Manganese(III) Acetate Oxidation of 1-Acetylindole Derivatives

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In the presence of malonic acid, the reaction of 1-acetylindole (**2**) with manganese(III) acetate resulted in the formation of 4-acetyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indol-2-one (**5**). The same reaction of 1-acetyl-2,3-dimethylindole yielded a mixture of 2-acetoxymethyl-1-acetyl-3-methylindole and 4-acetyl-3a,8b-dimethyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indol-2-one, furthermore, the oxidation of 1-acetylindoline proceeded to the formation of **2, 5** and 1-acetylindoline-5-carboxylic acid.

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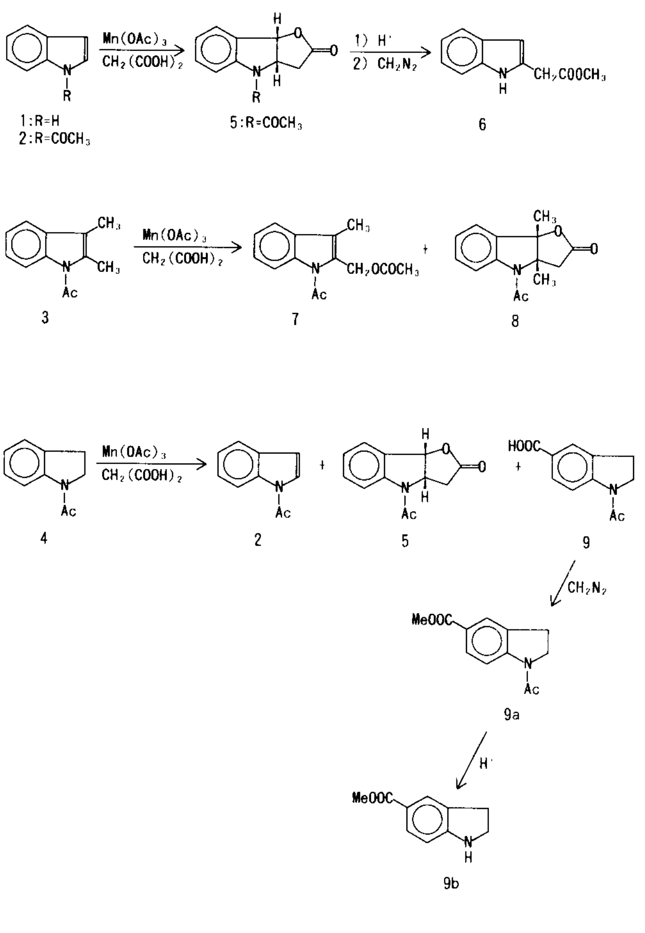
Various literature exists on manganese(III) acetate as source of electrophylic radicals, which can be trapped by alkenes or aromatics, to give interesting functionalized products [1]. Bush and Finkbeiner [2], and Heiba *et al.* [3] have reported that the reaction of alkenes with manganese(III) acetate in acetic acid leads to the formation of γ-lactones with high efficiency, and they suggested that the reactions proceed by a free radical mechanism involving the selective generation and oxidation of organic free radicals ($\cdot CH_2COOH$). On the other hand, Fristad and Hershberger [4] reported that, in the presence of malonic acid, manganese(III) oxidation of alkenes results in the formation of spiro-fused lactones, and they suggested that the dicarboxymethyl radicals [$\cdot CH(COOH)_2$] which was produced in the oxidation system, participated in the spiroannulation. Nishino *et al.* [5] also described that, in the presence of manganese(III) acetate, the reaction of aromatic compounds with malonic acid leads to formyl-

Scheme 1



Scheme 2

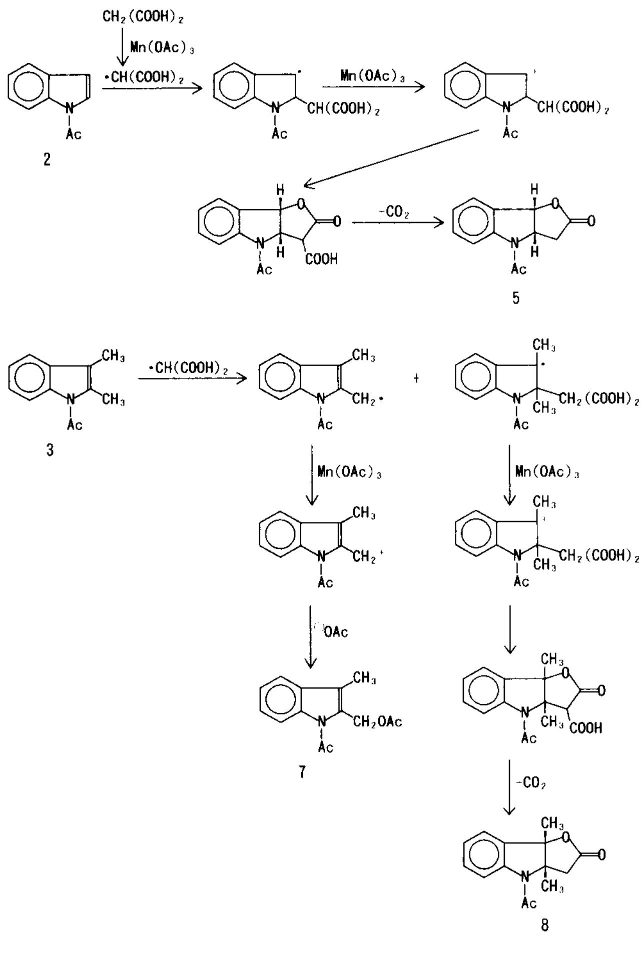


Table 1

Manganese (III) Acetate Oxidation of 2,3 and 4 in the Presence of Malonic Acid

Entry	Starting Material	Molar ratio [a]	Time (hours)	Temperature (°C)	Product Yield (%) [b]	Recovered Starting Material, yield (%)
1	**2**	1 : 4 : 4	0.5	70	**5** (44)	**2** (25)
2	**3**	1 : 4 : 4	1	70	**7** (23), **8** (46)	–
3	**4**	1 : 4 : 4	1	70	**2** (3), **5** (3) **9** (1)	**4** (70)
4	**4**	1 : 4 : 4	0.5	reflux	**2** (11), **5** (8) **9** (3)	**4** (65)
5	**4**	1 : 4 : 8	1	reflux	**2** (4), **5** (18) **9** (2)	**4** (63)

[a] Molar ratio = substrate:Mn (III):malonic acid. [b] Isolated yield based on the substrate used.

ated and carboxylated products. Therefore it is considered that indole (**1**) possesses some characteristic of an olefin, in addition of a generally aromatic character [6]. Herein, we wish to report the results obtained in the manganese(III) acetate oxidation of **1**, 1-acetylindole (**2**), 1-acetyl-2,3-dimethylindole (**3**) and 1-acetylindoline (**4**) in the presence of malonic acid (Scheme 1).

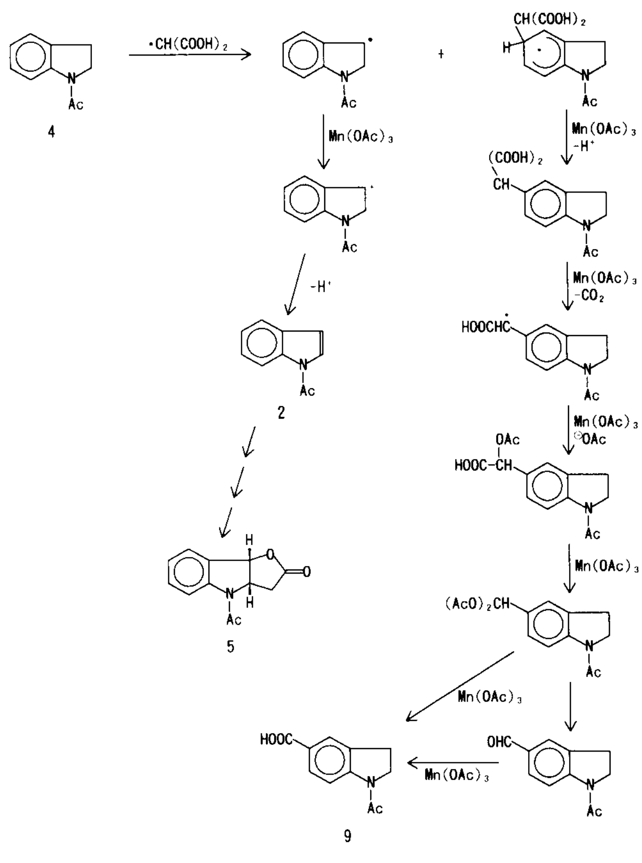
Results and Discussion.

A mixture of **1** and manganese(III) acetate [**1**:Mn(III) = 1:4] was heated in refluxing acetic acid until the dark brown color of Mn(III) had disappeared, however, the reaction was troublesome and proceeded to the formation of polymerization products. Therefore, in the manganese(III) oxidation with malonic acid in acetic acid, we carried the reaction out using *N*-acetyl derivatives **2**, **3** and **4**, instead of **1**, 2,3-dimethylindole and indoline.

In the presence of malonic acid, compound **2** was oxidized at 70° with manganese(III) acetate at a molar ratio of **2**:[Mn]:malonic acid = 1:4:4, and after 30 minutes, 4-acetyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indol-2-one (**5**) was obtained in moderate yield (44%) (see Table 1, entry 1). The structure of **5** was established by the spectral and elemental analyses, and by the derivation to methyl 2-indoleacetate (**6**) by hydrolysis and following esterification with diazomethane. Under the same conditions, the oxidation of **3** afforded 2-acetoxymethyl-1-acetyl-3-methylindole (**7**) and 4-acetyl-3a,8b-dimethyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indol-2-one (**8**) (Entry 2). Furthermore, the reaction of **4** in the presence of malonic acid yielded a mixture of **2**, **5** and 1-acetylindoline-5-carboxylic acid (**9**) (Entries 3, 4, 5).

Generally, in the presence of alkenes, the manganese(III) oxidation of malonic acid produced the dicarboxymethyl radicals [$\cdot CH(COOH)_2$] in the oxidation system, and the reactions proceeded to the formation of spirofused lactones [4]. However, the manganese(III) oxidation of **2** and **3** with malonic acid resulted in the formation of the simple lactones **5** and **8**, respectively. Moreover, without malonic acid, the manganese(III) oxidation of **2** did not take place, and led to non-formation of lactone **5**, even though the mixture of **2** and manganese(III) acetate was refluxed in acetic acid for 12 hours. In the manganese(III)-mediated spiro-lactonization of alkenes, Fristad and Hershberger [4] observed that rapid ligand exchange in manganese(III) acetate occurred with the solvent, electron-withdrawing substituents on acetic acid ligands greatly enhancing the reactivity of these ligands, and the rate of manganese(III) oxidation was found to increase in the following order: acetic < chloroacetic < malonic < cyanoacetic acid. Therefore, in the manganese(III) oxidation of **2** or **3** with malonic acid, the lactones **5** or **8** were produced

Scheme 3



by the attack with dicarboxymethyl radicals at the 2-position of the highest electron density on the indole ring, and following decarboxylation, rather than by the attack with carboxymethyl radicals [$\cdot CH_2COOH$] formed by the thermolysis of manganese(III) acetate; this mechanism is shown in Scheme 2. The formation of **7** from **3** also indicates that dicarboxymethyl radicals react at the 2-methyl group in **3** and lead to the formation of 3-methyl-2-indolylmethyl radicals, followed by manganese(III) oxidation.

In the manganese(III) oxidation of **4** with malonic acid, the formation of **2** and **9** indicates that dicarboxymethyl radicals directly attack at both the 3-position in **4** and the position (C_5) of the highest electron density on the aromatic ring, respectively, and the formation of **5** indicates that dicarboxymethyl radicals react again with compound **2**, formed from **4**; this mechanism is shown in Scheme 3.

EXPERIMENTAL

Melting points were determined with a Gallenkamp melting point determination apparatus and are uncorrected. The ir spectra were taken with a Hitachi 260-10 spectrometer. The ^{1}H nmr spectra were recorded with a Hitachi R-90H (90 MHz) instrument in deuteriochloroform using TMS as the internal standard. Mass spectra were measured on a Hitachi RMU-6M mass spectrometer.

Literature methods were used to prepare the following compounds: Manganese(III) acetate [3], 1-acetylindole (**2**) [7], 1-acetyl-2,3-dimethylindole (**3**) [8] and 1-acetylindoline (**4**) [9].

Oxidation of **2, 3** and **4** with Manganese(III) Acetate in the Presence of Malonic Acid.

To a solution of the compound **2, 3** or **4** (12 mmoles) and malonic acid (5.2 g, 50 mmoles) in acetic acid (80 ml), manganese(III) acetate (13.4 g, 50 mmoles) was added at room temperature under a nitrogen atmosphere. The mixture was heated at 70° under stirring until its dark brown color became opaque white. The solvent was removed *in vacuo*, and the residue was triturated with 2 *M* hydrochloric acid (30 ml) and then extracted with chloroform. The chloroform extracts were washed with an aqueous sodium hydrogencarbonate solution and concentration. The aqueous solution was acidified with concentrated hydrochloric acid and subsequently extracted with ethyl acetate. The solvent was removed under reduced pressure and the residue was treated with diazomethane in methanol. The neutral and esterified products, respectively, were purified by silica gel column chromatography [chloroform-ethyl ether (1:3) as eluent]. The results are summarized in Table 1.

4-Acetyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indol-2-one (**5**).

This compound was obtained from **2** as pale yellow crystals, mp 146-147°; ir (potassium bromide): 1770 (-COO-), 1660, 1390 (-NCO-), 1605, 1585, 760 cm^{-1} (*o*-disubstituted Ar-H); ^{1}H nmr: δ 2.38 (s, 3H, -COCH_3), 2.78 (d-d, 1H, $J_{3,3a}$ = 3 Hz, $J_{3,3'}$ = 18.5 Hz, -C_3-*H*), 3.25 (d-d, 1H, $J_{3',3a}$ = 9 Hz, $J_{3,3'}$ = 18.5 Hz, -$C_{3'}$-*H*), 4.94-5.26 (m, 1H, -C_{3a}-*H*), 6.06 (d, 1H, $J_{3a,8b}$ = 7.5 Hz, -C_{8b}-*H*), 6.80-7.68 ppm (m, 4H, Ar-*H*); ms: m/z 217 (M$^+$).

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.17; H, 5.02; N, 6.34.

The structure of **5** was determined by an observation of its spectral data and by derivation to methyl 2-indolylacetate (**6**) with 10% hydrochloric acid hydrolysis, followed by an esterification with diazomethane. Compound **6** was obtained as pale yellow crystals, mp 70-72° (lit [11], mp 71-73°); ir (potassium bromide): 3400 (-NH), 1750 (-COOMe), 1600, 1580, 760 cm^{-1}; ^{1}H nmr: δ 3.68 (s, 3H, -OCH_3), 3.80 (s, 2H, -CH_2-), 6.31 (s, 1H, -C_3-*H*), 6.91-7.70 ppm (m, 4H, Ar-*H*); ms: m/z 205.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.25; H, 5.29; N, 6.75.

2-Acetoxymethyl-1-acetyl-3-methylindole (**7**).

This compound was obtained from **3**, accompanied by **8** as colorless crystals, mp 64-65°; ir (potassium bromide): 1735 (-OCOMe), 1700, 1370 (-NCOMe), 1600, 1580, 750 cm^{-1} (*o*-disubstituted Ar-H); ^{1}H nmr: δ 2.05 (s, 3H, -OCOCH_3), 2.30 (s, 3H, -CH_3), 2.73 (s, 3H, -NCOCH_3), 5.45 (s, 2H, -CH_2-), 7.19-7.60 (m, 3H, -C_4-*H* + -C_5-*H* + -C_6-*H*), 7.84 ppm (d-d, 1H, $J_{5,7}$ = 3 Hz, $J_{6,7}$ = 7.5 Hz, -C_7-*H*); ms: m/z 245 (M$^+$); {lit [11], mp 65-66°; ir (chloroform): 1736 (-OCOMe), 1708 (-NCOMe); ^{1}H nmr: δ 2.05 (s, 3H, -COCH_3), 2.32 (s, 3H, -CH_3), 2.75 (s, 3H, -NCOCH_3), 5.47 (s, 2H, -CH_2-), 7.1-8.0 ppm (m, 4H, Ar-*H*)}.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.48; H, 6.02; N, 5.57.

4-Acetyl-3a,8b-dimethyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indol-2-one (**8**).

This compound was obtained from **3** , accompanied by **7** as colorless crystals, mp 206-208°; ir (potassium bromide): 1760 (-COO-), 1650, 1380 (-NCOMe), 1605, 1585, 760 cm^{-1} (*o*-disubstituted Ar-H); ^{1}H nmr: δ 1.54 (s, 3H, -CH_3), 1.73 (s, 3H, -CH_3), 2.48 (s, 3H, -NCOCH_3), 2.83 (d, 1H, $J_{3,3'}$ = 19 Hz, -C_3-*H*), 3.83 (d, 1H, $J_{3,3'}$ = 19 Hz, -$C_{3'}$-*H*), 7.00-7.58 ppm (m, 4H, Ar-H); ms: m/z 245 (M$^+$); {lit [11], mp 208-210°; ir (chloroform): 1770 (-COO-), 1662 (-NCOMe); ^{1}H nmr: δ 1.53 (s, 3H, -CH_3), 1.73 (s, 3H, -CH_3), 2.83 (d, 1H, -CH_3-*H*), 3.83 (d, 1H, -C_3-*H*), 7.0-7.7 ppm (m, 4H, Ar-*H*)}.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.51; H, 6.09; N, 5.65.

1-Acety-5-methoxycarbonylindoline (**9a**).

This compound was obtained from **4**, accompanied with **2** and **5** as colorless crystals, mp 64-66°; ir (potassium bromide): 1710 (-COOMe), 1670, 1390 (-NCOMe), 1600, 1585, 850, 770 cm^{-1} (1,2,4-trisubstituted Ar-H); ^{1}H nmr: δ 2.26 (s, 3H, -COCH_3), 3.21 (t, 2H, J = 9 Hz, -CH_2-Ar), 3.88 (s, 3H, -COOCH_3), 4.11 (t, 2H, J = 9 Hz, -N-CH_2-), 7.77-7.98 (m, 2H, -C_4-*H* + -C_6-*H*), 8.19 ppm (d, 1H, -C_7-*H*); ms: m/z 219 (M$^+$).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.69; H, 5.84; N, 6.32.

The structure of **9a** was determined by derivation to 5-indolinecarboxylic acid (**9b**) by hydrolysis with 10% hydrochloric acid in methanol. Compound **9b** was obtained as pale yellow crystals, mp 168-169° (lit [12], mp 168-170°).

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