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Synthesis of 4,4-bis(2-hydroperoxyalkyl)pyrazolidine-3,5-diones using manganese(III)-catalyzed autoxidation

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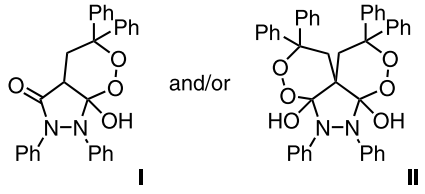
Abstract—The autoxidation of a mixture of 1,2-disubstituted pyrazolidine-3,5-diones **1** and alkenes **2** in the presence of a catalytic amount of manganese(III) acetate dihydrate in air gave 4,4-bis(2-hydroperoxyalkyl)pyrazolidine-3,5-diones **3** in 75–96% yields. The structure of the bis(2-hydroperoxyethyl)pyrazolidine-3,5-dione **3** ($R^1=R^2=Ph$, $R^3=R^4=4\text{-}FC_6H_4$) has been corroborated by an X-ray single crystallographic analysis. On the other hand, the manganese(III) acetate oxidation of a mixture of **1** ($R^1=R^2=Ph$) and **2** ($R^3=R^4=Ph$) at elevated temperature gave 4,4-bis(2,2-diphenylethenyl)-1,2-diphenylpyrazolidine-3,5-dione (**4**) in good yield.

Derivatives of the pyrazolidine-3,5-diones possess a wide variety of biological and pharmaceutical activities along with other uses, e.g. as color agents, photographic light-sensitive and thermal printing materials.[1] In recent years, interest in the synthesis and pharmacological evaluation of numerous pyrazolidine-3,5-diones as AT_1 angiotensin II receptor antagonists and study on the inhibition of enzyme activity for PGH synthase has increased.[2,3] In order to synthesize functionalized pyrazolidine-3,5-dione derivatives with potent biological activities, we carried out the manganese(III) acetate-catalyzed oxidation of pyrazolidine-3,5-diones in the presence of electron-rich alkenes.[4] The reactions were investigated with particular attention being paid to the use of a combination of a catalytic amount of manganese(III) acetate and air. It was known that the manganese(III)-based oxidation of alkenes with 1,3-dicarbonyl compounds gave cyclic peroxides, and in the case of 1,3-cyclopentanedione, the reaction resulted in a unique double 1,2-dioxane ring formation to produce octahydro-3,4,7,8-tetraoxabenz[*c*]indene-4a,6a-diols in good yields.[5a] Therefore, we expected a similar single **I** and/or double cyclic peroxidation product **II** of pyrazolidine-3,5-diones with alkenes. Contrary to our prediction, the oxidation led to free double hydroperoxides instead of cyclic peroxides. Recently, it was reported that the manganese(III)-based oxidation of alkenes with barbituric acid and its derivatives, another cyclic diamide, furnished 5,5-bis(2-hydroperoxyalkyl)-barbituric acids in 62–99% yields.[5b] We obtained similar results using the pyrazolidine-3,5-dione system.



The pyrazolidine-3,5-diones **1** were prepared by methods described in the literatures.[3,6] 1,2-Diphenylpyrazolidine-3,5-dione (**1**: $R^1=R^2=Ph$) (1 mmol) was treated with 1,1-diphenylethene (**2**: $R^3=R^4=Ph$) (1 mmol) in the presence of manganese(III) acetate (1 mmol) in acetic acid (25 mL) at 23°C for 12 h under a dry air stream. From the reaction mixture, 4,4-bis(2-hydroperoxy-2,2-diphenylethyl)-1,2-diphenylpyrazolidine-3,5-dione (**3**: $R^1=R^2=R^3=R^4=Ph$) was obtained in 67% yield (Table 1, entry 1). By using a catalytic amount of Mn(III) acetate rather than the stoichiometric quantity and carrying out the reaction for a shorter time period, the yield of the product **3** ($R^1=R^2=R^3=R^4=Ph$) could be improved up to 96% yield (entry 4).[7] The structural assignment of **3** ($R^1=R^2=Ph$, $R^3=R^4=4\text{-}FC_6H_4$), which was obtained from the reaction of **1** ($R^1=R^2=Ph$) with 1,1-bis(4-fluorophenyl)ethene (**2**: $R^3=R^4=4\text{-}FC_6H_4$) (entry 6), was based on the ^1H,

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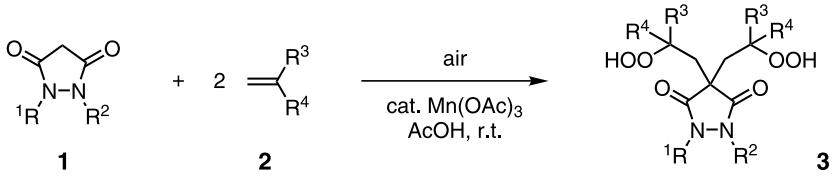
Table 1. Reaction of pyrazolidine-3,5-diones **1** with alkenes **2** in the presence of manganese(III) or manganese(II) acetate[a]

Entry	**1**		**2**		**1**:**2**:$Mn(OAc)_3$	Reaction time (h)	Product **3** (yield/%)[b]
	R^1	R^2	R^3	R^4			
1	Ph	Ph	Ph	Ph	1:1:1	12[c]	67
2	Ph	Ph	Ph	Ph	1:1:1	1	80
3	Ph	Ph	Ph	Ph	1:2:0.2	3	85
4	Ph	Ph	Ph	Ph	1:1:0.1	2	96
5	Ph	Ph	4-MeC_6H_4	4-MeC_6H_4	1:1:0.1	5	80
6	Ph	Ph	4-FC_6H_4	4-FC_6H_4	1:1:0.1	3	95
7	Ph	Ph	4-ClC_6H_4	4-ClC_6H_4	1:1:0.1	2	98
8	Ph	Ph	Me	Me	1:Excess:0.5[d]	2	91[e]
9	Ph	Ph	Et	Et	1:1:0.1	5	95
10	Ph	Ph	Me	Ph	1:1:0.1	3	95
11	Ph	Ph	4-MeC_6H_4	Ph	1:1:0.1	14	75
12	Bn	Ph	Ph	Ph	1:2:0.2	3	85
13	Bn	Ph	4-FC_6H_4	4-FC_6H_4	1:2:0.2	2	90
14	Bn	Ph	4-ClC_6H_4	4-ClC_6H_4	1:2:0.2	4	87
15	$(-CH_2-)_4$		Ph	Ph	1:2:0.2	13	95
16	Bn	Bn	Ph	Ph	1:1:1[f]	15	93
17	Bn	Bn	4-MeC_6H_4	4-MeC_6H_4	1:1:1[f]	10	78
18	Bn	Bn	4-FC_6H_4	4-FC_6H_4	1:1:1[f]	1	98

[a] The reaction was carried out at 23°C in glacial acetic acid (25 mL) under air.
[b] Isolated yield based on the alkene **2** used except for entry 7.
[c] Manganese(III) acetate was completely consumed.
[d] 2-Methypropene and dry air were bubbled through the reaction mixture.
[e] The yield based on the pyrazolidine-3,5-dione **1** used.
[f] Manganese(II) acetate was used instead of manganese(III) acetate.



1 **2** **3**

^{13}C NMR, and IR spectra.[8] In the ^{13}C NMR spectrum, the amide carbonyl carbon appeared at δ 170.7 ppm, and the peak at δ 86.0 ppm was assigned to the C-2 carbon of the ethyl group, attached to the hydroperoxyl group. In addition, the elemental analysis and high resolution FAB mass spectral data supported the molecular formula of $C_{43}H_{36}F_4N_2O_6$. This structure was finally confirmed by X-ray crystallography.[9]

The ORTEP drawing of **3** ($R^1=R^2=Ph$, $R^3=R^4=4$-FC_6H_4) is shown in Figure 1. The most characteristic feature of the structure was that two hydroperoxyl groups are individually hydrogen-bonded to the two amide carbonyl oxygens since the interatomic distance between the carbonyl O(1′) and the peroxyl O(3) was 2.688 Å. As a result, it appears that the hydroperoxyl group must be stabilized in the solid state. A similar stabilization of the hydroperoxyl group was also observed in 5,5-bis(hydroperoxy-2,2-diphenylethyl)-barbituric acid in which the corresponding interatomic distance was 2.73 and 2.81 Å, respectively.[5b] In addition, the hydroperoxyl O–O bond length of O(2)–O(3) (1.465 Å) in **3** was analogous to those of the bis-(hydroperoxyethyl)barbituric acid (1.450 and 1.464 Å).[5b] The reactions of other pyrazolidine-3,5-diones **1**

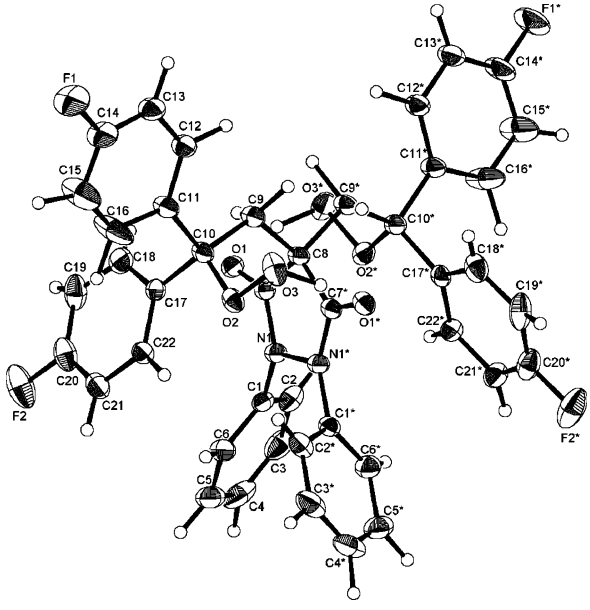
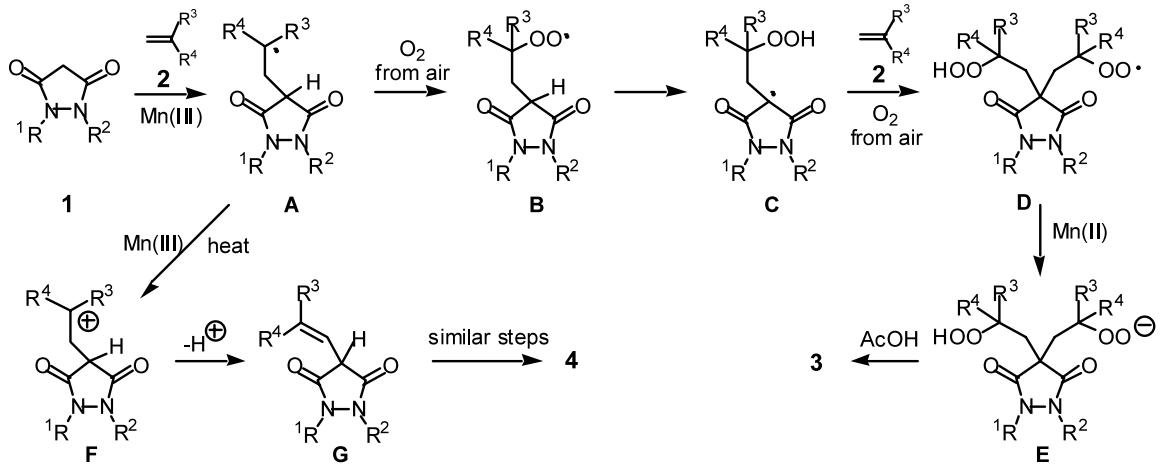


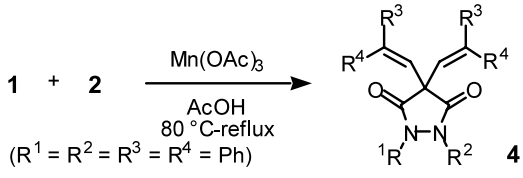
Figure 1. ORTEP drawing of **3** ($R^1=R^2=Ph$, $R^3=R^4=4$-FC_6H_4).



Scheme 1.

(R^1, R^2 = Ph and/or benzyl) were also applicable with different substituted ethenes **2** (R^3, R^4 = Ph, 4-MeC_6H_4, 4-ClC_6H_4, Me, or Et), giving the corresponding bis(hydroperoxyethyl)pyrazolidinediones **3** in comparable yields (entries 5–14). The tetrahydropyrazolo[1,2-*a*]pyridazine-1,3-dione **1** (R^1,R^2 = -$(CH_2)_4$-) also reacted with 1,1-diphenylethene **2** (R^3 = R^4 = Ph) under similar manganese(III) acetate-catalyzed oxidation conditions to give the corresponding **3** in high yields (entry 15). Using manganese(II) acetate instead of manganese(III) acetate was also effective for the double hydroperoxialkylation of **1** (entries 16–18).

On the other hand, the oxidation of a mixture of **1** (R^1 = R^2 = Ph) and **2** (R^3 = R^4 = Ph) with manganese(III) acetate at reflux temperature for 45 min under an argon atmosphere gave **4** (57%) in which no molecular oxygen incorporation took place.[10a] The yield of **4** was improved (74%) when the oxidation was carried out at 80°C in air.[10b]



The formation of 4,4-bis(hydroperoxyalkyl)pyrazolidine-3,5-diones **3** could be accounted for in terms of the oxidative radical reaction of pyrazolidine-3,5-diones and alkenes with manganese(III) acetate producing radical **A** (Scheme 1). At room temperature, the radical **A** trapped dissolved molecular oxygen in the solvent to form the peroxyl radical **B**.[11] The peroxyl radical **B** could be converted to radical **C** either by intramolecular hydrogen abstraction or by a series of reactions, that is, reduction of peroxyl radical with manganese(II), protonation,[12] and further oxidation at the C-4 position.[13] A similar process from **C** to the peroxyl anion **E** would yield **3**. When the manganese(II) acetate was used as the catalyst, manganese(II)-pyrazolidinedionate complex should be formed and aerobically oxidized to produce active manganese(III) species in situ.[5,14b] For the reactions at elevated temperature and in a higher concentration of manganese(III) acetate, the alternative path, i.e. the oxidation of the tertiary alkyl radical **A** to the corresponding cation **F**, becomes more facile than the molecular oxygen trapping process,[14] and the carbocation **F** loses a proton to give the mono-alkenylated intermediate **G** which could not be isolated from the reaction mixture. The intermediate **G** undergoes similar processes to give the double alkenylated product **4**.

In summary, we have demonstrated that the double 2-hydroperoxyakylation of the pyrazolidine-3,5-diones **1** at the C-4 position was achieved by the reaction of 1,1-disubstituted ethenes **2** in the presence of manganese(III) or manganese(II) acetate in air. The bis(hydroperoxyethyl)pyrazolidinedione **3** (R^1 = R^2 = R^3 = R^4 = Ph) showed a weak antimalarial activity.[15,16]

Acknowledgements

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7. A typical procedure is as follows. To a solution of pyrazolidine-3,5-dione **1** (1 mmol) and alkene **2** (1 mmol) in glacial acetic acid (25 mL), manganese(III) acetate dihydrate (0.1 mmol) was added. The mixture was stirred at 23°C in air until the alkene was completely consumed, and then the reaction was quenched by adding water (25 mL) to the mixture. The aqueous reaction mixture was extracted three times with CH_2Cl_2 (30 mL) and the combined extract was washed with water, saturated aqueous solution of sodium hydrogencarbonate, dried over anhydrous sodium sulfate, and then concentrated to dryness. The residue was separated by silica gel column, eluted with diethyl ether/hexane (7:3 v/v). The obtained bis(hydroperoxide) **3** was further purified by recrystallization from diethyl ether–hexane.
8. 4,4-Bis[2-hydroperoxy-2,2-bis(4-fluorophenyl)ethyl]-1,2-diphenylpyrazolidine-3,5-dione: Colorless blocks (from diethyl ether–hexane); mp 170°C (decompd); IR (KBr) ν 3232 (OOH), 1706, 1662 (C=O); ^{1}H NMR (300MHz, $CDCl_3$) δ 9.32 (2H, s, OOH), 7.36–6.62 (26H, m, arom H), 3.52 (4H, s, 2×-CH_2-); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7 (C=O), 163.4, 160.1, 138.3, 133.0 (arom C), 128.5, 127.5, 127.4, 127,1, 122.9, 115.3, 115.0 (arom CH), 86.0 (2×C-O), 48.6 (C-4), 44.0 (2×-CH_2-). Anal. calcd for $C_{43}H_{32}F_4N_2O_6$: C, 68.98; H, 4.31; N, 3.74. Found C, 69.06; H, 4.37; N, 3.80. FAB HRMS (acetone–NBA). Found: m/z 748.2173. Calcd for $C_{43}H_{32}F_4N_2O_6$: M, 748.2197.
9. X-Ray crystallographic data of **3** ($R^1=R^2=$Ph, $R^3=R^4=$4-FC_6H_4): empirical formula $C_{43}H_{36}F_4N_2O_6$; formula weight 748.73; colorless cube; crystal dimensions 0.40×0.43×0.36 mm; monoclinic; space group $P2/c$ (# 13); $a=12.062(1)$, $b=9.637(1)$, $c=16.136(2)$ Å, $\beta=107.484(2)°$, $V=1789.1(3)$ Å^3, $Z=2$; $D_{calcd}=1.390$ g/cm^3; $F_{000}=776.00$; μ(Mo Kα)=1.07 cm^{-1}; $2\theta_{max}=55.0°$; no. of reflections measured 16676; no. of observations ($I>0.00\sigma(I)$, $2\theta<54.97°$) 3895; no. of variables 249; reflection/parameter ratio 15.64; $R=0.128$; $R_w=0.164$.
10. (a) The reaction was carried out at a molar ratio of **1**:**2**:manganese(III) acetate=1:4:8; (b) **1**:**2**:manganese(III) acetate=1:2:4.
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16. The antimalarial test was performed at the Laboratory of Drug Informatics, Faculty of Pharmaceutical Science, Okayama University, Japan.