Mn(III)-Initiated Facile Oxygenation of Heterocyclic 1,3-Dicarbonyl Compounds

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Received: 27 September 2011; in revised form: 7 November 2011 / Accepted: 9 November 2011 / Published: 16 November 2011

Abstract: The Mn(III)-initiated aerobic oxidation of heterocyclic 1,3-dicarbonyl compounds, such as 4-alkyl-1,2-diphenylpyrazolidine-3,5-diones, 1,3-dialkylpyrrolidine-2,4-diones, 3-alkyl-1,5-dimethylbarbituric acids, and 3-butyl-4-hydroxy-2-quinolinone gave excellent to good yields of the corresponding hydroperoxides, which were gradually degraded by exposure to the metal initiator after the reaction to afford the corresponding alcohols. The synthesis of 30 heterocyclic 1,3-dicarbonyl compounds, the corresponding hydroperoxides and the 10 alcohols, their characterization, and the limitations of the procedure are described. In addition, the mechanism of the hydroperoxidation and the redox decomposition of the hydroperoxides are discussed.

Keywords: hydroperoxides; peroxy radicals; aerobic oxidation; redox; 2-hydroxy-1,3-dicarbonyl compounds

1. Introduction

Oxygenation of enolates has been considered as an important organic transformation [1-3], because the \(\alpha\)-hydroxycarbonyl moiety is used as a starting material or an intermediate for the synthesis of some natural products [4-8]. In particular, the 2-hydroxy-1,3-dicarbonyl moiety can be found in biologically important compounds such as indole alkaloids, e.g., vindorosine and vindoline [9-12], the cyclopentenoid kjellamanianone [13], and tetracycline-type antibiotics such as doxycycline [14,15]. 4-Butyl-1,2-diphenylpyrazolidine-3,5-dione (phenylbutazone), a nonstereoidal drug, is an efficient
reducing cofactor for the peroxidase activity of prostaglandin H synthase [16,17]. Phenylbutazone inhibits the production of lipid mediators causing inflammation but paradoxically performs this via the intermediacy of the peroxy radical and hydroperoxide, which may themselves be proinflammatory. 4-Hydroperoxyphenylbutazone shows a significantly stronger cardiodepressive and coronary constricting effects compared to phenylbutazone itself, 4-hydroxyphenylbutazone, and the ring-opened decomposition product of the hydroperoxide [18]. These phenomena could shed light on the significance of the 4-hydroperoxyphenylbutazone regarding the antiinflammatory or other biological activities of phenylbutazone [19,20] and could explain the side effects such as gastric irritation and toxicity associated with phenylbutazone. Although many reagents have been utilized for the introduction of an oxygen functionality at the 2-position of 1,3-dicarbonyl compounds, the hydroxyl functionality could be introduced at the α-position in most of the cases [21-30].

In connection with our current investigation of the Mn(OAc)$_3$-assisted aerobic oxidation [31-36], we found the double hydroperoxyalkylaton of barbituric acids [37], pyrazolidine-3,5-diones (Scheme 1) [38-39], 4-hydroxy-1H-quinolin-2-ones [40], and tetronic acid [41]. The reaction could not be stopped at the monohydroperoxyalkylaton stage.

Scheme 1. Mn(III)-assisted aerobic oxidation of 1,2-diphenylpyrazolidine-3,5-dione (R = H) [38-39] and phenylbutazone (R = Bu) [42].

Surprisingly, when phenylbutazone was treated under similar reaction conditions in the absence of an alkene, direct hydroperoxidation occurred and the corresponding solid 4-hydroperoxyphenylbutazone was produced quantitatively (Scheme 1) [42]. We foresaw that the reaction could be very useful for the synthesis of hydroperoxides under very mild aerobic oxidation conditions. Therefore, in order to examine the applicability of Mn(OAc)$_3$-assisted α-hydroperoxidation, biologically important heterocyclic 1,3-dicarbonyl compounds, e.g., 1,3-dialkylpyrrolidine-2,4-diones 3, 3-alkyl-1,5-dimethylbarbituric acids 5, and 3-butyl-4-hydroxy-2-quinolinone (7) as well as various 4-monoalkyl-substituted pyrazolidine-3,5-diones 1 were subjected to the reaction, and we obtained very similar results, whereby the corresponding hydroperoxides were obtained in excellent to good yields. In this paper, the full results of the earlier work [42], applications and limitations of the Mn(III)-initiated direct α-hydroperoxidation, and the related reactions are described. Specifically, the full characterization of all the starting materials 1, 5, and 7, and all the hydroperoxides published in the reference [42], the full results of the hydroperoxidation of 1,3-dialkylpyrrolidine-2,4-diones 3, including the characterization of the corresponding hydroperoxides, and the mechanism of the Mn(III)-initiated autoxidation are discussed. In addition, the limitations of the hydroperoxidation are mentioned using the reaction of acyclic amides, cyclic ketones and esters as model, and the synthesis of 2-hydroxy-1,3-dicarbonyl compounds using the reduction of the hydroperoxides is described.
2. Results and Discussion

2.1. aerobic oxidation of 4-alkyl-substituted pyrazolidine-3,5-diones 1a–h

4-Alkyl-1,2-diphenylpyrazolidine-3,5-diones 1a–h were prepared by a simple condensation reaction between the corresponding alkyl malonate and 1,2-diphenylhydrazine in the presence of NaH in boiling chlorobenzene [17]. With the pyrazolidinediones 1a–h in hand, a mixture of phenylbutazone (1e, 1 mmol) and Mn(OAc)₃ (0.1 mmol) in glacial AcOH (30 mL) was stirred at 23 °C under an aerobic atmosphere, and the desired 4-hydroperoxypyrazolidinedione 2e was produced in quantitative yield (Scheme 2 and Table 1, entry 9). To scrutinize the role of Mn(OAc)₃ in the aerobic oxidation, we carried out some reactions of 4-i-propyppyrazolidinedione 1d under different reaction conditions. When the pyrazolidinedione 1d was stirred in the absence of Mn(OAc)₃, no conversion to the hydroperoxide 2d was observed (entry 4). Using Cu(OAc)₂ and ammonium cerium(IV) nitrate (CAN) as the catalyst was not effective in the autoxidation (entries 5 and 6). Therefore, it could be inferred that Mn(OAc)₃ was essential for the hydroperoxidation and that the reaction is neither thermal nor it is induced by sunlight or visible light. While carrying out the reaction of 1d in the presence or absence of light (entries 7 and 8), there is no alteration in the yield of the hydroperoxide 2d. Thus, the reaction is not light-assisted. Various alkyl groups were used as the substituent at the 4-position of the pyrazolidinedione, but in all cases similar quantitative conversion to the corresponding hydroperoxides was observed. The results are summarized in Table 1.

Scheme 2. Autoxidation of 4-alkyl-substituted 1,2-diphenylpyrazolidine-3,5-diones 1a–h.

![Diagram]

Table 1. Aerobic oxidation of 4-alkyl-substituted pyrazolidinediones 1a–h in the presence of a metal oxidant.

| Entry | 1 | Oxidant       | 1:oxidant | Time/h | Product/yield (%) |
|-------|---|---------------|-----------|--------|-------------------|
| 1     | 1a| Mn(OAc)₃     | 1:0.1     | 2      | 2a (95)           |
| 2     | 1b| Mn(OAc)₃     | 1:0.1     | 2      | 2b (95)           |
| 3     | 1c| Mn(OAc)₃     | 1:0.1     | 2      | 2c (99)           |
| 4     | 1d| none         | -         | 3      | Recovery of 1d (100) |
| 5     | 1d| Cu(OAc)₂     | 1:0.2     | 15     | Recovery of 1d (94) |
| 6     | 1d| CAN          | 1:0.1     | 1      | 2d (40)           |
| 7     | 1d| Mn(OAc)₃     | 1:0.1     | 2      | 2d (97)           |
Table 1. Cont.

| Entry | 1     | Oxidant       | 1:oxidant b | Time/h | Product/yield (%) c |
|-------|-------|---------------|-------------|--------|---------------------|
| 8     | 1d    | Mn(OAc)₃      | 1:0.1       | 2      | 2d (96)             |
| 9     | 1e    | Mn(OAc)₃      | 1:0.1       | 2      | 2e (99)             |
| 10    | 1f    | Mn(OAc)₃      | 1:0.1       | 10 min | 2f (95)             |
| 11    | 1g    | Mn(OAc)₃      | 1:0.1       | 2      | 2g (97)             |
| 12    | 1h    | Mn(OAc)₃      | 1:0.1       | 2      | 2h (99)             |

a The reaction of 1 (1 mmol) was carried out in AcOH at ambient temperature in air; b Molar ratio; c Isolated yield is based on the pyrazolidinedione 1 used; d The reaction was carried out in MeOH at 0 °C; e Ammonium cerium(IV) nitrate; f The reaction was carried out in the dark.

2.2. Aerobic Oxidation of 3-Alkyl-substituted Pyrrolidine-2,4-diones 3a–p

We were pleased to confirm that the specific hydroperoxidation succeeded using pyrazolidinediones 1a–h, so we next applied the reaction to 1,3-dialkyl-substituted pyrrolidine-2,4-diones 3a–p which are structurally similar to the pyrazolidinediones. The pyrrolidine-2,4-diones 3a–p were prepared by the Dieckmann condensation of N-alkanoyl-N-alkylglycinates which were produced by the reaction of α-bromoacetate with alkylamines followed by alkanoylation with the corresponding alkanoyl chloride (see Experimental section) [43-47]. The 2,4-pyrrolidinediones 3a–p exist as an enol form (3-alkyl-4-hydroxy-3-pyrrolin-2-ones) in an aprotic polar solvent, such as DMSO-d₆ [48]. With the 2,4-pyrrolidinediones 3a–p in hand, we first explored the hydroperoxidation of 3a. When the reaction was carried out using a stoichiometric amount of Mn(OAc)₃, the oxidant was consumed after 2 h, and the desired hydroperoxide 4a was obtained in 65% yield (Scheme 3 and Table 2, entry 1).

Scheme 3. Aerobic oxidation of 1,3-dialkyl-substituted pyrrolidine-2,4-diones 3a–p.

In order to optimize the hydroperoxidation, the reaction was conducted under various reaction conditions, and we finally obtained the hydroperoxide 4a in 94% yield under the conditions of room temperature reaction in air for 2 h using a catalytic amount of Mn(OAc)₃ (entry 3). To expand the scope of the reaction, the reaction of other 2,4-pyrrolidinediones 3b–p was conducted under the
optimized reaction conditions and similar hydroperoxides 4b–p were obtained in excellent yields (entries 4–18). However, the reactions using 1-ethyl-3-methylpyrrolidine-2,4-dione (3q) and ethyl 1-benzylpyrrolidine-2,4-dione-3-carboxylate (3r) gave intractable mixtures and the corresponding hydroperoxides were not isolated. In addition, the reaction of 1-benzyl-3-phenylpyrrolidine-2,4-dione (3s) failed because of the solubility problem. Although the 4-hydroperoxypyrazolidinediones 2a–h were stable at ambient temperature in air, the 3-hydroperoxypyrrolidinediones 4a–p gradually decomposed within 2 or 3 days and even when stored in a refrigerator at −20 °C for a half year.

Table 2. Aerobic oxidation of 1,3-dialkyl-substituted pyrrolidinediones 3a–p.

| Entry | 3   | 3:Mn(OAc)₃ b | Time/h | Product/yield (%) c |
|-------|-----|--------------|--------|---------------------|
| 1     | 3a  | 1:1          | 2      | 4a (65)             |
| 2     | 3a  | 1:0.1        | 14     | 4a (68)             |
| 3     | 3a  | 1:0.1        | 2      | 4a (94)             |
| 4     | 3b  | 1:0.1        | 2      | 4b (95)             |
| 5     | 3c  | 1:0.1        | 2      | 4c (98)             |
| 6     | 3d  | 1:0.1        | 2      | 4d (93)             |
| 7     | 3e  | 1:0.1        | 2      | 4e (96)             |
| 8     | 3f  | 1:0.1        | 1.5    | 4f (91)             |
| 9     | 3g  | 1:0.1        | 1.5    | 4g (90)             |
| 10    | 3h  | 1:0.1        | 1.5    | 4h (95)             |
| 11    | 3i  | 1:0.1        | 1.5    | 4i (90)             |
| 12    | 3j  | 1:0.1        | 1.5    | 4j (96)             |
| 13    | 3k  | 1:0.1        | 1.5    | 4k (99)             |
| 14    | 3l  | 1:0.1        | 1.5    | 4l (99)             |
| 15    | 3m  | 1:0.1        | 1.5    | 4m (98)             |
| 16    | 3n  | 1:0.1        | 1.5    | 4n (95)             |
| 17    | 3o  | 1:0.1        | 1.5    | 4o (97)             |
| 18    | 3p  | 1:0.1        | 1.5    | 4p (98)             |

a The reaction of 3 (1 mmol) was carried out in AcOH (25 mL) at ambient temperature in air; b Molar ratio; c The yield is based on the amount of 3 used.

2.3. Aerobic Oxidation of 3-Alkyl-1,5-dimethylbarbituric Acids 5a–e and 3-Butyl-4-hydroxy-2-quinolinone (7)

We next investigated the reaction of other biologically important heterocyclic 1,3-dicarbonyl compounds, such as 5-monosubstituted barbituric acids 5a–e and 3-butyl-4-hydroxy-2-quinolinone 7. The barbituric acids 5a–e were prepared by Pd-catalyzed reductive alkylation of 1,3-dimethylbarbituric acid with acetone and aldehydes [49]. The quinolinone 7 was prepared by condensation of aniline and diethyl butylmalonate followed by dehydration (see Experimental section) [50-52]. With the barbituric acids 5a–e and the quinolinone 7 in hand, the aerobic oxidation was carried out under similar reaction conditions, and very similar results were obtained, giving the corresponding hydroperoxides 6a–e and 8, respectively, in excellent to good yields (Scheme 4 and Table 3).
Scheme 4. Aerobic oxidation of barbituric acids 5a–e and 4-hydroxy-2-quinolinone 7.

Table 3. Aerobic oxidation of barbituric acids 5a–e and 4-hydroxy-2-quinolinone 7.

| Entry | Amide | Amide:Mn(OAc)$_3$ | Time/h | Product/yield (%) |
|-------|-------|-------------------|--------|------------------|
| 1     | 5a    | 1:0.1             | 4      | 6a (80)          |
| 2     | 5b    | 1:0.1             | 2      | 6b (90)          |
| 3     | 5c    | 1:0.1             | 4      | 6c (94)          |
| 4     | 5d    | 1:0.1             | 4      | 6d (94)          |
| 5     | 5e    | 1:0.1             | 2      | 6e (88)          |
| 6     | 7     | 1:0.1             | 2      | 8 (57)           |

* The reaction of 5 (1 mmol) was carried out in AcOH (30 mL) at ambient temperature in air;
* Molar ratio; * The yield is based on the amount of 5 or 7 used.

2.4. Mechanism for the Formation of Hydroperoxides 2, 4, 6, and 8

The aerobic oxidation might be explained by a radical chain mechanism. To rationalize our experimental results, we presume the formation of Mn(III)-enolate complex A in situ undergoing single-electron transfer (SET) to give 1,3-dicarbonyl radical B and the reduced Mn(II) (Scheme 5) [31-36]. This is the initiation step of the radical chain reaction. The 1,3-dicarbonyl radical B could be trapped by dissolved molecular oxygen in solution to produce the peroxy radical C [53,54]. The radical C could simply abstract a hydrogen atom from the cyclic amides to give the product hydroperoxides and another molecule of 1,3-dicarbonyl radical B, which continues the radical chain reaction. Since the redox potential ($E^\circ$) of Mn(III)/Mn(II) is 1.54 V, it seems that the Mn(III) acts as an initiator rather than as a catalyst such as Cu(II)/Cu(I) ($E^\circ = 0.123$ V) [55-67].
Scheme 5. Mn(III)-initiated autoxidation of cyclic amides.

Involvement of the peroxy radical as well as the hydroperoxide intermediate in the course of transition metal-catalyzed autoxidation with different 1,3-dicarbonyl compounds has been proposed earlier [58,59]; however, there is only one report on the detection and identification of such a peroxy radical by electron spin resonance (ESR) [60]. To the best of our knowledge, there are no reports on the isolation and characterization of 2-hydroperoxy-1,3-dicarbonyl compounds in the transition metal-mediated autoxidation of the 1,3-dicarbonyl compounds, except for Hasegawa’s work [61]. They showed that introduction of the hydroperoxy functionality at the active methylene position of 1,3-dicarbonyl compounds could be accomplished by dye-sensitized photoreaction of singlet oxygen with the enolic 1,3-dicarbonyl compounds [61]. Although CAN also mediated the hydroperoxidation (Table 1, entry 6), the role of CAN could be accounted for by a similar function of Mn(III) during the reaction [62-64].

2.5. Conversion of the Hydroperoxides 2 and 6 into the Alcohols 9 and 10

When the aerobic oxidation of the pyrazolidinedione 1d was carried out for a longer reaction period with a catalytic amount of Mn(OAc)₃ in AcOH or for shorter reaction time in EtOH, a substantial amount of hydroxylated product 9d was produced along with the hydroperoxide 2d (Scheme 6 and Table 4, entries 2–4). Furthermore, utilizing a stoichiometric amount of CAN as a stronger oxidant than Mn(OAc)₃ also gave a similar result (entry 5). The formation of the alcohol 9d might be attributed to the degradation of the corresponding hydroperoxide 2d. As we have mentioned earlier, metal ion-mediated conversion of the 1,3-dicarbonyl compounds into their corresponding 2-hydroxylated derivatives has been well studied [21-30], nevertheless the mechanism associated with this conversion was not well explored and remained more or less ambiguous. In order to scrutinize the production of 9d, the hydroperoxide 2d was stirred at 23 °C in AcOH without the presence of any metal catalyst and under sunlight for 23 h. As a result, no conversion of 2d to 9d took place and 100% recovery of 2d was possible after the removal of the solvent (entry 6). Thus, while many alkylhydroperoxides are known to be sensitive to heat [65,66] and light [67,68], the conversion of 2d into 9d is not thermal or photochemical. However, in the presence of a catalytic amount of Mn(OAc)₃ (0.01 equiv.) in the same reaction system, 47% of the 2d was converted into its corresponding alcohol 9d (entry 7). Carrying out a similar reaction under darkness did not alter the course of the reaction,
which implies that the Mn(III)-catalyzed degradation is not light-assisted. We then carried out the reaction of 2d under an argon atmosphere with Mn(OAc)$_2$, and we found that Mn(OAc)$_2$ was also effective in the degradation (entry 8). With cerium(IV), 47% of the alcohol 9d was formed from 2d (entry 9). A similar degradation was also observed in the reaction of the hydroperoxides 2c, 2g (entries 10 and 11), the barbituric acid 5b and the hydroperoxide 6b (entries 12–17). Therefore, we could draw the conclusion that the transformation of hydroperoxides 2 and 6 into their corresponding alcohols 9 and 10 was due to a similar redox reactions using copper salt which has been extensively studied [69-71]. If the Mn(III) and Ce(IV) would function such as Cu(II), the mechanism of the degradation might be depicted in Scheme 7.

Scheme 6. Conversion of the hydroperoxides into the corresponding alcohols.

Table 4. Aerobic oxidation of amides under various conditions followed by decomposition.

| Entry | Amide | Catalyst | 1:Catalyst $^b$ | Solvent | Time/h | Product/yield (%) $^c$ | Recovery/% |
|-------|-------|----------|----------------|---------|--------|------------------------|------------|
| 1     | 1d    | Mn(OAc)$_3$ | 1:0.1         | AcOH    | 2      | 2d (97)                |            |
| 2     | 1d    | Mn(OAc)$_3$ | 1:0.1         | AcOH    | 12     | 2d (87)                | 9d (8)     |
| 3     | 1d    | Mn(OAc)$_3$ | 1:0.2         | AcOH    | 27     | 2d (52)                | 9d (46)    |
| 4     | 1d    | Mn(OAc)$_3$ | 1:0.28        | EtOH    | 3      | 2d (54)                | 9d (41)    |
| 5     | 1d    | CAN$^d$    | 1:1           | MeOH    | 1      | 2d (35)                | 9d (55)    |
| 6     | 2d    | none       | AcOH          | 23      |        |                        | 100        |
| 7     | 2d    | Mn(OAc)$_3$ | 1:0.01        | AcOH    | 23     | 9d (47)                | 32         |
| 8$^a$ | 2d    | Mn(OAc)$_2$ | 1:1           | AcOH    | 14     | 9d (25)                | 66         |
| 9     | 2d    | CAN$^d$    | 1:1           | MeOH    | 2      | 9d (47)                | 33         |
| 10    | 2c    | Mn(OAc)$_3$ | 1:0.01        | AcOH    | 17     | 9c (45)                | 48         |
| 11    | 2g    | Mn(OAc)$_3$ | 1:0.01        | AcOH    | 17     | 9g (40)                | 28         |
| 12    | 5b    | Mn(OAc)$_3$ | 1:0.1         | AcOH    | 3      | 6b (88)                | 10b (7)    |
| 13    | 5b    | Mn(OAc)$_3$ | 1:0.1         | AcOH    | 5      | 6b (79)                | 10b (18)   |
| 14    | 5b    | CAN$^d$    | 1:1           | MeOH    | 0.5    | 6b (47)                | 10b (43)   |
| 15    | 6b    | none       | AcOH          | 12      |        |                        | 100        |
| 16    | 6b    | Mn(OAc)$_3$ | 1:0.1         | AcOH    | 14     | 10b (14)               | 88         |
| 17    | 6b    | Mn(OAc)$_3$ | 1:0.4         | AcOH    | 23     | 10b (40)               | 50         |

$^a$ The reaction of an amide (1 mmol) was carried out in AcOH (30 mL) at room temperature in air; $^b$ Molar ratio; $^c$ Isolated yield is based on the amide used; $^d$ The reaction with ammonium cerium(IV) nitrate (CAN) was carried out at 0 °C; $^e$ The reaction was carried out under an argon atmosphere.
2.6. Application of the Mn(III)-Mediated Oxygenation

In order to apply the hydroperoxidation to acyclic $\beta$-oxoamides, cyclic ketones, and esters, the reactions of malonamides 11a,b, cyclopentanonecarboxylate derivatives 13a,b, and substituted dinedones 15 were examined (Scheme 8).

Scheme 7. Degradation of hydroperoxides by a redox system [69].

\[
\begin{align*}
2\text{ROOH} & \rightleftharpoons (\text{ROOH})_2 \\
(M^{n+})_2 + \text{ROOH} & \rightleftharpoons (M^{n+})_2 (\text{ROOH}) \\
(M^{n+})_2 (\text{ROOH}) + \text{ROOH} & \rightleftharpoons (M^{n+})_2 (\text{ROOH})_2 \\
(M^{n+})_2 (\text{ROOH})_2 & \rightarrow M^{n+}M^{(n-1)+} (\text{ROOH})(H^+) + \text{ROO}^- \\
M^{n+}M^{(n-1)+} (\text{ROOH})(H^+) & \rightarrow (M^{n+})_2 + H_2O + \text{RO}^- \\
2\text{ROO}^- & \rightarrow 2\text{RO}^- + \text{O}_2 \\
\text{RO}^- + \text{ROOH} & \rightarrow \text{ROH} + \text{ROO}^- \\
2\text{RO}^- & \rightarrow \text{ROOR}
\end{align*}
\]

For $M$, $\text{Mn}: n = 3$; $\text{Ce}: n = 4$

Scheme 8. Aerobic oxidation of malonamides, cyclic $\beta$-diketones and $\beta$-ketoesters.

11a: $R = \text{Pr}$  
11b: $R = \text{Bu}$  
12a: $R = \text{Pr} (18\%)$  
12b: $R = \text{Bu} (25\%)$

13a: $R = \text{Me}, X = \text{O}$  
13b: $R = \text{Et}, X = \text{CH}_2$

14a (75%)  
14b (89%)

15

cat. $\text{Mn(OAc)}_3$  
MeOH, rt, air

cat. $\text{Mn(OAc)}_3$  
MeOH, rt, air

AcOH, rt, air
Surprisingly, the malonamides 11a, b were inactive under the aerobic conditions and only afforded the corresponding alcohols 12a and 12b, respectively, under an oxygen atmosphere (1 atm) instead of air. Because the reaction of 13a, b in AcOH gave an intractable mixture, the reaction was carried out in MeOH and the corresponding alcohols 14a, b were isolated (Scheme 8). The dimedone derivatives 15 did not produce any oxygenated products, but 15 were recovered. Therefore, the hydroperoxidation must be characteristic for the cyclic amide derivatives. We also assumed that the corresponding hydroperoxides of 11 and 13 were too unstable in the solution containing Mn(III), and thus readily decomposed to give the corresponding alcohols 12 and 14, respectively, according to the redox system mentioned above (Scheme 7).

The hydroperoxides 2a–d and 6b could be transformed by reduction into their corresponding alcohols 9a–d and 10b, respectively. Simple stirring of equimolar amounts of the hydroperoxide and Ph₃P in Et₂O at room temperature gave the corresponding alcohol after a very simple work-up procedure (see Experimental section). The results are summarized in Table 5.

### Table 5. Reduction of the hydroperoxides 2a–d and 6b using Ph₃P a.

| Entry | ROOH | ROOH:Ph₃P | Time/h | Product/Yield (%) b |
|-------|------|-----------|--------|---------------------|
| 1     | 2a   | 1:1       | 3      | 9a (96)             |
| 2     | 2b   | 1:1       | 3      | 9b (97)             |
| 3     | 2c   | 1:1       | 3      | 9c (98)             |
| 4     | 2d   | 1:1       | 3      | 9d (97)             |
| 5     | 6b   | 1:1       | 3      | 10b (80)            |

a The reaction of the hydroperoxides 2a–d and 6b with Ph₃P was carried out in Et₂O in air at room temperature; b Isolated yield is based on 2 or 6b used.

### 2.7. Structural Determination of the Hydroperoxides and the Hydroxyl Derivatives

Characterization of the hydroperoxides and the alcohols deserves comment. All the obtained hydroperoxides in CH₂Cl₂ showed a positive potassium iodide-starch test. The structural assignment of the hydroperoxides 2, 4, 6, and 8 was based on their ¹H-NMR, ¹³C-NMR, IR spectra as well as their elemental analyses. For example, the 4-hydroperoxypyrazolidinedione 2g showed a singlet at δ 11.21 ppm in the ¹H-NMR spectrum due to OOH group. In the ¹³C-NMR spectrum, the amide carbonyl carbon appeared at δ 167.7 ppm and a quaternary carbon C-4 bearing the OOH group at δ 86.7 ppm. In addition, the elemental analysis and FAB HRMS supported the molecular formula of C₂₂H₁₈N₂O₄. The structure was finally confirmed by X-ray crystallography. A colorless single crystal of 2g was successfully grown from CH₂Cl₂-benzene of approximate dimensions of 0.25 × 0.50 × 0.10 mm was mounted on a glass fiber. All measurements were made on an imaging plate diffractometer with graphite monochromated Mo-Kα radiation. Cell constants and an orientation matrix for data collection corresponded to a primitive triclinic cell with dimensions were obtained as the triclinic space group P-1 with cell constants a = 10.3233, b = 10.4273, c = 12.9985 Å, V = 1283.0 Å³, and α = 95.792, β = 104.504, γ = 105.643°. The structure was solved by direct methods and expanded using Fourier techniques (see Supplementary data). The ORTEP drawing of 2g is shown in Figure 1. The intramolecular hydrogen-bonding in 2g could be visualized between the terminal hydroperoxy
oxygen and the carbonyl oxygen, O(4)-O(1) (2.705 Å) [32,33,37-40,42]. The other hydroperoxides obtained from the aerobic oxidation showed similar spectroscopic features.

**Figure 1.** ORTEP drawing of 4-benzyl-4-hydroperoxy-1,2-diphenylpyrazolidine-3,5-dione (2g).

In the case of the alcohol derivatives 9, 10, 12, and 14, the characteristic spectral features of the OH group were observed in the IR and NMR spectra. For example, 9g showed an absorption band at 3298 cm\(^{-1}\) in the IR spectrum corresponding to the OH group and a singlet at \(\delta\) 4.88 ppm in the \(^1\)H-NMR spectrum due to the OH group. In the \(^{13}\)C-NMR spectrum, the quaternary carbon C-4 bearing the OH group appeared at \(\delta\) 75.8 ppm and this is significantly different from that having the OOH group (Table 6) [72]. In addition, the elemental analysis of 9g supported the molecular formula of C\(_{22}\)H\(_{18}\)N\(_2\)O\(_3\). Therefore, it is easy to distinguish the corresponding alcohols from the hydroperoxides.

**Table 6.** \(^{13}\)C-NMR chemical shifts of the quaternary carbon bearing the OOH and OH group \(^{a}\).

| Hydroperoxide | \(^{13}\)C-OOH/ppm | Alcohol | \(^{13}\)C-OH/ppm |
|---------------|-------------------|---------|------------------|
| 2a            | 81.6              | 9a      | 71.1             |
| 2b            | 85.8              | 9b      | 74.7             |
| 2c            | 85.3              | 9c      | 74.0             |
| 2d            | 87.6              | 9d      | 76.3             |
Table 6. Cont.

|    | Structure |  
|----|-----------|  
| 2g | ![Structure](image) | 86.7 |
| 6b | ![Structure](image) | 87.2 |
| 9g | ![Structure](image) | 75.8 |
| 10b| ![Structure](image) | 76.6 |

*The $^{13}$C-NMR spectrum was measured in CDCl$_3$."

3. Experimental

3.1. Measurements

Melting points were taken using a Yanagimoto micromelting point apparatus and were not corrected. The NMR spectra were recorded using a JNM AL300 or ECX 500 FT-NMR spectrometer at 300 or 500 MHz for $^1$H and 75 or 125 MHz for $^{13}$C, with tetramethylsilane as the internal standard. The chemical shifts are reported in δ values (ppm) and the coupling constants in Hz. The IR spectra were measured in CHCl$_3$ or KBr using a Shimadzu 8400 FT IR spectrometer and expressed in cm$^{-1}$. The EI MS spectra were measured by a Shimadzu QP-5050A gas chromatograph-mass spectrometer with the ionizing voltage of 70 eV. The high-resolution mass spectra and the elemental analysis were performed at the Instrumental Analysis Center, Kumamoto University, Kumamoto, Japan.

3.2. Materials

Manganese(II) acetate tetrahydrate, Mn(OAc)$_2$•4H$_2$O, was purchased from Wako Pure Chemical Ind., Ltd. Manganese(III) acetate dihydrate, Mn(OAc)$_3$•2H$_2$O, was prepared according to the method described in the literature [73,74]. 4-Alkyl-1,2-diphenylpyrazolidine-3,5-diones 1a–h were prepared by the condensation of a suitable alkylmalonate with 1,2-diphenylhydrazine in the presence of NaH in boiling chlorobenzene [17]. Methyl 2-oxotetrahydrofurane-3-carboxylate (13a) and ethyl 2-oxocyclopentanecarboxylate (13b) were purchased from Tokyo Chemical Industry Co., Ltd., and used as received. The physical data for the pyrazolidinediones 1a–h are given in supplementary data.

1,3-Dialkyl-substituted pyrrolidine-2,4-diones 3a-s were prepared as follows [75-81]. To a mixture of ethyl (benzylamino)acetate (3.22 mL; 17.4 mmol) and triethylamine (4.85 mL; 34.8 mmol) in CHCl$_3$ (25 mL) was dropwise-added propanoyl chloride (1.65 mL; 19.2 mmol) at 0 °C over 15 min. After stirring for another 1.5 h at room temperature, the mixture was diluted with CHCl$_3$ to 50 mL and washed with a 5% aqueous AcOH solution (25 mL), water (50 mL), brine (25 mL), dried over anhydrous MgSO$_4$, and then concentrated to dryness, affording the liquid propanoyl-protected (benzylamino)acetate with sufficient purity for use in the next step.

To a refluxing suspension of NaH (60% dispersion in mineral oil) (500 mg; 11.03 mmol) and tetrahydrofuran (50 mL) in a 300 mL three-necked flask was dropwise-added the prepared propanoyl-protected (benzylamino)acetate (2.5 g; 10.03 mmol) in tetrahydrofuran (50 mL). After this addition, the mixture was continuously heated under reflux for 12 h. A pale yellow solid was formed during the heating and then filtered under suction. The obtained solid was dissolved in a minimum volume of water and very carefully acidified with 2 M H$_2$SO$_4$, giving 1-benzyl-3-methyl-2,4-pyrrolidinedione..."
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(keto form of 3a) as a crude precipitate. The precipitate was purified by silica gel column chromatography, eluting with a mixture of EtOAc and hexane followed by recrystallization using the appropriate solvent. The other 2,4-pyrrolidinediones 3b–s were prepared in a manner similar to that described above. The physical data for the pyrrolidinediones 3a–s are given in the Supplementary Data.

5-Alkyl-1,3-dimethylbarbituric acids 5a–e were prepared as follows [49]: 1,3-Dimethylbarbituric acid (5 mmol) and 10%Pd-C (0.2 g) were added to a mixture of acetone (20 mL), AcOH (20 mL), and water (10 mL). A few drops of concentrated H2SO4 were added and the mixture was heated at 50 °C under hydrogen (2 atm) for 4 h using a glass reactor. The mixture was filtered in a Celite column and the filtrate was extracted with CHCl3. The extract was washed with water several times and a saturated aqueous solution of NaHCO3, and then dried over anhydrous MgSO4. After removal of the solvent, the crude product was recrystallized from Et2O/hexane, giving 1,3-dimethyl-5-i-proprylbarbituric acid (5a) in 90% yield. A similar reaction of the barbituric acid (5 mmol) with 2-naphthaldehyde (5 mmol) was carried out in MeOH (30 mL) at the reflux temperature for 10 h. After the same work-up, 5-(2-naphthyl)methyl-1,3-dimethylbarbituric acid 5e was obtained in 88% yield. Other benzyl-substituted barbituric acids 5b–d were prepared in the same manner. The physical data for the barbituric acids 5a–e are given in supplementary data.

3-Butyl-4-hydroxy-2-quinolinone 7 was prepared according to the standard procedure described in the literature [50-52]. Aniline (2.80 g; 30 mmol) and diethylbutyl malonate (6.51 g; 30 mmol) were heated at 150 °C for 20 h. Water (30 mL) was added and the mixture was extracted with CH2Cl2. The extract was washed with 2 M HCl, water and dried over anhydrous Na2SO4. After removal of the solvent, ethyl 2-(phenylcarbamoyl)hexanoate (28 mmol) was obtained. The hexanoate in EtOH (10 mL) was hydrolyzed with 6 M NaOH (20 mL) in EtOH (20 mL) at room temperature for 1 h. After acidifying the solution with 2 M HCl, the precipitates were filtered with suction. The obtained solid acid was dehydrated in PPA, which was poured into water and then neutralized using 6 M NaOH to pH 4, giving 7 as a precipitate (3.67 g; 56%). The physical data for the quinolinone 7 are given in the Supplementary Data.

2-Benzyl-N1,N3-dipropylmalonamide (11a) and 2-benzyl-N1,N3-dibutylmalonamide (11b) were prepared by the reaction of diethyl 2-benzylmalonamide (2.50 g) with propylamine and butylamine (50 mL), respectively, at reflux temperature for 24 h followed by removal of the amine unchanged under reduced pressure to give a colorless solid which was recrystallized with CHCl3/hexane [82]. The physical data for the malonamides 11a and 11b are given in the Supplementary Data.

3.3. Mn(III)-Initiated Aerobic Oxidation of Heterocyclic 1,3-Dicarbonyl Compounds 1a–h, 3a–p, 5a–e, and 7

A typical procedure is as follows: to a solution of the cyclic amide (1 mmol) in glacial AcOH (25 mL), Mn(OAc)3•2H2O (26.8 mg; 0.1 mmol) was added. The mixture was stirred at room temperature in air for 1.5–2 h, and then the reaction was quenched by adding water (25 mL) to the mixture. The aqueous reaction mixture was extracted three times with CH2Cl2 (30 mL) and the combined extract was washed with water, then a saturated aqueous solution of NaHCO3, dried over anhydrous MgSO4, and concentrated to dryness. Although the product was almost pure, it was further purified by silica gel flash column
chromatography, eluting with Et₂O/hexane (7:3 v/v) or EtOAc/hexane (8:2 v/v) if needed. The physical data for the hydroperoxides 2a–h, 4a–p, 6a–e, and 8 are given in the Supplementary Data.

3.4. Conversion of the Hydroperoxides 2 and 6 into the Alcohols 9 and 10

The redox reaction of the hydroperoxide 2c, 2d, 2g, 6b (1 mmol) was carried out in AcOH (30 mL) at room temperature in air. The molar ratio of the catalyst and the reaction times are described in Table 4. After the usual work-up, the corresponding alcohols 9c, 9d, 9g, and 10b were obtained. On the other hand, the reduction of the hydroperoxides 2a–d and 6b using Ph₃P is as follows: to the hydroperoxide (0.5 mmol) in Et₂O (10 mL), a solution of Ph₃P (0.5 mmol) in Et₂O (10 mL) was dropwise added and stirred for 3 h at room temperature. Water (20 mL) was added to the reaction mixture and then extracted with CH₂Cl₂. The extract was dried over anhydrous Na₂SO₄ and then evaporated to dryness. Simple recrystallization from Et₂O/hexane gave the pure crystalline alcohol. The physical data for the alcohols 9a–d, 9g, and 10b are given in the Supplementary Data.

3.5. Aerobic Oxidation of 1d, 2d, and 5b Using Ammonium Cerium (IV) Nitrate (CAN)

A typical procedure is as follows: to an ice-cooled solution of the substrate 1d, 2d, or 5b (1 mmol) in MeOH (20 mL), a solution of ammonium cerium(IV) nitrate (CAN) (1 mmol) in MeOH (10 mL) was dropwise-added and stirred in air until the orange color of Ce(IV) disappeared. The reaction was quenched by adding water (25 mL). The aqueous reaction mixture was extracted three times with CH₂Cl₂ (30 mL), and the combined extract was washed with water, saturated brine, dried over anhydrous Na₂SO₄, and then concentrated to dryness. The residue was separated by a silica gel column, eluted with EtOAc/hexane (7:3 v/v). The obtained products 2d, 9d, 6b, and 10b were further purified by recrystallization from the solvent described above.

3.6. Mn(III)-Initiated Aerobic Oxidation of Acyclic Amides 11a,b, ketones 13b, and Esters 13b,15

The oxidation of 11a and 11b (0.7 mmol) was carried out at room temperature in glacial AcOH (10 mL) in the presence of Mn(OAc)₃•2H₂O (0.42 mmol) under an oxygen atmosphere (1 atm) for 29 h. After the usual work-up, the corresponding alcohols 12a and 12b were obtained in poor yields. The physical data for the alcohols 12a and 12b are given in the Supplementary Data.

The aerobic oxidation of cyclopentanonecarboxylate derivatives 13a and 13b was as follows. To a solution of the cyclopentanonecarboxylate (1 mmol) in MeOH (10 mL), a mixture of Mn(OAc)₃•2H₂O (0.1 mmol) in MeOH (20 mL) was dropwise-added, and the mixture was stirred at room temperature for 12 h in air. The reaction mixture was then filtered through the silica gel column (eluted with Et₂O) to remove the catalyst. After removal of all volatile components using an evaporator, the corresponding alcohols 14a and 14b were obtained as oil. The physical data for the alcohols 14a and 14b are given in the Supplementary Data.

2-Alkyl-5,5-dimethylcyclohexane-1,3-diones 15 (R = Et, Pr, i-Pr, Bu, Bn) were prepared by the reaction of dimedone with the corresponding alkylbromide in the presence of sodium ethoxide in boiling ethanol [83]. The Mn(III)-catalyzed aerobic oxidation of 15 was carried out under various conditions; however, no reaction occurred.
4. Conclusions

The facile \( \alpha \)-oxygenation of cyclic amides was achieved by Mn(III)-initiated aerobic oxidation under very mild conditions. The direct hydroperoxidation was characteristic for the cyclic amides, such as 4-alkyl-1,2-diphenylpyrazolidine-3,5-diones 1a–h, 3-alkylpyrrolidine-2,4-diones 3a–p, 3-alkyl-1,5-dimethylbarbituric acids 5a–e, and 3-butyl-4-hydroxy-2-quinolinone 7. It was found that the obtained hydroperoxides gradually underwent redox degradation in the presence of Mn(III)/Mn(II) or Ce(IV)/Ce(III) under the conditions to convert into the corresponding alcohols. Acyclic amides and esters, such as malonamides 11a,b and cyclopentanonecarboxylates 13a,b, afforded the alcohols 12a,b and 14a,b, probably derived from a similar redox degradation of the corresponding hydroperoxides. Cyclic diketones, such as dimedone 15, was inactive under the aerobic oxidation conditions. The reason why the hydroperoxides were isolated in this reaction is assumed to be that, (1) it is difficult for the nucleophilic attack of the hydroperoxy group to occur at the amide carbonyl because the electrophilicity of the amide carbonyl carbon should be weak, and (2) the hydroperoxy group is stabilized by intramolecular hydrogen-bonding with the carbonyl group. The hydroperoxides are easily transformed into the corresponding alcohols by normal reduction using \( \text{Ph}_3\text{P} \).

Antimalarial testing of the hydroperoxide 2g was also performed using \textit{Plasmodium falciparum} FCR-3 strain (ATCC 30932), and a weak antimalarial activity (14% inhibition) was confirmed. In addition, in order to examine an inhibitory effect toward mRNAs in cells, HeLa cells were treated with the hydroperoxide 2g or 6b. However, an appreciable effect on the intracellular distribution of mRNAs was not observed (data not shown).

Supplementary Materials

Supplementary materials can be accessed on: http://www.mdpi.com/1420-3049/16/11/9562/s1.

Acknowledgements

This research was supported by Grants-in-Aid for Scientific Research (C), No. 15550039, No. 19550046, and No. 22550041, from the Japan s of Science. We gratefully acknowledge Teruo Shinmyouzu, Institute for Materials Chemistry and Engineering, Kyushu University, Japan, and Mikio Yasutake, Graduate School of Science and Engineering, Saitama University, Japan, for the measurement of the high resolution FAB mass spectrum and X-ray analysis, and also thank to Yusuke Wataya, Laboratory of Drug Informatics, Faculty of Pharmaceutical Science, Okayama University, Japan, for the antimalarial testing. We deeply appreciate Tokio Tani and Miss Yuko Azuma, Department of Biological Science, Graduate School of Science and Technology, Kumamoto University, Japan, for the mRNAs inhibitory testing.

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Sample Availability: Samples are available from the authors.

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