Direct Conversion of *N*-Methylindoles into Indoxyl, Oxindole, and Dioxindole *O*-Benzoates*

YUICHI KANAOKA, MASATO AIURA, AND SACHIKO HARIYA

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan

Received July 9, 1970

Benzoyl peroxide in benzene solution at room temperature converts indoles into indoxyl, oxindole, and dioxindole *O*-benzoates. The mono- and di-*O*-benzoates of 1-methylindoxyl, 1,2-dimethylindoxyl, 1,3-dimethyloxindole, and 1-methyldioxindole were prepared from the corresponding *N*-methylindoles by this convenient one-step procedure in yields of 10–80% depending on the ratio of substrate to reagent. The mechanism is discussed in terms of both homolytic and heterolytic cleavage of the reagent.

Oxidative transformations of the pyrrole moiety of indoles involve both the 2 and 3 positions, leading to oxindoles and indoxyls, respectively. In 1952 Witkop, *et al.*, investigated and reviewed *in vitro* and *in vivo* oxidation of indole compounds with emphasis on natural substrates and biologically important substances, such as tryptophan and its derivatives.[1]

Oxindoles can be directly obtained from indoles. Witkop oxidized certain 3-substituted indoles to the corresponding oxindoles either by hydrogen peroxide in acetic acid or by *N*-bromosuccinimide.[2] The same conversion is possible by chlorination or bromination and subsequent hydrolysis.[3] The oxidation of indole is difficult to arrest at the indoxyl stage, because it is so sensitive to autoxidation. The only known *direct* synthesis of indoxyl acetate from indole proceeds by 3-iodination of indole followed by solvolysis.[4] Dioxindoles can be obtained by oxidation of 3-alkylated oxindoles or indoles.[5] The present paper describes the direct formation of indoxyl, oxindole, and dioxindole *O*-benzoates by oxidation of indoles with benzoyl peroxide.

Thermal decomposition of diacyl peroxide provides a convenient source of aryl radicals for the arylation of aromatic substrates.[6a,7a] For example, thermolysis of benzoyl peroxide **1** yields two benzoyloxy radicals **2**, some of which, by loss of carbon dioxide, yield phenyl radicals **3** which participate in the arylation reaction, usually by way of a σ complex **5** with radical character, to give phenyl products **7**. Alternatively, benzoyloxy radical **2** also reacts with aromatic substrates to give esters by way of a related σ complex **4**, which loses a hydrogen atom in the presence of appropriate hydrogen acceptors to form benzoyloxy products **6**. In homolytic substitution of aromatics with benzoyl peroxide, usually phenylation to **7** is a major reaction accompanied by benzoyloxylation to form **6** as a side reaction. Benzoyloxylation increases with the reactivity of the aromatic substrates toward homolytic attack.[6b] For example, with reactive substrates, such as naphthalene[8,9] and other polynuclear aromatics,[9,10] benzoyloxylation becomes an important pathway. Appreciable benzoyloxylation is also observed with anisole[11] and trimethoxybenzene.[12]

Excess 1-methylindole **8** was heated with benzoyl peroxide **1** at 80° for 17 hr following a standard procedure of aromatic phenylation.[6a,7b] Phenylated indoles expected from "normal" homolytic aromatic substitution with **1** were not detected. Instead, the only isolable product (56% yield) arising from **8** was a crystalline ester of benzoic acid with an indole chromophore of the composition $C_9H_8N + C_7H_5O_2$, *m/e* 251, a 1:1 reaction product. Structure **9**, 1-methylindoxyl benzoate, was supported by the nmr data [δ 7.4 (1 H), singlet, $CDCl_3$; 2 H of indole] and the ir spectrum (1720 cm^{-1}, ester). The assignment was confirmed by an independent synthesis, *viz.*, thermal cyclization of *N*-methyl-*N*-(α-carboxyphenyl)glycine (**11**) in the presence of benzoic anhydride, an adaptation of the known synthesis of its acetyl analog.[13] Benzoyloxylation of indole itself was difficult to control and the results were inconclusive. Apparently the abstraction of H· from the free NH group of indole leads to side reactions. When aromatic hydrocarbons react with benzoyl peroxide, benzoyloxylation usually supervenes at lower temperature, where the benzoyloxy radicals decarboxylate more slowly. When the reaction of **8** with **1** was repeated in benzene solution at room temperature, preparative tlc gave a small amount (4%) of a new crystalline product in addition to a lower yield of **9** (Table I). Elemental analysis and mass spectrometry (*m/e* 371) established formula $C_{23}H_{17}NO_4$, *i.e.*, a 1:2 ratio for this new reaction product. In support of the structure of 1-methyldioxindole dibenzoate, the nmr spectrum of **10** lacked the characteristic signals of the 2- and 3-indole protons.[14] Since oxindole benzoate was not detected in the reaction mixture, the formation of **10** may be explained by subsequent benzoyloxylation of initially formed **9**. In fact, **9** was directly converted into **10** in 8% yield on treatment with **1**. When an equimolar mixture of **8** and **1** was allowed to react at room temperature for 2 days, **9** was produced in 21% yield based on the starting indole. Benzoyloxylation at 50° slightly raised this yield. Yields of up to 64% of **9** were obtained when pyridine was used as a solvent. The results are summarized in Table I.

---

* Correspondence should be addressed to Dr. Bernhard Witkop, Public Health Service, National Institutes of Health, Bethesda, Md. 20014.

(1) A. Ek, H. Kissman, J. B. Patrick, and B. Witkop, *Experientia*, **8**, 36 (1952), and papers cited therein.

(2) B. Witkop, *Justus Liebigs Ann. Chem.*, **558**, 98 (1947); W. B. Lawson and B. Witkop, *J. Org. Chem.*, **26**, 263 (1961).

(3) W. B. Lawson, A. Patchornik, and B. Witkop, *J. Amer. Chem. Soc.*, **82**, 5918 (1960).

(4) R. D. Arnold, W. M. Nutter, and W. L. Stepp, *J. Org. Chem.*, **24**, 117 (1959).

(5) E. C. Kendall and A. E. Osterberg, *J. Amer. Chem. Soc.*, **49**, 2047 (1927).

(6) (a) G. H. Williams in "Homolytic Aromatic Substitution," Pergamon Press, London, 1960, p 34; (b) p 116.

(7) (a) W. A. Pryer in "Free Radicals," McGraw-Hill, New York, N. Y., 1966, p 253; (b) p 91.

(8) R. L. Dannley and M. Gippin, *J. Amer. Chem. Soc.*, **74**, 332 (1952).

(9) D. E. Davies, D. H. Hey, and G. H. Williams, *J. Chem. Soc.*, 1878 (1958).

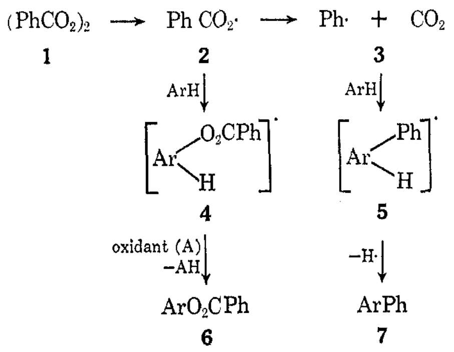
(10) I. M. Roit and W. A. Waters, *ibid.*, 2695 (1952).

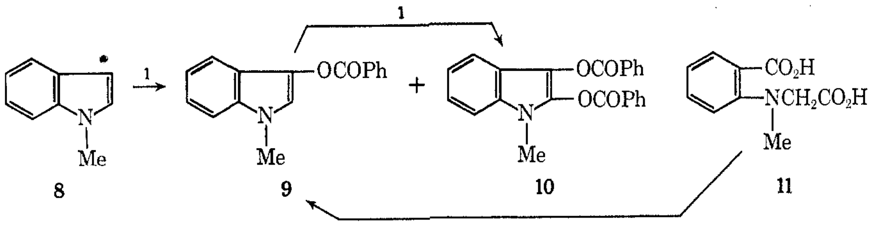
(11) B. M. Lynch and R. B. Moore, *Can. J. Chem.*, **40**, 1461 (1962).

(12) P. L. Pauson and B. C. Smith, *J. Org. Chem.*, **18**, 1403 (1953).

(13) L. Ettinger and P. Friedländer, *Ber.*, **45**, 2074 (1912).

(14) L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, *J. Amer. Chem. Soc.*, **82**, 2184 (1960).





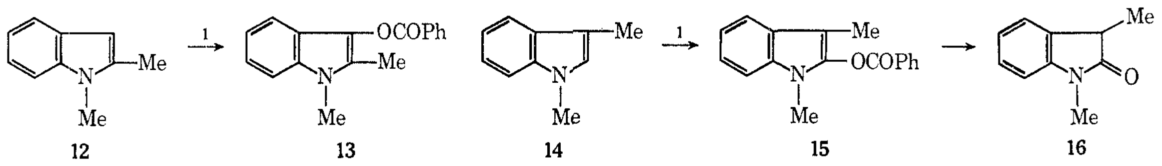


TABLE I

BENZOYLOXYLATION OF INDOLES

Expt no.	Substrate	Ratio[a]	Solvent[b]	Temp,[c] °C	Time, hr	Product,[d] yield[e] 2-OBz	3-OBz	2,3-(OBz)2	Benzoic acid
1	8	8		80	17		56		94
2	8	5	B	R	24		33	4	136
3	8	1	B	50	77		27	15	106
4	8	1	B	R	48		21	10	125
5	8	1	P	R	24		64	5	123
6	12	8		65	1.5		60		63
7	12	5	B	R	2		81		106
8	12	1	B	R	1		50		88
9	14	5	B	R	5	43			128
10	14	1	B	R	3	28			112
11	14	1	B[f]	R	4	15			152
12	14	1	P	R	5	62			156
13	9	1	B	R	96				158

[a] Substrate *vs.* reagent (mole). [b] B, benzene; P, pyridine; the atmosphere is nitrogen, unless otherwise stated. [c] R, room temperature. [d] Bz, benzoyl. [e] Mole per cent based on **3**. [f] Oxygen was bubbled through the reaction mixture.

The oxidation of 1,2- and 1,3-dimethylindole, **12** and **14**, was next examined to study the influence of alkyl substituents on benzoyloxylation. When **12** reacted with **1** at 65°, the expected 1,2-dimethylindoxyl *O*-benzoate **13** was isolated as the sole nitrogen-containing product. Elemental analysis, spectral data, the parent molecular ion (*m/e* 265), ir (1735 cm^{-1}, ester), and nmr spectra (no signal for 3 H) supported structure **13**. At room temperature the yield was raised to 81% based on the amount of **1**. An experiment with an equimolar mixture of substrate and reagent gave the indoxyl **13** in 50% yield based on the starting indole **12**.

When a benzene solution of **14** reacted with **1** at room temperature, the 1:1 reaction product **15** was obtained in moderate yield. Structure **15** was supported by analytical data and mass (*m/e* 265) and ir (1750 cm^{-1}, ester) spectra. Alkaline hydrolysis liberated authentic 1,3-dimethyloxindole (**16**).[15] With 1 equiv of **1** the indole **14** was converted to the oxindole **15** in 28% yield. When pyridine was employed as a solvent, oxindole **16** was obtained as the major product apparently as the result of hydrolysis of the benzoate **15** in the course of work-up.

Certain diacyl peroxides have recently found application as oxygenating agents of aromatic substrates particularly in conjunction with another oxidant. The prototype of this reaction is the formation of alkenyl benzoates from olefins with **1** and copper salts.[16] Kovacic, *et al.*, have developed a diisopropyl peroxydicarbonate–aromatic–cupric chloride system as an effective oxy-

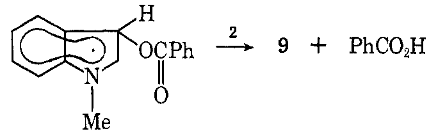
---

[15] P. L. Julian, J. Pikl, and D. Boggess, *J. Amer. Chem. Soc.*, **56**, 1797 (1934).

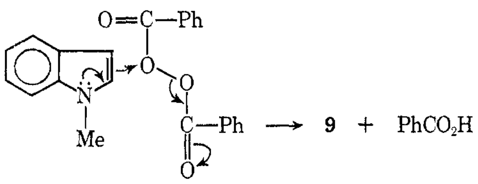
[16] M. Kharasch and A. Fono, *J. Org. Chem.*, **24**, 606 (1956); J. K. Kochi, *J. Amer. Chem. Soc.*, **84**, 1572 (1962).

genating agent.[17] A related aromatic-benzoyl peroxide-iodine system has been proposed for aromatic benzoyloxylation.[18,19]

Probably benzoyloxy radical **2** is the species which accepts a hydrogen radical from an intermediate **17**. This inference is supported by good recovery of benzoic acid (Table I), which may arise both from **2** by abstraction of a hydrogen atom from **17** and by heterolytic cleavage of **18** → **9**. Studies on the mechanism of these reactions are in progress. Since this benzoyloxylation procedure affords a simple, one-step method for preparation of oxygenated indoles in acceptable yields, this may open a new route to hydroxyindoles. The scope of these reactions is currently under investigation.



17



18

Experimental Section[20]

1-Methylindoxyl *O*-Benzoate (9) (Expt 1, at 80°).—A mixture of 1-methylindole (**8**) (4.2 g, 32 mmol) and **1** (1.0 g, 4 mmol) was heated at 80° for 17 hr in an atmosphere of N_2. After cooling, benzene was added to the mixture, which was extracted with a saturated aqueous solution of $NaHCO_3$ to remove benzoic acid. On acidification of the aqueous layer benzoic acid (460 mg) was obtained. The organic layer was washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to leave **9** as colorless needles (180 mg). The filtrate was evaporated *in vacuo* and the residue was distilled *in vacuo* to remove unreacted **8** (3.2 g). When ether was added to the residue, a second crop of **9** (270 mg) was isolated. The residue obtained on removal of ether was subjected to preparative tlc (benzene-hexane, 1:1). With the isolation of an additional fraction of **9** (120 mg), the total yield of **9** was 570 mg or 56%. Recrystallization from ethyl acetate gave colorless needles: mp 133-133.5°; uv λ_{max} (CH_3CN) 226 mμ (log ε 4.64), 277 (shoulder, 3.85), 283 (3.88), 290 (shoulder, 3.87).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.40; H, 5.34; N, 5.68.

1-Methyldioxindole Dibenzoate (10) and 1-Methylindoxyl *O*-Benzoate (9) (Expt 2, at Room Temperature).—A solution of **8** (2.0 g, 15 mmol) in benzene (3 ml) was mixed with **1** (740 mg, 3 mmol) at room temperature and the mixture stirred in an atmosphere of N_2 for 24 hr. The reaction mixture was washed with aqueous $NaHCO_3$ to remove benzoic acid (450 mg). The organic layer was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was distilled *in vacuo* to remove unreacted **8** (1.4 g). The residue, after preparative tlc (benzene), gave **8** (250 mg) and **10** (40 mg). The latter was recrystallized from benzene-hexane to give almost colorless fine prisms: mp 155-155.5°; uv λ_{max} (CH_3CN) 229 mμ (log ε 472), 279 (4.03); ir ν_{max}^{Nujo} 1740, 1755 cm^{-1} (ester); nmr (CCl_4) no indolic 2 H and 3 H; mass spectrum *m/e* 271.

Anal. Calcd for $C_{23}H_{17}NO_4$: C, 74.38; H, 4.61; N, 3.17. Found: C, 74.40; H, 4.65; N, 3.92.

In expt 3 and 4, 1-methylindole (**8**, 400 mg, 3 mmol) was reacted with **1** (740 mg, 3 mmol) in benzene (3 ml) solution, at 50° and at room temperature, respectively. The organic layer was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue after preparative tlc (benzene) yielded **9** and **10**. In expt 5, after the evaporation of pyridine *in vacuo* and the addition of benzene, the work-up was as above.

Independent Synthesis of 1-Methylindoxyl *O*-Benzoate (9).—*N*-Methyl-*N*-(α-carboxyphenyl)glycine (**11**), prepared as described in the literature,[18] formed colorless plates from water, mp 180-185° (lit.[18] mp 189°). A mixture of **11** (209 mg, 1 mmol), benzoic anhydride (2.3 g, 10 mmol), and sodium benzoate (144 mg, 1 mmol) was heated at 190° (bath temperature) for 4 hr. After cooling, dichloromethane was added and the solution was washed with aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated *in vacuo*. Distillation *in vacuo* removed excess benzoic anhydride, and the residue, after preparative tlc (benzene-hexane, 2:3), gave **9** as colorless needles from ethyl acetate, mp 133-133.5°. This sample showed no depression of melting point on admixture with the compound obtained in expt 1. Their ir spectra were superimposable.

1,2-Dimethylindoxyl *O*-Benzoate (13). A (Expt 6, at 65°).—1,2-Dimethylindole (**12**) (1.16 g, 8 mmol) was melted at 50° and to the melt **1** (242 mg, 1 mmol) was added portionwise (N_2). A vigorous reaction took place. The mixture was heated at 65° (bath temperature) for 4 hr. Ether was added and the mixture extracted with aqueous $NaHCO_3$ to remove benzoic acid (77 mg). The organic layer was washed with water, dried (Na_2SO_4), and evaporated. After tlc (benzene-hexane, 1:1), **13** was obtained as colorless prisms (160 mg) from ethyl acetate: mp 135.5-136.5°; uv λ_{max} (CH_3CN) 229 mμ (log ε 4.68), 277 (shoulder, 3.89), 283.5 (3.93), 292 (shoulder, 3.88); ir ν_{max}^{Nujol} 1735 cm^{-1} (ester); nmr, no 3 H of indole; mass spectrum *m/e* 265.

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.83; H, 5.66; N, 5.27.

B. At Room Temperature (Expt 7).—To a solution of **12** (2.2 g, 15 mmol) in benzene (3 ml) was added **1** (740 mg, 3 mmol) with stirring at room temperature in an atmosphere of N_2. A slightly exothermic reaction took place. After stirring for 2 hr the mixture was washed first with aqueous $NaHCO_3$ to remove benzoic acid (380 mg) and then with water and dried (Na_2SO_4). After removal of the solvent distillation *in vacuo* gave unreacted **12** (1 g). The resultant residue was recrystallized from dichloromethane-hexane to give **13** (470 mg). Additional **13** (170 mg) was obtained from the mother liquor by tlc, total yield 640 mg. Experiment 8 was performed in a similar manner.

1,3-Dimethyloxindole Benzoate (15) (Expt 9).—To a solution of **14** (2.2 g, 15 mmol) in benzene (3 ml) was added **1** (740 mg, 3 mmol) with stirring at room temperature for 5 hr. The reaction mixture was worked up as in expt 2. After tlc (benzene), **15** was obtained as colorless crystals (340 mg) from benzene-hexane: mp 105-106°; uv λ_{max} (CH_3CN) 230 mμ (log ε 4.67), 278-280 (3.94), 290 (shoulder, 3.85); ir ν_{max}^{Nujol} 1755 cm^{-1} (ester); nmr, no 2 H of indole; mass spectrum *m/e* 265.

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.11; H, 5.77; N, 5.25.

Experiments 10 and 11 were performed similarly except that vacuum distillation to recover starting material was unnecessary. Experiment 12 was performed as expt 5 to give **15** (110 mg) and **16** (230 mg).

Hydrolysis of 15 to 1,3-Dimethyloxindole (16).—To a solution of **15** (93 mg) in a mixture of methanol (0.9 ml) and tetrahydrofuran (0.3 ml) was added dropwise 0.35 *N* NaOH-methanol (1 ml) with stirring. After the addition, formic acid was immediately added to neutralize excess alkali. The mixture was evaporated *in vacuo* to remove methanol. Ether was added and the organic layer was washed with water, dried (Na_2SO_4), and evaporated (the residue after tlc (dichloromethane) gave **16** as colorless oil (33 mg) (the ir spectrum of this sample was superimposable with that of an authentic specimen): bp 133-135° (11 mm) [lit.[14] bp 136-138° (11 mm)]; ir λ_{max}^{neat} 1720 cm^{-1} (carbonyl of oxindole); mass spectrum *m/e* 161.

Registry No.—9, 26595-98-2; **10,** 26595-99-3; **13,** 26596-00-9; **15,** 26596-01-0.

---

[17] (a) P. Kovacic and M. E. Kurz, *Tetrahedron Lett.*, 2689 (1966); (b) M. E. Kurz, P. Kovacic, A. K. Bose, and I. Kugajevsky, *J. Amer. Chem. Soc.*, **90**, 1818 (1967); (c) P. Kovacic, C. G. Reid, and M. E. Kurz, *J. Org. Chem.*, **34**, 3302 (1969).

[18] R. Perret and R. Perret, *Helv. Chim. Acta*, **28**, 558 (1945).

[19] S. Hashimoto, W. Koike, and M. Yamamoto, *Bull. Chem. Soc. Jap.*, **42**, 2733 (1969).

[20] Melting and boiling points are uncorrected. Preparative thin layer chromatography (tlc) was performed on silica gel.