SYNTHESIS OF AZABICYCLIC PEROXIDES CONNECTED BY METHYLENE CHAIN USING MANGANESE(III)-CATALYZED SIMULTANEOUS CYCLIZATION ON BOTH ENDS

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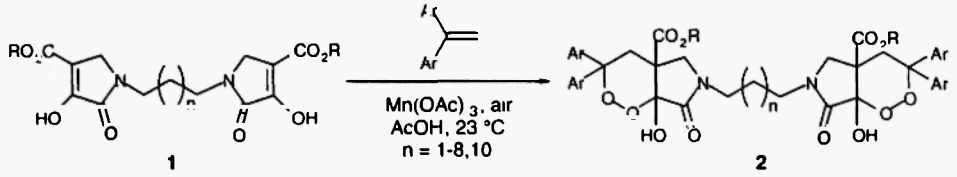
Abstract: Dialkyl *N,N'*-oligomethylenebis(2,3-pyrrolidinedione-4-carboxylate)s reacted with 1,1-diarylethenes in the presence of manganese(III) acetate in a dry air stream to give dialkyl *N,N'*-oligomethylenebis(1-hydroxy-4,4-diaryl-8-aza-2,3-dioxabicyclo[4.3.0]nonan-9-one-6-carboxylate)s in good yields. It was observed that the longer the methylene chain length of the *N,N'*-oligomethylenebis(2,3-pyrrolidinedione)s, the higher the yield of the corresponding bis(8-aza-2,3-dioxabicyclo[4.3.0]nonan-9-one)s. Dialkyl *N,N'*-oligooxamethylenebis(2,3-pyrrolidinedione-4-carboxylate)s also reacted with 1,1-diphenylethene under similar reaction conditions to give a similar result. The *N,N'*-octamethylenebis(8-aza-2,3-dioxabicyclo[4.3.0]nonan-9-one) derivative was easily converted to the corresponding bis(7-aza-2-oxabicyclo[3.3.0]octan-8-one) under palladium-catalyzed reduction conditions.

Pyrrolidinedione derivatives are very useful not only as starting materials in biologically active natural product synthesis,[1] but also as the carbon radical source in the manganese(III) oxidation system.[2,3] Pyrrolidinedione reacts with manganese(III) acetate in glacial acetic acid to form a new complex *in situ*[2,5] which electrophilically attacks a 1,1-disubstituted alkene to give an alkenyl-substituted pyrrolidinedione at reflux temperature[3] or an azabicyclic peroxide at 23 °C in air.[3] In order to prepare structurally interesting azabicyclic peroxides, we attempted the synthesis of dumbbell-type compounds which connected two azabicyclic peroxides in the methylene or oxamethylene chain since such bioactive peroxides have been isolated from some marine sponges,[6] and they can be used in the rotaxane synthesis as dumbbell-type molecules.[7] In addition, the bis(peroxide)s might be synthetically useful since the 1,2-dioxan-3-ols can be converted into the furan derivatives by acidic cleavage[8] and catalytic hydrogenation.[9]

Dialkyl *N,N'*-oligomethylenebis(2,3-pyrrolidinedione-4-carboxylate)s **1** were synthesized by the Dieckmann condensation of dialkyl oxalates and *N,N'*-bis(alkoxycarbonylethyl)-α,ω-alkanediamines which were prepared by the



Scheme 1. Mn(III)-Catalyzed Reaction of **1** with Alkenes at 23 °C under Air

Table 1. Reaction of Dialkyl *N,N'*-Oligomethylenebis(2,3-pyrrolidinedione-4-carboxylate)s **1** with 1,1-Diarylethenes in the Presence of Manganese(III) Acetate[a]

Entry	1		Ethene	Time	Product **2**
	R	n	Ar	h	yield/%[b]
1	Et	1	Ph	36	46
2	Et	2	Ph	40	61
3	Et	3	Ph	40	73
4	Et	4	Ph	48	74
5	Me	4	Ph	48	71
6	Et	4	4-MeC_6H_4	40	93
7	Et	4	4-$MeOC_6H_4$	36	64
8	Et	4	4-ClC_6H_4	40	72
9	Et	4	4-FC_6H_4	48	70
10	Et	5	Ph	46	80
11	Et	6	Ph	48	82
12	Me	6	Ph	48	76
13	Bu	6	Ph	44	54
14	Et	7	Ph	54	83
15	Et	8	Ph	40	87
16	Et	10	Ph	24	91

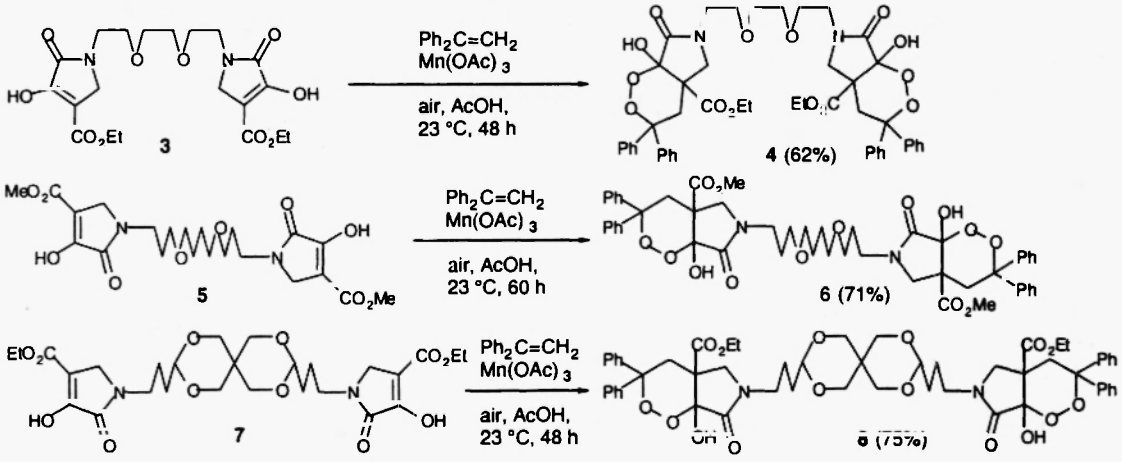
[a] The reaction was carried out at the molar ratio of bis(2,3-pyrrolidinedione):ethene:$Mn(OAc)_3 \cdot 2H_2O$ = 1:3:1 in glacial acetic acid (100 mL) at 23 °C under a dry air stream. [b] Isolated yield based on the amount of the bis(2,3-pyrrolidinedione) **1** used.

addition of alkyl acrylates with the corresponding alkanediamines. A mixture of diethyl *N,N'*-trimethylenebis(2,3-pyrrolidinedione-4-carboxylate) **1** (R = Et, n = 1) (1 mmol), 1,1-diphenylethene (3 mmol), and manganese(III) acetate dihydrate (1 mmol) was stirred in glacial acetic acid (100 mL) at 23 °C in a dry air stream. After 36 h, the dark-brown color of the reaction mixture turned colorless. The solvent was removed *in vacuo* and the residue was ultrasonicated with water to give a colorless solid of which the structure was deduced to be diethyl *N,N'*-trimethylenebis(1-hydroxy-4,4-diphenyl-8-aza-2,3-dioxabicyclo[4.3.0]nonan-9-one-6-carboxylate) **2** (R = Et, n = 1) based on the NMR and IR spectra (Scheme 1 and Table 1, Entry 1).[10] In the reaction, the Mn(III)-pyrrolidinedione enolate complex would be formed during the first step, followed by oxidatively reacting with 1,1-diphenylethene to produce a tertiary radical, 1,1-diphenyl-2-(4-pyrrolidinyl)ethyl radical, and manganese(II) acetate. The tertiary radical should immediately react with molecular oxygen under the reaction conditions to produce peroxyl radicals which would be easily reduced by Mn(II). Therefore, the reaction should be catalytic. A similar catalytic oxidation

of other diethyl *N,N'*-oligomethylenebis(2,3-pyrrolidinedione-4-carboxylate)s **1** (R = Et, n = 2-8,10) with 1,1-diphenylethene also gave the corresponding bis(8-aza-2,3-dioxabicyclo[4.3.0]nonan-9-one-6-carboxylate)s **2** in good yields (Table 1, Entries 2-5, 10, 11, 14-16). It was observed that the longer the methylene chain length of **1** (n = 1→ 10), the higher the yield of the corresponding azabicyclic peroxides **2**. This reaction was also applicable for use with the methyl and butyl carboxylates **1** (R = Me and Bu, n = 4 and 6) (Table 1, Entries 5, 12, and 13) and other 1,1-disubstituted ethenes (Table 1, Entries 6-9).

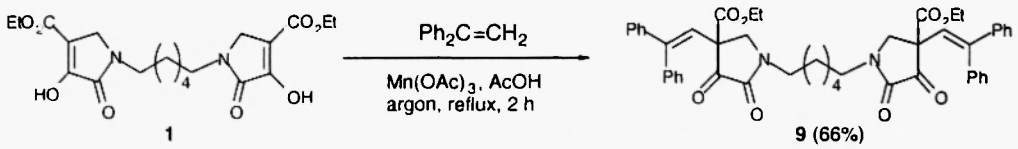
Although dialkyl *N,N'*-oligomethylenebis(2,3-pyrrolidinedione-4-carboxylate)s **1** were not very soluble in acetic acid, and therefore, the catalytic cyclization took a long reaction time (normally two days), only the almost pure solid product **2** could be easily isolated after the treatment of the reaction residue by the ultrasonication with water.[11]

Dialkyl *N,N'*-oligooxamethylenebis(2,3-pyrrolidinedione-4-carboxylate)s **3**, **5**, and **7** were also prepared by a similar reaction of 1,2-bis(2-aminoethoxy)ethane, 1,4-bis(3-aminopropoxy)butane, and 3,9-bis(3-aminopropyl)-2,4,8,10-tetraoxaspiro[5.5]undecane with ethyl acrylate followed by the Dieckmann condensation with dialkyl oxalate, and then the manganese(III)-catalyzed oxidation with 1,1-diphenylethene was carried out. The reaction also gave the corresponding azabicyclic peroxides **4**, **6**, and **8** connected by an oligooxamethylene chain in acceptable yields (Scheme 2).



Scheme 2. Mn(III)-Catalyzed Reaction of **3**, **5**, and **7** with 1,1-Diphenylethene at 23 °C under Air

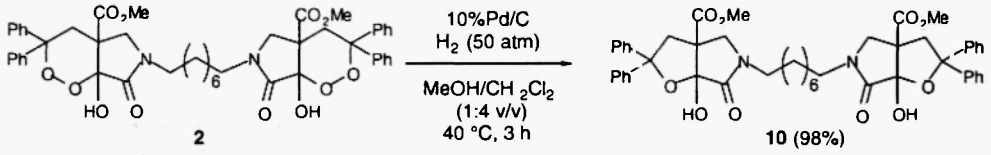
An approach to prepare the 7-aza-2-oxabicyclo[3.3.0]octan-8-ones was also performed in the absence of molecular oxygen since the tertiary radical formed during the reaction under an argon atmosphere should be oxidized with manganese(III) acetate to give the corresponding carbocation which would easily cyclize. To a boiling solution of 1,1-diphenylethene (2 mmol) and acetic acid (30 mL) degassed before use, bis(pyrrolidinedione) **1** (R = Et, n = 4) (0.5 mmol) and manganese(III) acetate (4 mmol) were added. The heating was continued for 2 h under an argon atmosphere and the Mn(III) was completely consumed. After the usual work-up, the desired bicyclo[3.3.0]octane



Scheme 3. Oxidation of **1** with $Mn(OAc)_3$ in the Presence of 1,1-Diphenylethene under Argon

was not isolated but ethenyl-substituted bis(pyrrolidinedione) **9** was obtained in 66% yield (Scheme 3).

We recently reported that the palladium-catalyzed hydrogenolysis of 1-hydroxy-8-aza-2,3-dioxabicyclo[4.3.0]-nonanes led to the formal extrusion of one of the peroxide oxygens and quantitatively produced 1-hydroxy-7-aza-2-oxabicyclo[3.3.0]octanes.[9c] In order to confirm the ring reduction of the bis(8-aza-2,3-dioxabicyclo[4.3.0]nonan-9-ones, the hydrogenolysis of azabicyclic peroxide **2** (R = Me, n = 6) was conducted in the presence of palladium-carbon. As a result, dimethyl *N,N'*-octamethylenebis(1-hydroxy-3,3-diphenyl-7-aza-2-oxabicyclo[3.3.0]octan-8-one-5-carboxylate) **10** was obtained in 98% yield (Scheme 4). This result strongly suggested that the hydrogenolysis could also be effective for other azabicyclic peroxides **2**.



Scheme 4. Pd-Catalyzed Hydrogenolysis of Peroxide **2**

In conclusion, we have achieved the facile dumbbell-type azabicyclic peroxide synthesis and confirmed that the azabicyclic peroxides were easily converted to azabicyclo[3.3.0]octanes connected by a methylene chain. Further investigations to apply the present Mn(III)-catalyzed reaction for synthesis of macrocyclic compounds[12] as the wheel and rotaxanes[7] which consist of the dumbbell-type azabicyclic peroxide as the axle molecule are now in progress.

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(10) Diethyl *N,N'*-Tetramethylenebis(1-hydroxy-4,4-diphenyl-8-aza-2,3-dioxabicyclo[4.3.0]nonan-9-one-6-carboxylate) (**2**) (R = Et, n = 2): colorless microcrystals (from ethanol); mp 146-148 °C; IR (KBr) 3600-3100 (OH), 1732, 1710 (C=O); ^{1}H NMR (DMSO-d_6) 8.14 (2H, br s, OH x 2), 7.56-7.01 (20H, m, Ph x 4), 4.07 (4H, m, CH_2 x 2), 3.56 (4H, m, CH_2 x 2), 3.08 (4H, m, CH_2 x 2), 2.82 (4H, m, CH_2 x 2), 1.13 (6H, t, J = 7.21, CH_3 x 2), 0.78 (4H, m, CH_2 x 2); ^{13}C NMR (DMSO-d_6) 170.9 (C=O x 2), 166.0 (O=C-N x 2), 145.1, 142.6 (arom C x 4), 128.4, 128.3, 127.5, 127.0, 125.7, 124.9 (arom CH x 20), 100.2 (C-1 x 2), 83.5 (C-4 x 2), 61.0 (CH_2 x 2), 48.1 (CH_2 x 2), 41.4 (CH_2 x 2), 32.0 (CH_2 x 2), 22.7 (CH_2 x 2), 46.9 (C-6 x 2), 13.7 (CH_3 x 2). HRMS Found: *m/z* 821.3293. Calcd for $C_{46}H_{48}N_2O_{12}$: M+1, 821.3286.

Diethyl *N,N'*-Hexamethylenebis(1-hydroxy-4,4-diphenyl-8-aza-2,3-dioxabicyclo[4.3.0]nonan-9-one-6-carboxylate) (**2**) (R = Et, n = 4): colorless microcrystals (from ethanol); 144-145 mp °C; IR (KBr) 3600-3065 (OH), 1736, 1711 (C=O); ^{1}H NMR (DMSO-d_6) 8.14 (2H, br s, OH x 2), 7.60-7.23 (20H, m, Ph x 4), 4.07 (4H, m, CH_2 x 2), 3.17 (4H, m, CH_2 x 2), 3.06 (4H, m, CH_2 x 2), 2.89 (4H, m, CH_2 x 2), 1.12 (6H, t, J = 7.21, CH_3 x 2), 1.00 (4H, m, CH_2 x 2), 0.71 (4H, m, CH_2 x 2); ^{13}C NMR (DMSO-d_6) 170.9 (C=O x 2), 165.9 (O=C-N x 2),

145.2, 142.5 (arom C x 4), 128.3, 128.2, 127.4, 127.0, 125.7, 124.8 (arom CH x 20), 100.2 (C-1 x 2), 83.4 (C-4 x 2), 60.9 (CH_2 x 2), 48.3 (CH_2 x 2), 41.9 (CH_2 x 2), 31.8 (CH_2 x 2), 25.8 (CH_2 x 2), 25.2 (CH_2 x 2), 47.0 (C-6 x 2), 13.7 (CH_3 x 2). HRMS Found: *m/z* 849.3596. Caled for $C_{48}H_{52}N_2O_{12}$: M+1, 849.3599.

(11) General Procedure for the Mn(III)-Catalyzed Reaction: Dialkyl bis(2,3-pyrrolidinedione-4-carboxylate) **1** (1 mmol), 1,1-diarylethene (3 mmol), manganese(III) acetate dihydrate (1 mmol), and glacial acetic acid (100 mL) were placed in a 300 mL three-necked flask equipped with a magnetic stirrer and gas inlet tube. The mixture was stirred at 23 °C in a dry air stream for the period shown in Table 1. The consumption of Mn(III) was checked by the potassium iodide paper test. The solvent was removed *in vacuo* and the residue was triturated with water.

Method 1: The aqueous mixture was sufficiently ultrasonicated and filtered. The obtained solid was washed with water, methylene chloride, and then hexane. After drying in a desiccator, almost pure azabicyclic peroxide **2** was obtained. Further purification was done by recrystallization from ethanol.

Method 2: The aqueous mixture was extracted three times with chloroform (30 x 3 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The products were separated by flash chromatography while eluting with 2% methanol in chloroform. The obtained azabicyclic peroxide **2** was further purified for analytical sample by recrystallization from ethanol.

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