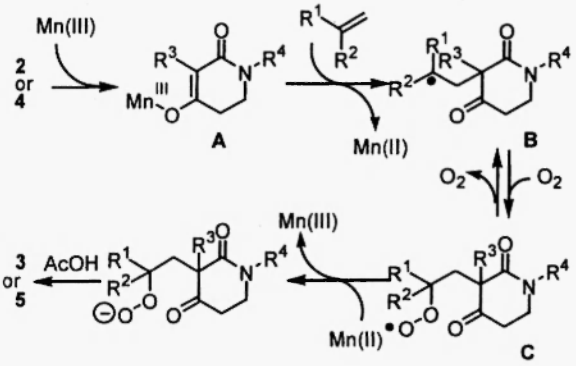


Fig. 1. ORTEP Drawing of **3** ($R^1 = R^2 = Ph$, $R^3 = CO_2Et$, $R^4 = Bn$)



Scheme-1

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12. A typical procedure is as follows. A mixture of an alkene **1** (0.5 mmol), 2,4-piperidinedione **2** (1 mmol), and manganese(III) acetate dihydrate (0.15 mmol) was stirred in glacial acetic acid (20 mL) at room temperature in air until the alkene **1** was completely consumed. The solvent was removed *in vacuo* and the residue was treated with water (20 mL). The aqueous mixture was extracted three times with chloroform (30 mL). The combined extracts were dried over magnesium sulfate and then concentrated to dryness. The residue was separated by silica gel TLC (Wakogel B-10) using 1% methanol/chloroform as the developing solvent. The obtained azadioxabicyclodecane derivatives **3** were further purified by recrystallization from the appropriate solvent.

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14. The characterization of ethyl 8-benzyl-1-hydroxy-4,4-diphenyl-8-aza-2,3-dioxabicyclo[4.4.0] decan-7-one-6-carboxylate (**3**: $R^1 = R^2 = Ph$, $R^3 = CO_2Et$, $R^4 = Bn$): $R_f = 0.21$ (chloroform : methanol = 99 : 1); Colorless microcrystals (from ethyl acetate); mp 209-210 °C; IR (KBr) ν 3400-3100 (OH), 1751, 1639 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.59-7.03 (15H, m, arom. H), 4.78 (1H, d, J = 15.0 Hz, Ph-C$\underline{H}_2$), 4.32-4.08 (3H, m, OC$\underline{H}_2$CH$_3$ and OH), 3.80 (1H, d, J = 14.7 Hz, H-5), 3.43 (1H, d, J = 14.7 Hz, H-5),

2.94 (1H, d, J = 15.0 Hz, Ph-C$\underline{H}_2$), 2.86 (2H, br. d, J = 9.6 Hz, H-9), 2.62 (1H, dt, J = 13.5, 9.6 Hz, H-10), 1.85 (1H, br. d, J = 13.5 Hz, H-10), 1.27 (3H, t, J = 7.2 Hz, OCH$_2$C$\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9 (C=O), 166.5 (C=O), 143.1, 139.7, 136.5 (3C, arom. C), 128.4, 128.0, 127.6, 127.5, 127.3, 127.2, 127.1, 125.5 (15C, arom. $\underline{C}$H), 96.5 (C-1), 85.1 (C-4), 62.4 (O$\underline{C}$H$_2$CH$_3$), 55.8 (C-6), 49.5 (Ph-$\underline{C}$H$_2$), 41.4 (C-9), 33.7 (C-5), 29.3 (C-10), 13.9 ($\underline{C}$H$_3$). Anal. Calcd for $C_{29}H_{29}NO_6$: C, 71.44; H, 6.00; N, 2.87. Found: C, 71.20; H, 5.85; N, 2.84.

15. X-ray crystallographic data of **3** (R^1 = R^2 = Ph, R^3 = CO_2Et, R^4 = Bn): empirical formula $C_{29}H_{29}NO_6$; formula weight 487.55; colorless plates; crystal dimensions 0.25×0.13×0.35 mm; triclinic; space group $P\bar{1}$ (#2); a = 9.0735(3), b = 11.9814(4), c = 12.1693(3) Å, α = 69.1821(6)°, β = 74.2866(9)°, γ = 78.5339(7)°, V = 1182.63(6) Å^3, Z = 2; D_{calcd} = 1.369 g/cm^3; F_{000} = 516.00; μ (MoKα) = 0.96 cm^{-1}; $2\theta_{max}$ = 55.0°; no. of reflections measured 10696; no. of reflections (All, 2θ<54.96°) 5327; no. of variables 325; reflection/parameter ratio 16.39; R = 0.065; R_w = 0.106; GOF 1.28. The X-ray crystallographic data have been deposited as supplementary publication numbers CCDC 272197. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

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