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The Oxidation of the 2-Methyl Group of 3-Substituted 2-Methylindoles by Autoxidation and with Silver Acetate in Carboxylic Acids

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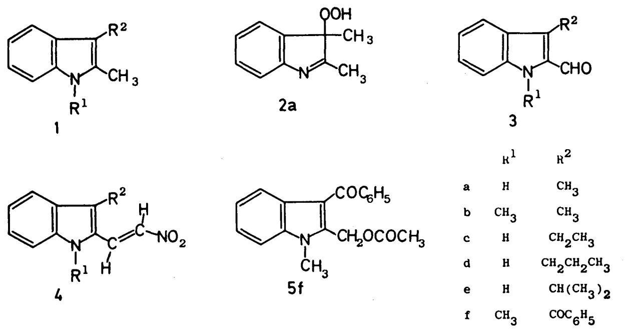
The autoxidation of 3-alkyl-2-methylindoles in carboxylic acids, such as propionic acid and acetic acid, at the reflux temperature resulted in the selective oxidation of the 2-methyl group and the formation of 3-alkyl-2-formylindoles. The formation of the 2-formylindoles was dependent on the nature of the solvent used. The treatment of 3-benzoyl-1,2-dimethylindole with silver acetate gave 2-acetoxymethyl-3-benzoyl-1-methylindole and 3-benzoyl-2-formyl-1-methylindole. The mechanistic implications for the autoxidation and the oxidation with silver acetate are presented.

The autoxidation of 3-alkyl-2-methylindoles (**1**) has been known to give several products. Beer *et al.*[1] reported that the autoxidation of 2,3-dimethylindole (**1a**) in hot petroleum gave 2,3-dimethyl-3*H*-indol-3-yl hydroperoxide (**2a**) and a non-peroxidic product. Taylor[2] also reported the formation of *N*-(2-acetylphenyl)acetamide, together with a small amount of 2-formyl-3-methylindole (**3a**), from **1a**. Recently, the non-peroxidic autoxidation product was reported to be a dimeric compound.[3] The autoxidation of 3-ethyl-2-methylindole (**1c**) was reported to give a similar dimeric compound.[4]

The present paper will deal with the autoxidation of 3-alkyl-2-methylindoles (**1a**—**e**) in carboxylic acids. The autoxidation in propionic acid or in acetic acid at the reflux temperature gave 3-alkyl-2-formylindoles (**3a**—**e**) in good yields. The treatment of **1a** in formic acid under oxygen at the reflux temperature gave 2,3-dimethyl-1-formylindole (**1g**), together with a small amount of **3a**. Also, the oxidation of 3-benzoyl-1,2-dimethylindole (**1f**) with silver acetate gave 3-benzoyl-2-formyl-1-methylindole (**3f**) and 2-acetoxymethyl-3-benzoyl-1-methylindole (**5f**).



	R^1	R^2
a	H	CH_3
b	CH_3	CH_3
c	H	CH_2CH_3
d	H	$CH_2CH_2CH_3$
e	H	$CH(CH_3)_2$
f	CH_3	COC_6H_5
g	CHO	CH_3

Fig. 1.

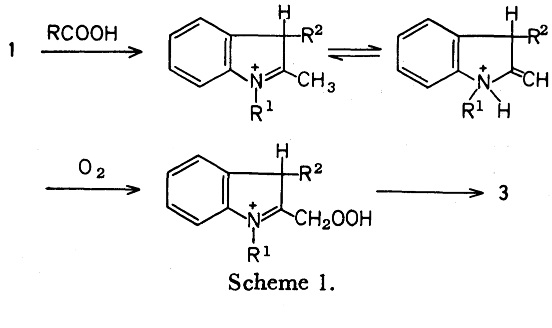
Results and Discussion

A solution of 2-methylindoles (**1a**—**e**) (100 mg), in propionic acid (100 ml) was bubbled with oxygen at the reflux temperature for 7 h. The reaction mixture was then evaporated and chromatographed on silica gel TLC to give the corresponding 2-formylindoles (**3a**—**e**). The autoxidation of **1a** in acetic acid under similar conditions also gave **3a**. The treatment of **3a**—**e** with nitromethane according to the known method[5] gave the corresponding 3-alkyl-2-(2-nitrovinyl)indoles (**4a**—**e**), which provides additional evidence for the structures of **3a**—**e**. The structures of **3** and **4** were confirmed on the basis of analytical and spectral(NMR, IR, and mass) data.

The formation of **3** is dependent on the nature of the solvent used. When the autoxidation of **1a** was carried out in formic acid at the reflux temperature, 1-formylindole **1g**[6] was obtained as the main product, together with a small amount of **3a**. Furthermore, no 2-formylindole **3a** was obtained from the reaction mixture in the autoxidation of **1a** in benzene, in methanol, in hexane, and in ethyl acetate. On the other hand, the autoxidation of **1a** in mixtures of methanol and acetic acid and of benzene and acetic acid gave **3a**, although attempts to prepare **3a** by the autoxidation of **1a** in methanol containing phosphoric acid and in benzene containing *p*-toluenesulfonic acid were unsuccessful.

The yield of **3a** is also dependent on the concentration of **1a**. That is to say, the autoxidation of **1a** (0.5 g or 1.0 g) in acetic acid (100 ml) decreased the yields of **3a**. These results are summarized in Table 1. Under similar conditions, an acylindole such as **1f** was unreactive to oxygen. The autoxidation of 2-methylindole and 1,2-dimethylindole gave complex reaction mixtures.

Previously it was reported that the exposure of **2a** to air in acetic acid and in ethyl acetate did not yield **3a**; the only product obtained was *N*-(2-acetylphenyl)acetamide, although the exposure of 2,3-diethyl-3*H*-indol-3-yl hydroperoxide to air gave 2-acetyl-3-ethylindole.[7] Furthermore, it was found that the autoxidation of a 1-substituted 2-methylindole such as 1,2,3-trimethylindole (**1b**) also gave the corresponding 2-formylindole, such as 1,3-dimethyl-2-formylindole (**3b**). These results suggest that the formation of **3** from **1** in carboxylic acids did not proceed *via* **2**. On the other hand, Gribble *et al.*[8] reported that indoles are protonated at the 3-position of the indole nucleus by carboxylic acids. Therefore, the following scheme might be given for the autoxidation of **1** in carboxylic acids:



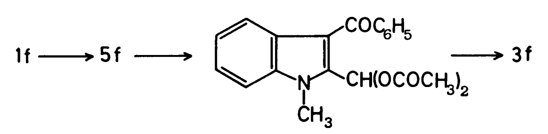
Scheme 1.

TABLE 1. SYNTHESIS OF 3-ALKYL-2-FORMYLINDOLES BY THE AUTOXIDATION OF 3-ALKYL- 2-METHYLINDOLES

Substrate	(g)	Solvent	(ml)	Conv./%	Product	Yield/%[a]
1a	(0.1)	CH_3CH_2COOH	(100)	100	**3a**	56
1a	(0.1)	CH_3COOH	(100)	100	**3a**	45
1a	(0.5)	CH_3COOH	(100)	70	**3a**	18
1a	(1.0)	CH_3COOH	(100)	50	**3a**	11
1a	(1.0)	CH_3COOH	(200)	62	**3a**	12
1a	(0.1)	CH_3COOH[b]	(100)	100	**3a**	60
1a	(0.1)	HCOOH	(100)	93	**3a**[c]	4
1a	(0.1)	Benzene	(50)	78	**3a**	8
		CH_3COOH	(50)			
1a	(0.1)	CH_3OH	(50)	76	**3a**	12
		CH_3COOH	(50)			
1b	(0.1)	CH_3CH_2COOH	(100)	100	**3b**	68
1c	(0.1)	CH_3CH_2COOH	(100)	100	**3c**	60
1d	(0.1)	CH_3CH_2COOH	(100)	100	**3d**	63
1e	(0.1)	CH_3CH_2COOH	(100)	100	**3e**	60

a) Yields based on the indole **1a**—**e** consumed. b) Adding 2 equiv. of AgOAc. c) 2,3-Dimethyl-1-formylindole (52%) was obtained as the main product.

Although **1f** was unreactive to oxygen, **1f** was reacted with silver acetate to give **3f** and **5f**. The treatment of **1f** with 2.0 equiv. of silver acetate in acetic acid at the reflux temperature under both air and nitrogen for 20 h gave **3f** as the main product, together with a small amount of **5f**. On the other hand, the treatment of **1f** with 0.7 equiv. of silver acetate under nitrogen for 15 h gave **5f** as the main product. Under similar conditions, **5f** was reacted with silver acetate to give **3f**, suggesting that **3f** was formed *via* **5f**. Therefore, a pathway for the oxidation of **1f** with silver acetate in acetic acid might be as is shown in the following scheme. In addition, although the oxidation of **1a** with silver acetate under nitrogen gave a complex reaction mixture, the autoxidation of **1a** in acetic acid containing silver acetate increased the yield of **3a** (Table 1).



Scheme 2.

Generally, replacement at the 2-position of the indole nucleus is attained with difficulty;[9] *e.g.*, the acylation of indoles normally gives 1- and 3-acylindoles.[10] The autoxidation of **1** in carboxylic acids and the oxidation of **1f** with silver acetate are, therefore, of interest as an effective method for the preparation of 2-formylindoles, although its scope is somewhat limited, *i.e.*, a substituent is needed at the 3-position of the indole nucleus. That is to say, in contrast to several reports concerning the preparation of **3a** by means of the oxidation of **1a** (*i.e.*, the oxidation of **1a** with H_5IO_6,[11] SeO_2,[12] and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ),[13] and by photo-oxygenation[14] gives **3a** in low yields), the method by means of the autoxidation of **1a** in carboxylic acids provides more satisfactory results.

Experimental

General. All the melting points are uncorrected. The elemental analyses were performed by the Analytical Center of Kyoto University. The infrared spectra were recorded with a JASCO IRA-1 spectrometer. The proton magnetic resonance spectra were recorded with a JEOL-60 spectrometer, using Me_4Si as the internal reference. 2-Methylindole, 1,2-dimethylindole, and 2,3-dimethylindole (**1a**) were obtained commercially. 3-Benzoylindole (**1f**) was prepared according to the procedure described before.[15]

1,2,3-Trimethylindole (1b). To a stirred solution of 2,3-dimethylindole (5.0 g) and sodium hydride (oil suspension, abt. 50%) (1.6 g) in *N*,*N*-dimethylformamide (100 ml), methyl iodide (5.0 g) in *N*,*N*-dimethylformamide (20 ml) was added under nitrogen. The solution was then stirred at room temperature for 4 h, after which the reaction mixture was poured into ice-cooled water and extracted with benzene. The benzene extract was dried with sodium sulfate and evaporated to give a brown oily residue. The residue was chromatographed on a silica-gel column with hexane/benzene to give **1b** (4.1 g).

3-Alkyl-2-methylindoles (1c—e). A solution of 2-methylindole (5.0 g) in ethyl iodide (25 ml) was heated at the reflux temperature for 40 h under nitrogen. The reaction mixture was then evaporated to give a red oily residue which was chromatographed on a silica-gel column with benzene to give 3-ethyl-2-methylindole (**1c**) (0.4 g) and 2-methylindole (3.3 g).

Similar treatments of 2-methylindole (5.0 g) in propyl iodide (25 ml) gave 2-methyl-3-propylindole (**1d**) (1.5 g) and 2-methylindole (1.9 g), while treatments in isopropyl iodide (25 ml) gave 2-methyl-3-isopropylindole (**1e**) (1.0 g) and 2-methylindole (2.6 g).

Autoxidation of 3-Alkyl-2-methylindoles. The indole **1a**—**e** (0.1 g) was dissolved in propionic acid (100 ml), and the solution was bubbled with oxygen at the reflux temperature for 7 h. The reaction mixture was then evaporated to give a brown oily residue, which was chromatographed on silica-gel TLC and developed with benzene to give 3-alkyl-2-formylindole (**3a**—**e**). The yields are summarized in Table 1. The spectral and analytical data are given below.

2-Formyl-3-methylindole (3a): Mp 139—140 °C (lit,[16] 139—

140 °C); IR (Nujol) 3300, 1640, 1570, 1430, 1330 cm^{-1}; NMR ($CDCl_3$) δ 2.73 (s, 3H), 7.1—7.6 (m, 3H), 7.75—8.0 (m, 1H) 9.5 (broad, 1H), 10.6 (s, 1H).

*1,3-Dimethyl-2-formylindole (**3b**)*: Mp 35—36 °C (lit,$^{17)}$ 36 °C); IR (Nujol) 1670, 1610, 1530, 1420, 1350, 1340 cm^{-1}; NMR ($CDCl_3$) δ 2.64 (s, 3H), 4.10 (s, 3H), 7.1—8.0 (m, 4H), 10.65 (s, 1H).

*3-Ethyl-2-formylindole (**3c**)*: Mp 72—73 °C (by distillation at 170 °C/6 Torr†); IR (Nujol) 3300, 1640, 1570, 1530, 1310, cm^{-1}; NMR ($CDCl_3$) δ 1.41 (t, 3H, J=7 Hz), 3.19 (q, 2H J=7 Hz), 7.05—7.6 (m, 3H), 7.8—8.0 (m, 1H), 9.7 (broad, 1H), 10.6 (s, 1H). Found: C, 76.54; H, 6.46; N, 7.91%. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09%.

*2-Formyl-3-propylindole (**3d**)*: Mp 40—41 °C (by distillation at 180 °C/6 Torr); IR (Nujol) 3300, 1650—1620 (broad), 1575, 1535, 1335 cm^{-1}; NMR ($CDCl_3$) δ 0.99 (t, 3H, J=7 Hz), 1.82 (sext. 2H, J=7 Hz), 3.13 (t, 2H, J=7 Hz), 7.05—7.65 (m, 3H), 7.8—8.05 (m, 1H), 9.6 (broad, 1H), 10.5 (s, 1H); High-resolution Mass: m/e (rel intensity) 187.0993 (M^+, 61), 172.0773 (100). Found: C, 76.79; H, 6.92; N, 7.21%. Calcd for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48%.

*2-Formyl-3-isopropylindole (**3e**)*: Mp 65—66 °C (by distillation at 170 °C/6 Torr); IR (Nujol) 3200, 1640, 1630, 1315 cm^{-1}; NMR ($CDCl_3$) δ 1.57 (d, 6H, J=7 Hz), 3.77 (sept, 1H, J=7 Hz), 7.05—7.75 (m, 3H), 7.86—8.10 (m, 1H), 9.6 (broad, 1H), 10.6 (s, 1H); High-resolution Mass: m/e (rel intensity) 187.1008 (M^+, 76), 172.0781 (100). Found: C, 76.36; H, 6.87; N, 7.31%. Calcd for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N,7.48%.

Similar procedure were applied for the autoxidation of **1a** in acetic acid, in benzene, in hexane, in methanol, and in ethyl acetate.

*3-Alkyl-2-(2-nitrovinyl)indoles (**4a**—**e**).* Into a solution of **3a**—**e** (0.1 g) and nitromethane (0.15 g) in methanol (5 ml), 50% aqueous sodium hydroxide (1.5 ml) was stirred, drop by drop, at 0 °C. After 1 h at 0 °C, ice water (5 ml) wasadded, and the resulting solution was poured into a mixture of concd hydrochloric acid (6.5 ml) and water (24 ml) at 0 °C. The crude product separated as a brownish-orange solid, which was collected and dried. Recrystallization from chloroform/hexane gave **4a**—**e** as brownish-orange needles. The yields and spectral and analytical data are given below.

*3-Methyl-2-(2-nitrovinyl)indole (**4a**)*: 88% yield; mp 181.5—182.5 °C; IR (Nujol) 3350, 1610, 1480, 1310 cm^{-1}; NMR ($CDCl_3$) δ 2.51 (s, 3H), 7.0—7.9 (m, 5H), 8.40 (d, 1H, J=14 Hz), 8.2—8.6 (broad, 1H); Mass: m/e (rel intensity) 202 (M^+, 95), 155 (94), 154 (100). Found: C, 65.74; H, 4.98; N, 13.40%. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86%.

*1,3-Dimethyl-2-(2-nitrovinyl)indole (**4b**)*: 89% yield; mp 159—160 °C; IR (Nujol) 1625, 1500, 1310 cm^{-1}; NMR ($CDCl_3$) δ 2.53 (s, 3H), 3.90 (s, 3H), 7.0—7.9 (m, 5H), 8.40 (d, 1H, J=14 Hz). Found: C, 66.84; H, 5.46; N, 12.95%. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96%.

*3-Ethyl-2-(2-nitrovinyl)indole (**4c**)*: 85% yield; mp 157—158 °C; IR (Nujol) 3350, 1610, 1480, 1330, 1315 cm^{-1}; NMR ($CDCl_3$) δ 1.29 (t, 3H, J=8 Hz), 2.99 (q, 2H, J=8 Hz), 7.0—7.9 (m, 5H), 8.37 (d, 1H, J=14 Hz), 8.1—8.6 (broad, 1H). Found: C, 66.96; H, 5.48; N, 12.58%. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.55; H, 5.59; N, 12.96%.

*2-(2-Nitrovinyl)-3-propylindole (**4d**)*: 89% yield; mp 158—159 °C; IR (Nujol) 3330, 1610, 1490, 1315 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (t, 3H, J=7 Hz), 1.75 (sext, 2H, J=7 Hz), 2.95 (t, 2H, J=7 Hz), 7.1—8.0 (m, 5H), 8.40 (d, 1H, J=14 Hz), 8.3—8.7 (broad, 1H). Found: C, 67.93; H, 6.02; N, 12.36%.Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17%.

*2-(2-Nitrovinyl)-3-isopropylindole (**4e**)*: 91% yield; mp 174—175 °C; IR (Nujol) 3360, 1610, 1480, 1330, 1305 cm^{-1}; NMR ($CDCl_3$) δ 1.50 (d, 6H, J=7 Hz), 3.45 (sept, 1H, J=7 Hz), 7.0—8.0 (m, 5H), 8.43 (d, 1H, J=14 Hz), 8.2—8.6 (broad, 1H). Found: C, 68.02; H, 6.16; N, 12.30%. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17%.

*Treatment of 2,3-Dimethylindole **1a** in Formic Acid.* A solution of **1a** (100 mg) in formic acid (100 ml) was bubbled with oxygen at the reflux temperature for 7 h. The reaction mixture was then evaporated to give a brown oily residue, which was chromatographed on silica-gel TLC with benzene to yield **1a** (7 mg), **3a** (5 mg), and 2,3-dimethyl-1-formylindole **1g**, mp 87—88 °C (lit,$^{18)}$ 87—88 °C) (58 mg).

*Oxidation of 3-Benzoyl-1,2-dimethylindole **1f** with Silver Acetate.* A solution of **1f** (249 mg) and silver acetate (334 mg) in acetic acid (100 ml) was heated at the reflux temperature for 20 h under air. The reaction mixture was then evaporated to dryness and chromatographed on silica-gel TLC with benzene to yield **1f** (35 mg; 14%), 2-acetoxymethyl-3-benzoyl-1-methylindole **5f** (40 mg; 15% yield based on **1f** consumed), and 3-benzoyl-2-formyl-1-methylindole **3f** (125 mg; 55% yield based on **1f** consumed). Furthermore, under nitrogen, the oxidation of **1f** (249 mg) with silver acetate (334 mg) in acetic acid (100 ml) for 20 h gave **1f** (53 mg; 21%), **5f** (38 mg; 17% yield based on **1f** consumed), and **3f** (114 mg; 55%yield based on **1f** consumed).

A similar treatment of **1f** (249 mg) and silver acetate (117 mg) in acetic acid (100 ml) for 15 h under nitrogen gave **1f** (75 mg; 30%), **5f** (100 mg; 47% yield based on **1f** consumed), and **3f** (12 mg; 7% yield based on **1f** consumed). The spectral and analytical data of **5f** and **3f** are given below.

5f: Mp 103—104 °C (from ether/hexane); IR (Nujol) 1740, 1630, 1600, 1580, 1530, 1480, 1410, 1330 cm^{-1}; NMR ($CDCl_3$) δ 2.07 (s, 3H), 3.85 (s, 3H), 5.50 (s, 2H), 7.1—8.1 (m, 9H). Found: C, 74.45; H, 5.48; N, 4.64%. Calcd for $C_{19}H_{17}NO_3$ C, 74.25; H, 5.58; N, 4.56%.

3f: Mp 124.5—125.5 °C (from chloroform/hexane); IR (Nujol) 1675, 1635, 1615, 1605, 1580, 1510, 1480, 1400, 1345 cm^{-1}; NMR ($CDCl_3$) δ 4.24 (s, 3H), 7.3—8.3 (m, 9H), 10.7 (s, 1H). Found: C, 77.57; H, 4.99; N, 5.36%. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32%.

*Oxidation of 2-Acetoxymethyl-3-benzoyl-1-methylindole (**5f**) with Silver Acetate.* A solution of **5f** (15 mg) and silver acetate (20 mg) in acetic acid (30 ml) was heated at the reflux temperature for 15 h under air. The reaction mixture was then evaporated and chromatographed on silica-gel TLC with benzene to yield **3f** (8 mg).

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