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Spontaneous Conversion of 3-Alkyl-substituted 3-Hydroperoxypyrrolidine-2,4-diones into 5-Alkyl-5-hydroxyoxazolidin-4-ones

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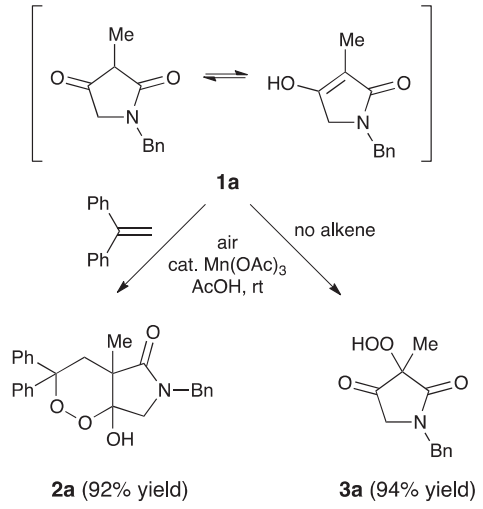
3-Hydroperoxypyrrolidine-2,4-diones substituted with an alkyl group at the 3-position were spontaneously transformed into 5-hydroxyoxazolidin-4-one derivatives at room temperature in air accompanied by the evolution of carbon monoxide.

Organic hydroperoxides are important not only as oxidation intermediates,[1] but also as organic oxidants.[2] The peroxides are also found in nature, some of which have several biological actvities.[3] In general, the oxygen–oxygen bond of peroxides is weak ($\Delta H°_{298}$ 158–194 kJ mol^{-1}),[4] and it is somewhat difficult to synthesize and isolate peroxide compounds. Recently, we reported a convenient peroxide synthesis using manganese(III)-catalyzed aerobic oxidation.[5] A mixture of 3-(2-oxoethyl)piperidine-2,4-diones and 1,1-diarylethenes underwent endoperoxidation to produce structurally interesting trioxaaza[4.4.3]propellanes.[6] The aerobic oxidation of arylacetylenes with pentane-2,4-dione gave the 1,2-dioxolane derivatives.[7] On the other hand, a similar reaction of cyclic amides such as barbituric acids,[6,8,9b] 1,2-disubstituted pyrazolidine-3,5-diones,[9] and 4-hydroxy-1*H*-qinolin-2-ones,[6,9b,10] afforded the corresponding hydroperoxy derivatives. Very recently, we found a similar endoperoxidation and hydroperoxidation of 3-alkyl-substituted pyrrolidine-2,4-diones in the presence[11] or absence[12] of 1,1-diarylethenes in connection with our aerobic oxidation study. For example, the reaction of 1-benzyl-3-methylpyrrolidine-2,4-dione (**1a**) gave the endoperoxide **2a** in the presence of 1,1-diphenylethene,[11] while the hydroperoxide **3a** was produced in the absence of the alkene (Scheme 1).[12] The endoperoxide **2a** was very stable and recrystallized from EtOAc/hexane as colorless needles (mp 210 °C), however, the solid hydroperoxide **3a** was not stable and gradually degraded in air at room temperature, giving a colorless viscous liquid. We were very interested in this spontaneous degeneration and scrutinized the reaction.

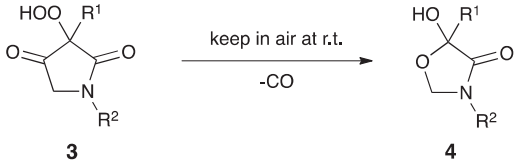


Scheme 1. Aerobic oxidation of pyrrolidinedione **1a**.

1-Benzyl-3-hydroperoxy-3-methylpyrrolidine-2,4-dione (**3a**) was prepared as follows. To a solution of the pyrrolidine-2,4-dione **1a** (1 mmol) in glacial acetic acid (25 mL), manganese(III) acetate dehydrate (26.8 mg, 0.1 mmol) was added. The mixture was stirred at room temperature in air for 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 CH_2Cl_2 (30 mL) and the combined extract was washed with water, then a saturated aqueous solution of sodium hydrogen carbonate, dried over anhydrous magnesium sulfate, and concentrated to dryness. Although the product was almost pure, it was further purified by silica gel flash column chromatography, eluting with EtOAc/hexane (8:2 v/v), and recrystallized from Et_2O/hexane to give the hydroperoxide **3a** in 94% yield as colorless blocks, mp 78–79 °C.[12,13]

When the colorless solid **3a** was kept in air in a glass vial at room temperature, the solid **3a** became a viscous liquid along with the evolution of a gas.[14] The liquid was purified by silica gel column chromatography eluting with EtOAc/hexane (5:5 v/v), and the obtained crude colorless solid was recrystallized from Et_2O/hexane to give **4a** as colorless needles that melted at 105 °C. Other detectable products were not isolated. In order to deduce the structure of **4a**, the spectroscopic data of **4a**[15] was compared with those of **3a**.[13] An important characteristic of the data was the fact that there were no *keto*-carbonyl groups in the compound **4a** and a ring methylene carbon (δ 77.1) and a ring quaternary carbon (δ 99.6) were shifted downfield (high frequency) compared to those of **3a** (δ 53.4 and 82.5, respectively) in the ^{13}C NMR spectrum. In fact, the molecular weight of **4a** was reduced m/z 28 from that of **3a** in the MS. Therefore, the structure of **4a** must be 3-benzyl-5-hydroxy-5-methyloxazolidin-4-one. The combustion analysis and HRMS also supported this structure (Scheme 2). It was suggested that the unique conversion must involve a rearrangement reaction accompanied by the extrusion of gas.

In order to scrutinize the reaction, other hydroperoxypyrrolidinediones **3b**–**3k** were prepared and kept in air at room temperature. Surprisingly, all the hydroperoxypyrrolidinediones degenerated, and the corresponding hydroxyoxazolidin-4-ones **4b**–**4i** were isolated after chromatographic separation except for the *N-tert*-butyl-protected hydroperoxypyrrolidinediones **3j** and **3k** (Scheme 2 and Table 1). In the case of **3j** and **3k**, a complex mixture was obtained after 72 h and no products could be isolated (Entries 13 and 14). Since the transformation of the hydroperoxides **3a** and **3c** into the oxazolidinones **4a** and **4c** was



a : R^1 = Me, R^2 = Bn
b : R^1 = Et, R^2 = Bn
c : R^1 = Pr, R^2 = Bn
d : R^1 = Me, R^2 = Bu
e : R^1 = Et, R^2 = Bu
f : R^1 = Bu, R^2 = Bu
g : R^1 = Me, R^2 = *i*-Pr
h : R^1 = Et, R^2 = *i*-Pr
i : R^1 = Pr, R^2 = *i*-Pr
j : R^1 = Bu, R^2 = *t*-Bu
k : R^1 = *n*-Hexyl, R^2 = *t*-Bu

Scheme 2. Conversion of hydroperoxypyrrolidinediones **3** into hydroxyoxazolidinones **4**.

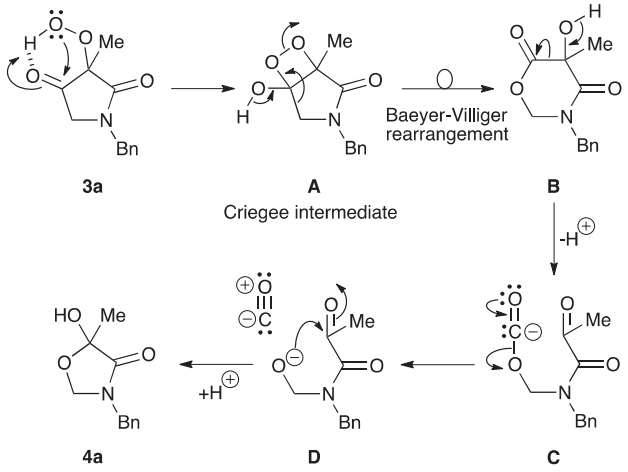
Table 1. Conversion of hydroperoxypyrrolidinediones **3** into hydroxyoxazolidin-4-ones **4**[a]

Entry	Pyrrolidinedione	Time/h	Oxazolidine/%[b]
1	**3a**	72	**4a** (30)
2[c]	**3a**	2	**4a** (40)
3	**3b**	72	**4b** (60)
4	**3c**	96	**4c** (20)
5[d]	**3c**	24	**4c** (35)
6[c]	**3c**	2	**4c** (60)
7	**3d**	24	**4d** (quant)
8	**3e**	24	**4e** (quant)
9	**3f**	24	**4f** (quant)
10	**3g**	48	**4g** (40)
11	**3h**	48	**4h** (45)
12	**3i**	48	**4i** (39)
13	**3j**	72	complex mixture
14	**3k**	72	complex mixture

[a]The hydroperoxypyrrolidinedione **3** (0.5 mmol) was stored in air at room temperature. [b]The yield based on the hydroperoxypyrrolidinedione **3** used. [c]The hydroperoxide (0.5 mmol) was heated under reflux in $CHCl_3$ (10 mL) for 2 h. [d]The reactant was heated at 100 °C without any solvent for 24 h.

not very efficient, the conversion was carried out at reflux temperature in $CHCl_3$ for 2 h to afford the oxazolidinones **4a** and **4c** in much better yields (Entries 2 and 6).

The degradation pathway was so mysterious. However, there were two hints to elucidate the pathway. One was that the hydroperoxy group of **3a** formed a hydrogen bond with the *keto*-carbonyl group. In fact, the hydroperoxy group appeared at δ 11.28 in the ^{1}H NMR spectrum.[16] In addition, the crystal structure of 4-benzyl-4-hydroperoxy-1,2-diphenylpyrazolidine-3,5-dione showed that the distance between the carbonyl oxygen and the terminal hydroperoxy oxygen was 2.705 Å, which means that the hydroperoxy group is stabilized by the formation of hydrogen bonding.[9b] The other hint was that a gas was evolved during the degradation. In order to determine the type of gas, we checked the gas using a short-term quick-measuring detector tube[17] and the evolved gas proved to be carbon monoxide. Accordingly, we deduced the degradation process as follows. The nucleophilic addition of the hydrogen-bonded hydroperoxy group to the *keto*-carbonyl group might form the Criegee-type intermediate **A**,[18] which must undergo the Baeyer–Villiger rearrangement to give the 5-hydroxy-1,3-oxazinane-4,6-dione intermediate **B**.[19] The hydroxyoxazinanedione **B** would spontaneously ring-open to generate an unstable oxomethanide **C** followed by the release of carbon monoxide and subsequent recyclization of **D**, affording the hydroxyoxazolidinone **4a**. The pathway is briefly depicted in Scheme 3. Unfortunately, the intermediates have not been isolated at this moment.



Scheme 3. Mechanistic pathway of conversion from **3a** to **4a**.

In summary, the hydroperoxypyrrolidinediones **3** were relatively stable in acetic acid, however, when the hydroperoxides **3** were once isolated and kept in air at room temperature, the hydroperoxides **3** spontaneously underwent degradation to afford the very stable hydroxyoxazolidinones **4**. The transformation of the hydroperoxides **3** depended on the *N*-protective group, that is, only the *N*-butyl group gave a good result, but the *N*-benzyl and *N*-isopropyl groups did not. The *N*-*tert*-butyl group was quite complicated. In order to control the production of the hydroxyoxazolidinones **4**, further exploration of the reaction is currently in progress.

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13 **1-Benzyl-3-hydroperoxy-3-methylpyrrolidine-2,4-dione (3a)**: Yield (221.1 mg, 94%); $R_f = 0.67$ (EtOAc:hexane = 8:2 v/v); colorless blocks (from Et_2O/hexane); mp 78–79 °C; IR ($CHCl_3$): ν 3400–3000 (OOH), 1786, 1666 (C=O); ^{1}H NMR ($CDCl_3$): δ 11.28 (1H, s, OOH), 7.36–7.27 (5H, m, arom H), 4.79 (1H, d, $J = 14.7$ Hz, CH_2), 4.64 (1H, d, $J = 14.7$ Hz, CH_2), 3.75 (2H, s, CH_2), 1.39 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 204.1 (C-4, C=O), 171.3 (C-2, C=O), 134.0, 129.1, 128.4, 128.3 (arom C), 82.5 (C-3), 53.4 (C-5, CH_2), 46.8 ($PhCH_2$), 16.7 (Me). FAB HRMS (acetone/NBA) m/z: calcd for $C_{12}H_{14}NO_4$ 236.0923 (M + H); found 236.0935.

14 The solid **3a** also changed into viscous liquid under an argon atmosphere, even when stored in a refrigerator at −20 °C.

15 **3-Benzyl-5-hydroxy-5-methyloxazolidin-4-one (4a)**: Yield (40%); $R_f = 0.32$ (EtOAc:hexane = 6:4 v/v); colorless needles (from Et_2O/hexane); mp 105 °C; IR (KBr): ν 3400–3100 (OH), 1678 (C=O); ^{1}H NMR ($CDCl_3$): δ 7.34–7.22 (5H, m, arom H), 5.00 (1H, d, $J = 3.3$ Hz, CH_2), 4.75 (1H, d, $J = 3.3$ Hz, CH_2), 4.63 (1H, br s, OH), 4.59 (1H, d, $J = 15.0$ Hz, CH_2), 4.38 (1H, d, $J = 15.0$ Hz, CH_2), 1.63 (3H, s, Me); ^{13}C NMR ($CDCl_3$): δ 169.5 (C=O), 134.7, 128.9, 128.2, 127.9 (arom C), 99.6 (C-5), 77.1 (C-2, CH_2), 44.7 ($PhCH_2$), 23.0 (Me). FAB HRMS (acetone/NBA/NaI) m/z: calcd for $C_{11}H_{13}NO_3Na$ 230.0793 (M + Na); found 230.0800. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76%. Found: C, 63.80; H, 6.48; N, 6.79%.[20]

16 The hydroperoxy group of the cyclic amides normally appeared at δ 8.6–9.8, for example, bis(hydroperoxyethyl)barbituric acids (δ 8.6–9.2),[6,8] bis(hydroperoxyethyl)pyrazolidinediones (δ 8.8–9.8),[9a] and bis(hydroperoxyethyl)quinolinediones (δ 9.2).[10]

17 The short-term quick-measuring detector tube was commercially available from the GASTEC Corporation, Japan, and a Polytec IV No. 27 detector tube was used to detect the gas.

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20 The physical data of the hydroxyoxazolidinones **4b**–**4i** are listed below.

3-Benzyl-5-ethyl-5-hydroxyoxazolidin-4-one (4b): Yield (60%); $R_f = 0.30$ (EtOAc:hexane = 6:4 v/v); pale yellow needle (from Et_2O/hexane); mp 103 °C; IR (KBr): ν 3400–3100 (OH), 1678 (C=O); ^{1}H NMR ($CDCl_3$): δ 7.33–7.25 (5H, m, arom H), 5.04 (1H, s, CH_2^a), 4.77 (1H, s, CH_2^b), 4.68 (1H, d, $J = 15.0$ Hz, $PhCH_2^a$), 4.33 (1H, d, $J = 15.0$ Hz, $PhCH_2^b$), 3.67 (1H, br s, OH), 1.97 (2H, m, CH_2), 0.94 (3H, t, $J = 7.5$ Hz, Me); ^{13}C NMR ($CDCl_3$): δ 169.0 (C=O), 134.7, 128.9, 128.0, 127.8 (arom C), 101.9 (C-5), 77.7 (C-2, CH_2), 44.6 ($PhCH_2$), 29.4 (CH_2), 7.5 (Me). FAB HRMS (acetone/NBA) m/z: calcd for $C_{12}H_{16}NO_3$ 222.1130 (M + H); found 222.1135.

3-Benzyl-5-hydroxy-5-propyloxazolidin-4-one (4c): Yield (60%); $R_f = 0.50$ (EtOAc:hexane = 6:4 v/v); pale yellow needle (from EtOAc/hexane); mp 103 °C; IR (KBr): ν 3500–3100 (OH), 1708 (C=O); ^{1}H NMR ($CDCl_3$): δ 7.28–7.15 (5H, m, arom H), 4.92 (1H, d, $J = 1.8$ Hz, CH_2), 4.69 (1H, d, $J = 1.8$ Hz, CH_2), 4.58 (1H, d, $J = 9.0$ Hz, $PhCH_2^a$), 4.28 (1H, d, $J = 9.0$ Hz, $PhCH_2^b$), 3.60 (1H, br s, OH), 1.82 (2H, m, CH_2), 1.37 (1H, m, CH_2), 1.28 (1H, m, CH_2), 0.86 (3H, t, $J = 4.5$ Hz, Me); ^{13}C NMR ($CDCl_3$): δ 169.0 (C=O), 134.7, 129.0, 128.2, 127.8 (arom C), 101.4 (C-5), 77.6 (C-2, CH_2), 44.6 ($PhCH_2$), 38.4, 16.5 (CH_2), 13.9 (Me). FAB HRMS (acetone/NBA/NaI) m/z: calcd for $C_{13}H_{17}NO_3Na$ 258.1106 (M + Na); found 258.1065.

3-Butyl-5-hydroxy-5-methyloxazolidin-4-one (4d): Yield (quant); $R_f = 0.45$ (EtOAc:hexane = 8:2 v/v); colorless liquid; IR ($CHCl_3$): ν 3585–3100 (OH), 1710 (C=O); ^{1}H NMR ($CDCl_3$): δ 5.03 (1H, d, $J = 2.1$ Hz, CH_2), 4.82 (1H, d, $J = 2.1$ Hz, CH_2), 4.44 (1H, br s, OH), 3.30 (1H, m, CH_2), 3.22 (1H, m, CH_2), 1.52 (3H, s, CH_3), 1.47 (2H, m, CH_2), 1.28 (2H, m, CH_2), 0.87 (3H, t, $J = 6.0$ Hz, Me); ^{13}C NMR ($CDCl_3$): δ 169.2 (C=O), 99.5 (C-5), 77.0 (C-2, CH_2), 40.5, 29.4, 19.9 (CH_2), 23.0, 13.6 (Me). FAB HRMS (acetone/NBA/NaI) m/z: calcd for $C_8H_{15}NO_3Na$ 196.0950 (M + Na); found 196.0923.

3-Butyl-5-ethyl-5-hydroxyoxazolidin-4-one (4e): Yield (quant); $R_f = 0.33$ (EtOAc:hexane = 6:4 v/v); colorless liquid; IR ($CHCl_3$): ν 3600–3100 (OH), 1708 (C=O); ^{1}H NMR ($CDCl_3$): δ 5.12 (1H, d, $J = 3.3$ Hz, CH_2), 4.92 (1H, d, $J = 3.3$ Hz, CH_2), 4.22 (1H, br s, OH), 3.44 (1H, m, $^aCH_2$), 3.26 (1H, m, $^bCH_2$), 1.88 (2H, m, CH_2), 1.54 (2H, m, CH_2), 1.33 (2H, m, CH_2), 0.96 (3H, t, $J = 7.5$ Hz, Me), 0.92 (3H, t, $J = 7.8$ Hz, Me); ^{13}C NMR ($CDCl_3$): δ 168.8 (C=O), 101.9 (C-5), 78.2 (C-2, CH_2), 40.4 (CH_2), 29.4 ($2CH_2$), 19.9 (CH_2), 13.5, 7.4 (Me). FAB HRMS (acetone/NBA/NaI) m/z: calcd for $C_9H_{17}NO_3Na$ 210.1106 (M + Na); found 210.1110.

3,5-Dibutyl-5-hydroxyoxazolidin-4-one (4f): Yield (quant); $R_f =$ 0.39 (EtOAc:hexane = 5:5 v/v); colorless liquid; IR ($CHCl_3$): ν 3585–3100 (OH), 1705 (C=O); ^{1}H NMR ($CDCl_3$): δ 5.10 (1H, br s, OH), 5.04 (1H, d, $J = 3.3$ Hz, CH_2), 4.83 (1H, d, $J = 3.3$ Hz, CH_2), 3.34 (1H, m, CH_2), 3.17 (1H, m, CH_2), 1.81 (2H, m, CH_2), 1.47 (2H, m, CH_2), 1.26 (6H, m, $3CH_2$), 0.87 (3H, t, $J = 7.2$ Hz, Me), 0.82 (3H, t, $J = 6.3$ Hz, Me); ^{13}C NMR ($CDCl_3$): δ 169.0 (C=O), 101.6 (C-5), 78.0 (C-2, CH_2), 40.3, 35.9, 29.3, 25.1, 22.4, 19.8 (CH_2), 13.8, 13.5 (Me). FAB HRMS (acetone/NBA) m/z: calcd for $C_{11}H_{22}NO_3$ 216.1600 (M + H); found 216.1598.

5-Hydroxy-3-isopropyl-5-methyloxazolidin-4-one (4g): Yield (40%); $R_f = 0.46$ (EtOAc:hexane = 9:1 v/v); Colorless liquid; IR ($CHCl_3$): ν 3500–3200 (OH), 1708 (C=O); ^{1}H NMR ($CDCl_3$): δ 5.05 (1H, d, $J = 2.1$ Hz, CH_2), 4.87 (1H, d, $J = 2.1$ Hz, CH_2), 4.20 (1H, sep, $J = 4.2$ Hz, CH), 2.29 (1H, br s, OH), 1.52 (3H, s, CH_3), 1.16 (6H, d, $J = 4.2$ Hz, 2Me); ^{13}C NMR ($CDCl_3$): δ 168.5 (C=O), 99.9 (C-5), 74.4 (C-2, CH_2), 43.2 (CH), 22.9, 20.0, 19.8 (Me). FAB HRMS (acetone/NBA) m/z: calcd for $C_7H_{14}NO_3$ 160.0974 (M + H); found 160.0956.

5-Ethyl-5-hydroxy-3-isopropyloxazolidin-4-one (4h): Yield (45%); $R_f = 0.46$ (EtOAc:hexane = 9:1 v/v); colorless liquid; IR ($CHCl_3$): ν 3500–3200 (OH), 1707 (C=O); ^{1}H NMR ($CDCl_3$): δ 5.13 (1H, d, $J = 2.1$ Hz, CH_2), 4.96 (1H, d, $J = 2.1$ Hz, CH_2), 4.32 (1H, sep, $J = 4.2$ Hz, CH), 3.22 (1H, br s, OH), 2.00–1.85 (2H, m, CH_2), 1.24 (3H, d, $J = 4.2$ Hz, Me), 1.22 (3H, d, $J = 4.2$ Hz, Me), 0.94 (3H, t, $J = 4.5$ Hz, Me); ^{13}C NMR ($CDCl_3$): δ 167.5 (C=O), 102.1 (C-5), 75.0 (C-2, CH_2), 43.1 (CH), 29.7 (CH_2), 20.2, 19.8, 7.4 (Me). FAB HRMS (acetone/NBA/NaI) m/z: calcd for $C_8H_{15}NO_3Na$ 196.0950 (M + Na); found 196.0976.

5-Hydroxy-3-isopropyl-5-propyloxazolidin-4-one (4i): Yield (39%); $R_f = 0.50$ (EtOAc:hexane = 8:2 v/v); colorless liquid; IR ($CHCl_3$): ν 3585–3100 (OH), 1705 (C=O); ^{1}H NMR ($CDCl_3$): δ 5.14 (1H, d, $J = 2.1$ Hz, CH_2), 4.94 (1H, d, $J = 2.1$ Hz, CH_2), 4.29 (1H, sep, $J = 4.2$ Hz, CH), 4.03 (1H, br s, OH), 1.93–1.76 (2H, m, CH_2), 1.48–1.42 (1H, m, CH_2), 1.36–1.31 (1H, m, CH_2), 1.27 (3H, d, $J = 4.2$ Hz, Me), 1.20 (3H, d, $J = 4.2$ Hz, Me), 0.93 (3H, t, $J = 4.8$ Hz, Me); ^{13}C NMR ($CDCl_3$): δ 167.8 (C=O), 101.8 (C-5), 74.9 (C-2, CH_2), 43.1 (CH), 38.5, 16.5 (CH_2), 20.1, 19.7, 13.9 (Me). FAB-HRMS (acetone/NBA/NaI) m/z: calcd for $C_9H_{17}NO_3$-Na 210.1106 (M + Na); found 210.1102.

