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A unique peroxide formation based on the Mn(III)-catalyzed aerobic oxidation ☆

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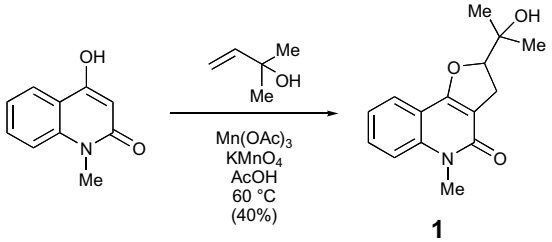
Abstract—The autoxidation of a mixture of 1,1-diarylsubstituted alkenes **4** and 4-hydroxy-1*H*-quinolin-2-ones **5** in the presence of a catalytic amount of manganese(III) acetate dihydrate in air gave 3,3-bis(2-hydroperoxyethyl)-1*H*-quinoline-2,4-diones **6** in 31–91% yields together with [4.4.3]propellane-type cyclic peroxides **7** (10–34%). A similar aerobic oxidation of 3-substituted quinolinones **8** yielded cyclic peroxide derivatives **9** and/or 3-hydroperoxyethylated quinolinediones **10** depending on the substituent. The structures of the bis(hydroperoxide) **6** ($R^1 = Me$, $Ar = 4\text{-}ClC_6H_4$) and the [4.4.3]propellane **7** ($R^1 = Me$, $Ar = Ph$) have been corroborated by X-ray crystallography.

A variety of quinoline alkaloids exists in plants, and it is known that the quinoline alkaloids exhibit a wide range of biological activities,[1] for example, antimalarial,[2] antitumor,[3] antiparasitic,[4] anthelmintic,[5] cytotoxic,[4a,6] local anesthetic,[7] and insect pheromone-like activities.[8] Recently, Parsons and co-workers reported the facile synthesis of (±)-araliopsine **1**, isolated from the Rutaceae family, and their derivatives using the manganese(III) acetate–potassium permanganate oxidation system.[9] They also showed that the angular isomer **1** was thermodynamically more stable than the linear isomer.[9c] On the other hand, we have investigated the manganese(III)-catalyzed cyclic peroxidation of 4-piperidone-3-carboxylates producing 1-hydroxy-8-aza-2,3-dioxabicyclo[4.4.0]decane-6-carboxylates **2**[10] from the standpoint of the synthesis of antimalarial analogues since azabicyclic peroxides have a more active antimalarial character like the azaartemisinins **3**.[11] Naturally occurring quinine and artificial chloroquine are the most well-known antimalarial agents using the quinoline skeleton.[12] The development of the reaction scheme of the quinoline-fused cyclic peroxides might also be significant in order to find a new class of artificial antimalarial reagents. Therefore, we synthesized eight 4-hydroxy-1*H*-quinolin-2-ones **5** according to the literature,[13] and investigated the feasibility of the formation of quinoline-fused cyclic peroxides using manganese(III)-catalyzed aerobic peroxidation.



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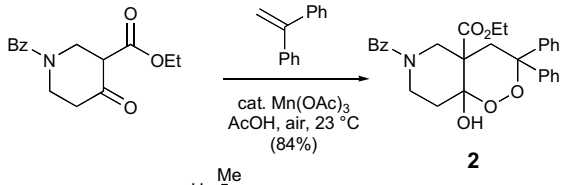

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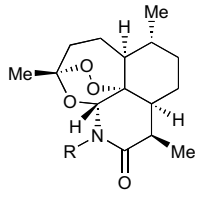

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Keywords: Peroxide formation; Aerobic oxidation; Quinoline alkaloid; Manganese(III) acetate.

☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2003.11.054

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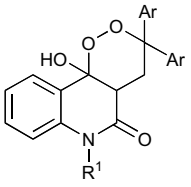
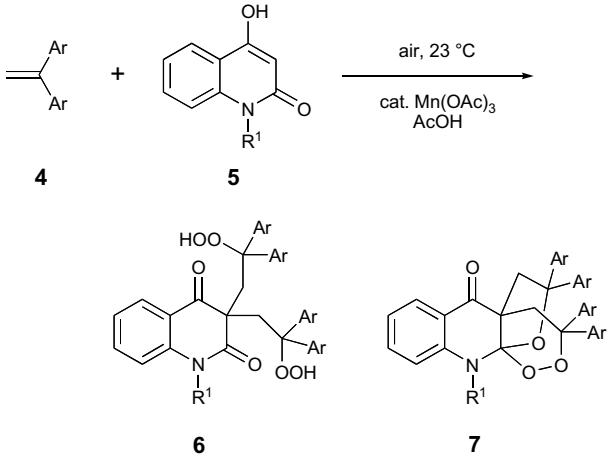
First, a mixture of ethene (**4**: Ar = Ph), quinolinone (**5**: R^1 = Me), and manganese(III) acetate dihydrate in the molar ratio of 1:2:1 was stirred in acetic acid (25 mL) at 23 °C in air. After 4 h, the quinolinone **5** was completely consumed; however, the reaction gave a tarry material, and it was difficult to isolate the products (Table 1, entry 3). When the reaction was carried out in the absence of the catalyst, the reaction with **4** did not occur (entry 1). Since it was found that the quinolinone **5** was sensitive to the metal oxidant, we carefully examined the aerobic oxidation of a mixture of **4** and **5** in the presence of a catalytic amount of manganese(III) acetate in order to synthesize a quinoline-fused cyclic peroxide such as **A**.



A

Use of a 0.1 equiv of manganese(III) acetate toward **5** did not afford the expected cyclic peroxide **A**, but bis(hydroperoxide) **6** (entry 4),[14] analogous to the manganese(III)-catalyzed autoxidation of 1,2-disubstituted pyrazolidine-3,5-diones.[15] The prolongation of the reaction period for 12 h and the use of 0.5 equiv of the catalyst resulted in the increase of the yield up to 43%. However, the thin-layer chromatographic separation on silica gel after the work-up led to decomposition of the product. We then adopted a procedure to quickly purify it using flush column chromatography, so that the product yield was improved (71%) (entry 5). It was very surprising why the free bis(hydroperoxide) **6** was relatively stable and isolated from the reaction mixture. In order to speculate on the unusual stability of the hydroperoxide **6**, a single crystal of **6** (Ar = 4-ClC_6H_4, R^1 = Me) was successively grown from dichloromethane–hexane and analyzed by X-ray crystallography (Fig. 1).[15] As a result, it was found that two hydroperoxy group seemed to be stabilized by intramolecular hydrogen-bonding with the quinolinedione carbonyls since the interatomic distance between the carbonyl O1 and peroxy O6 and between the carbonyl O2 and peroxy O4 was 2.712 and 2.756 Å, respectively. A similar stabilization of the hydroperoxy group was also observed in 5,5-bis(2-hydroperoxyethyl)barbituric acid (2.73 and 2.81 Å)[16] and 4,4-bis(2-hydroperoxyethyl)pyrazolidine-3,5-dione systems (2.688 Å).[17]



6 **7**

Table 1. Mn(III)-catalyzed aerobic oxidation of a mixture of 1,1-disubstituted alkenes **4** and quinolinones **5**, **8**[a]

Entry	Alkene **4**	Quinolinone	**4**:**5** or **8**:$Mn(OAc)_3$	Time (h)	Product (yield/%)[b]			
					6	**7**	**9**	**10**
1[c]	Ar = Ph	**5**: R^1 = Me	1:2:0	4	No reaction[d]			
2	Ar = Ph	**5**: R^1 = Me	1:2:0.5($Mn(OAc)_2$)[e]	4	No reaction[d]			
3[f]	Ar = Ph	**5**: R^1 = Me	1:2:1	4	Intractable mixture			
4	Ar = Ph	**5**: R^1 = Me	1:2:0.1	4	29			
5	Ar = Ph	**5**: R^1 = Me	1:2:0.5	4	71	13		
6	Ar = 4-ClC_6H_4	**5**: R^1 = Me	1:2:0.5	12	76	10		
7	Ar = 4-MeC_6H_4	**5**: R^1 = Me	1:2:0.5	4	59	10		
8	Ar = Ph	**5**: R^1 = Et	1:2:0.5	15	91	5		
9	Ar = Ph	**5**: R^1 = Bn	1:2:0.5	12	31	Trace		
10	Ar = 4-ClC_6H_4	**5**: R^1 = Bn	1:2:0.5	24	48	Trace		
11	Ar = 4-MeC_6H_4	**5**: R^1 = Bn	1:2:0.5	4	44	Trace		
12	Ar = Ph	**5**: R^1 = H	1:2:0.5	4		34		
13	Ar = 4-ClC_6H_4	**5**: R^1 = H	1:2:0.5	12		13		
14	Ar = 4-MeC_6H_4	**5**: R^1 = H	1:2:0.5	4		20		
15	Ar = Ph	**8**: R^2 = Me	1:2:0.5	15			89	
16	Ar = Ph	**8**: R^2 = Pr	1:2:0.5	18			22	60
17	Ar = Ph	**8**: R^2 = Bu	1:2:0.5	15			24	52
18	Ar = Ph	**8**: R^2 = Ph	1:2:0.5	15			32	43
19	Ar = 4-ClC_6H_4	**8**: R^2 = Me	1:2:0.5	18			88	
20	Ar = 4-MeC_6H_4	**8**: R^2 = Me	1:2:0.5	15			38	58

[a] The reaction was carried out at 23 °C in acetic acid (25 mL) in air.
[b] The yield was based on the amount of alkene **4** used.
[c] The reaction was carried out at 23 °C in acetic acid (25 mL) under bubbling dry air.
[d] 1,1-Diphenylethene (**4**: Ar = Ph) was recovered (99%).
[e] Manganese(II) acetate tetrahydrate was used instead of manganese(III) acetate.
[f] After work-up, an intractable mixture was obtained, and no products were isolated.

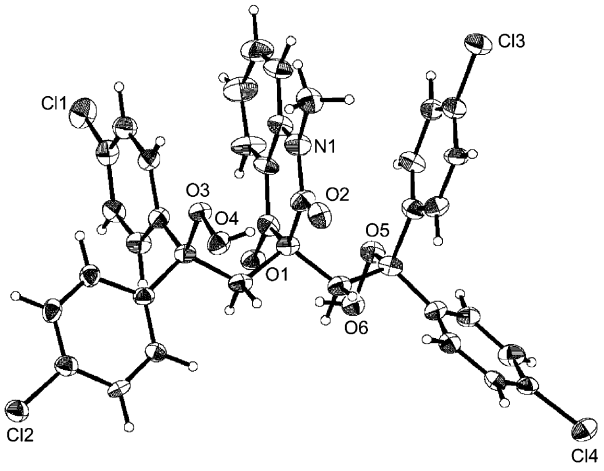


Figure 1. ORTEP drawing of bis(hydroperoxide) **6** (Ar = 4-ClC_6H_4, R^1 = Me).

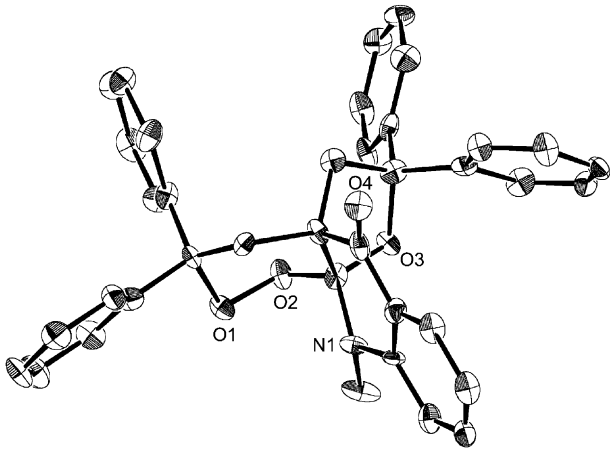
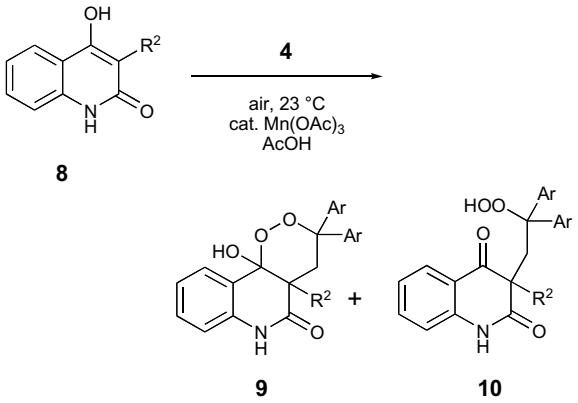


Figure 2. ORTEP drawing of [4.4.3]propellane-type compound **7** (Ar = Ph, R^1 = Me).

In order to find other products, we scrutinized the rest of the residue by flush column chromatography, and isolated a quite unique compound **7** (13% yield) (entry 5), of which the NMR spectra were similar to **6**, but not a hydroperoxide since the hydroperoxy and amide carbonyl groups did not appear in the IR and NMR spectra.[18] The structure of **7** was eventually determined by the X-ray crystallography, and found to be a [4.4.3]propellane-type cyclic peroxide (Fig. 2).[15] The peroxy O–O bond length of O1–O2 (1.464 Å) was analogous to that of the reported crystalline 1,2-dioxanes (normally 1.44–1.47 Å).[10,19] The use of 4-chlorophenyl-**4** (Ar = 4-ClC_6H_4) and 4-methylphenyl-substituted ethene **4** (Ar = 4-MeC_6H_4) led to the corresponding bis(hydroperoxide)s **6** along with [4.4.3]propellanes **7** (entries 6, 7). The best yield of **6** (91%) was obtained in the reaction of **4** (Ar = Ph) with **5** (R^1 = Et) (entry 8). Use of nonprotection quinolinone **5** (R^1 = H) resulted in a complex mixture, and only the propellane-type compounds **7** were isolated (entries 12–14). The mechanism for the formation of **7** was not clear at this moment.



Since it was found that the α carbon of the amide carbonyl in **5** was very easily oxidized by manganese(III) to form double hydroperoxyalkylated quinolinediones **6** even when the excess amount of quinolinone **5** was employed under very mild aerobic reaction conditions,[15] we prepared 3-substituted quinolinones **8** and examined the aerobic oxidation with alkenes **4** in order for the double hydroperoxyalkylation not to take place but to elaborate the cyclic peroxide such as **A**. This process was successful and the corresponding cyclic peroxides **9** were obtained in good yields (entries 15–20). However, the quinolinones substituted by a bulky group rather than the methyl group preferentially gave the corresponding acyclic hydroperoxides **10** (entries 16–18).

The selectivity for the peroxide formation of **6**, **7**, **9**, and **10** is not clear at this time. As Parsons et al. reported, it might be rather stable angler cyclic peroxides **9** than the corresponding linear one. In addition, since the ketonic carbon is more electrophilic than the amide carbonyl carbon, which is stabilized by the adjacent amino group, it seems that the endoperoxide formation tends to occur at the ketone carbonyl of **8**.

In conclusion, we have demonstrated that manganese(III) acetate is an excellent catalyst for the aerobic peroxidation. The quinolinones **5** bearing no substituent at the C-3 position reacted with ethenes **4** under aerobic oxidation conditions to give bis(hydroperoxyethyl)quinolinediones **6** together with [4.4.3]propellane-type cyclic peroxides **7**. However, we revealed that the reaction of ethenes **4** with quinolinones **8** substituted at the C-3 position gave the desired 1,2-dioxane-fused quinolinones **9** and/or hydroperoxyethyl derivatives **10**. Biological activity testing for these obtained peroxides is now under way,[20] since the analogs of **6**, **7**, **9**, and **10** are already known to have analgetic, anticonvulsant, sedative properties,[21] potential atypical antipsychotics,[22] antibacterial, antifungal, antiviral (HIV) activities, and also cytotoxic, phototoxic, mutagenic activities.[23]

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Sports, Science and Technology, Japan, and also by Grants-in-Aid for Scientific Research, No. 13640539 and No. 15550039, from the Japan Society for the Promotion of Science. We thank Professor Emeritus Kazu Kurosawa, Kumamoto University, Japan, for his helpful discussions and suggestions. We also gratefully acknowledge Professor Teruo Shinmyozu and Dr. Mikio Yasutake, Institute for Materials Chemistry and Engineering, Kyushu University, Japan, for their crystallographic assistance.

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15. The X-ray crystallographic data of **6** ($R^1 = Me$, Ar = 4-ClC_6H_4) and **7** ($R^1 = Me$, Ar = Ph) have been deposited as supplementary publication numbers CCDC217001 and CCDC218561, respectively. Copies 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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