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Oxidative Cleavage of Indoles using Copper-Pyridine Complex

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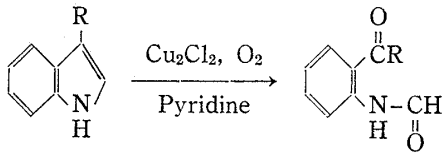
Cu_2Cl_2-pyridine-O_2 system oxidize 2- and 3-substituted indole derivatives to form C_2-C_3 double bond cleaved products. By this reaction, 2-substituted indole (**6a**), 3-substituted indoles (**1a—5a**) and 2,3-disubstituted indole (**7a**) give N-acetylanthranic acid (**6b**), 2-acylformanilides (**1b—5b**) and quinolone derivative (**7b**), respectively. The reaction could represent a mimic of tryptophan 2,3-dioxygenase reaction, in which tryptophan undergoes oxidative cleavage to give N-formylkynurenin.

Keywords——oxygenation; indole; copper chloride; biomimetic reaction; quinolone; 2-acylformanilide

Nonenzymic model reactions of oxygenases are subject of current interest.[2,3] Copper, cobalt and iron complexes are employed as a catalyst in the reactions. Copper-pyridine-O_2 system is known to oxidize phenols and catechols.[4] In this paper we will report the oxidative cleavage of various indole derivatives by using copper-pyridine-O_2 system.

In a typical experiment, Cu_2Cl_2 was added to a solution of 3-methylindole (**1a**) in pyridine, and the reaction mixture was stirred under O_2. The oxidative cleavage of C_2-C_3 double bond of indole ring took place to give 2-acetylformanilide (**1b**) in 36% yield. Besides, several kinds of colored oxidative products were formed in low yields. In the same manner, Cu_2Cl_2 oxidizes various 3-substituted indole derivatives [3-(methoxycarbonylmethyl)indole (**2a**), 3-(β-methoxy-

TABLE I.



	R	Time (hr)		y: (%)
1a	CH_3	24	**1b**	36
2a	CH_2–$COCH_3$ (O)	24	**2b**	42
3a	CH_2CH_2–$COCH_3$ (O)	24	**3b**	42
4a	CH_2CH_2–N(H)–CCH_3 (O)	24	**4b**	12
5a	CH_2–CH(–N(H)–CCH_3 (O))–$COCH_3$ (O)	72	**5b**	22

Reactions were carried out at room temperature.

1) Location: *a) Hongo, Bunkyo-ku, Tokyo, 113 Japan; b) Niihari-gun, Ibaraki, 300-31, Japan.*
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3) A. Nishinaga, *Chem. Lett.*, **1975**, 273.
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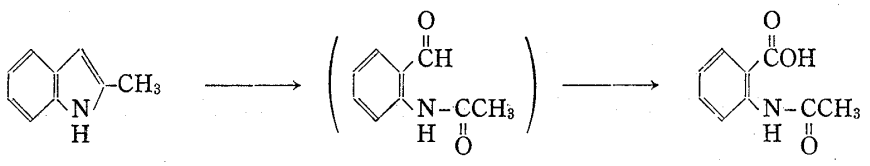


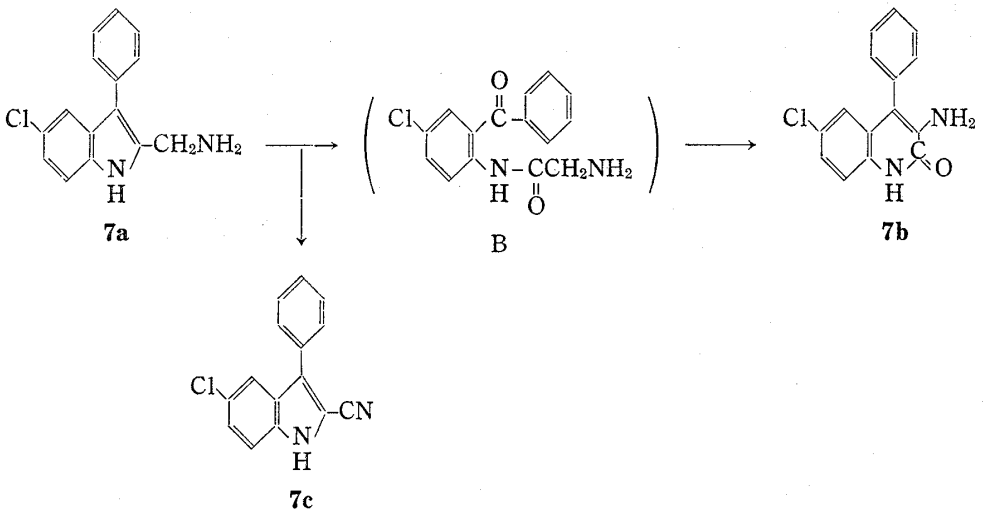
6a A **6b**

Chart 1

carbonylethyl)indole (**3a**), 3-(β-acetamidoethyl)indole (**4a**) and 3-(β-acetamido-β-methoxycarbonylethyl)indole (**5a**)]. The reaction conditions and the results are listed in Table I.

2-Methylindole (**6a**) was oxygenated to give N-acetylanthranilic acid (**6b**) in 33% yield. The product (**6b**) could be formed *via* oxidation of aldehyde group of 2-acetamidobenzaldehyde (A) which was formed from the oxidative cleavage of **6a**.

2,3-Disubstituted indole also underwent oxygenation by this complex. Oxygenation of 5-chloro-2-aminomethyl-3-phenylindole (**7a**) gave 3-amino-6-chloro-4-phenyl-2(1H)-quinolone (**7b**) in 62% yield. 5-Chloro-2-cyano-3-phenylindole (**7c**) was obtained in 28% yield as a minor product in this reaction. The product (**7b**) could be formed by the oxidative cleavage of **7a** and subsequent cyclization through an intermediate (B). Intramolecular condensation of methylene group and carbonyl group of B gives six membered ring compound quinolone. No seven membered ring compound benzodiazepine was obtained in the reaction. Benzodiazepine is known to be prepared from B by intramolecular condensation of amino group and carbonyl group in the absence of copper ion.[5,6] The coordination of amino group of B to a copper ion probably decreases the nucleophilicity of amino group and enhances the activity of methylene group.



7a B **7b**

7c

Chart 2

Under an atmospheric pressure of nitrogen, very small amount of **1b** was formed from **1a**. Addition of water in the reaction mixture does not affect the yield of **1b**. No oxidative cleavage took place in the absence of copper chloride. These results indicate that copper ion is essential for this oxygenation of indole derivatives. Tryptophan 2,3-dioxygenase has been demonstrated to contain iron and catalyze the oxidative cleavage of tryptophan to form N-formylkynurenin.

Our system could serve a model reaction of tryptophan 2,3-dioxygenase.

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Experimental

All melting points were taken in an Yanaco micro melting point apparatus and were uncorrected. Infrared (IR) spectra were determined in Nujol with a JASCO A-102 Diffraction Infrared Spectrophotometer. Nuclear magnetic resonance (NMR) spectra were run on a Hitachi R-24 spectrometer (60 MHz) using TMS as an internal standard.

Oxidative Cleavage of 3-Methylindole——To a solution of **1a** (200 mg, 1.52 mmol) in pyridine (10 ml) was added solid Cu_2Cl_2 (181 mg, 0.91 mmol) and stirring under O_2 at room temperature for 24 h. The reaction mixture turned homogeneous gradually. After the reaction, the mixture was evaporated under reduced pressure and chromatographed on a silica gel thin-layer chromatography (TLC). The product was extracted with CH_2Cl_2 from TLC plate, and the solvent was removed under reduced pressure. The resultant solid was recrystallized from CH_2Cl_2/*n*-hexane to give purified **1b** (90 mg, 36%) mp 79° (lit.[3] 79—80°), NMR ($CDCl_3$) δ: 2.6 (s, 3H), 6.9—8.8 (m, 6H). IR cm^{-1}: 1680, 1645. *Anal* Calcd. for $C_9H_9NO_2$: C, 66.25; H, 5.59; N, 8.58. Found: C, 66.14; H, 5.57; N, 8.30.

The reaction and treatment of the reaction products of other 3-substituted indole derivatives were carried out in the same procedures as described above. Melting points and spectral and analytical data of these products are in the following.

2-(α-Methoxycarbonylacetyl)formanilide (2b)——mp 44° (CH_2Cl_2/*n*-hexane). NMR ($CDCl_3$) δ: 3.7 (s, 3H), 4.1 (s, 2H), 7.0—8.9 (m, 6H). IR cm^{-1}: 1740, 1695, 1660. *Anal.* Calcd. for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.44; H, 5.03; N, 6.11.

2-(β-Methoxycarbonylpropionyl)formanilide (3b)——mp 73—74° (CH_2Cl_2/*n*-hexane) (lit.[3] 76—78°). NMR ($CDCl_3$) δ: 2.6—3.5 (m, 4H), 3.7 (s, 3H), 7.0—8.8 (m, 6H). IR cm^{-1}: 1740, 1695, 1660. *Anal.* Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 60.98; H, 5.68; N, 5.81.

2-(β-Acetamidopropionyl)formanilide (4b)——mp 122—124° (CH_2Cl_2/*n*-hexane) (lit.[3] 117—119°). NMR ($CDCl_3$) δ: 2.0 (s, 3H), 3.0—3.8 (m, 4H), 6.4 (s, 1H), 7.0—8.8 (m, 6H). IR cm^{-1}: 1690, 1650. *Anal.* Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.91; H, 5.99; N, 11.77.

2-(β-Acetamido-β-methoxycarbonylpropionyl)formanilide (5b)——Very strong hygroscopic syrupy state. NMR ($CDCl_3$) δ: 2.1 (s, 3H), 3.75 (s, 3H), 3.75 (d, 2H), 4.8—5.1 (m, 1H), 6.7 (s, 1H), 7.0—8.8 (m, 6H). IR cm^{-1}: 1740, 1690, 1650.

N-Acetylanthranilic Acid (6b)——To a solution of **6a** (200 mg, 1.52 mmol) in pyridine (10 ml) was added solid Cu_2Cl_2 (181 mg, 0.91 mmol) and stirring under O_2 at room temperature for 24 h. After the reaction, the mixture was evaporated under reduced pressure and chromatographed on a silica gel TLC. The product was extracted with CH_2Cl_2 from TLC plate, and the solvent was removed under reduced pressure. The resultant solid was recrystallized from CH_2Cl_2/*n*-hexane to give purified **6b** (90 mg, 33%) mp 181° (lit.[7] 183°). NMR ($CDCl_3$) δ: 2.2 (s, 3H), 7.4—8.8 (m, 5H), 11.0 (s, 1H). IR cm^{-1}: 3600—2400 (broad), 1690, 1645. *Anal* Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.72; H, 5.09; N, 7.41.

3-Amino-6-chloro-4-phenyl-2(1H)-quinolone (7b), 5-Chloro-2-cyano-3-phenylindole (7c)——To a solution of **7a** (200 mg, 0.78 mmol) in pyridine (10 ml) was added solid Cu_2Cl_2 (94 mg, 0.47 mmol) and stirring under O_2 at 60—70° for 4 h. After the reaction, the mixture was evaporated under reduced pressure and chromatographed on a silica gel TLC. The products were extracted with CH_2Cl_2 from TLC plate, and the solvent was removed under reduced pressure. The resultant solids were recrystallized from acetone and from $CHCl_3$ to give purified **7b** (131 mg, 62%) and **7c** (55 mg, 28%), respectively. **7b** mp 235° (lit.[8] 239—242°). NMR ($CDCl_3$) δ: 6.3—7.6 (m, 11H). IR cm^{-1} 1655. *Anal* Calcd. for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10; N, 10.35. Found: C, 66.98; H, 3.96; N, 9.93. MS 270, 272 (M^+). **7c** mp 206—207°. NMR (d_6-acetone) δ: 7.4—7.8 (m, 8H), 11.5 (s, 1H). IR cm^{-1}: 2240. *Anal* Calcd. for $C_{15}H_9ClN_2$: C, 71.29; H, 3.59; N, 11.09. Found: C, 71.12; H, 3.50; N, 10.95.

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