authentic 6-chloro-3(2H)-pyridazinone⁸⁾ by usual criteria. Yield, 1.96 g (75%). The starting material, 0.18 g (8%) was recovered from the mother liquor.

The same treatment of I with paraformaldehyde and conc. hydrobromic acid gave 6-bromo-3(2H)-pyridazinone (IIIb) in 37% yield and 3(2H)-pyridazinone (IIIc) in 3% yield. 6-Bromo-3(2H)-pyridazinone: Straw yellow leaflets, mp 154° (from benzene). The authentic sample was synthesized from 3,6-dibromo-pyridazine⁹⁾ by heating with a 10% sodium hydroxide solution.

Reaction of 3-Pyridazinol 1-Oxide (I) with Paraformaldehyde and Hydroiodic Acid—A mixture of 0.45 g (0.004 mole) of I, 0.30 g (0.01 mole) of paraformaldehyde and 5 ml of conc. hydroiodic acid, was heated in a sealed tube for 5 hr. The reaction mixture was evaporated to dryness under reduced pressure, the residue was extracted with ethyl acetate, and the extract was dried over anhyd. sodium sulfate. The solution was poured into an alumina column, the column was washed with ethyl acetate, and the eluant was collected. The eluant was evaporated to dryness under reduced pressure and the residue was treated with a small amount of pet. benzene. The product was filtered and recrystallized from a mixture of ethanol and pet. benzene to colorless needles, mp 79–81°. This compound was identical with authentic 3(2H)-pyridazinone by all usual criteria. Yield, 0.08 g (21%).

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3H-Indoles. IV.¹⁾ Photo- and Peroxide-induced Oxygenation of 2-Ethyl-3H-indoles²⁾

YUICHI KANAOKA, KOICHI MIYASHITA
and OSAMU YONEMITSU

Faculty of Pharmaceutical Sciences, Hokkaido University³⁾

(Received September 27, 1969)

Although autoxidation of indoles is well-documented,⁴⁾ very little is known about autoxidation of 3H-indole system.^{5,6)} In the course of our studies on alkylation of 3H-indoles with polyphosphate ester (PPE),⁶⁾ a facile autoxidation of 2-ethyl-3,3-disubstituted 3H-indoles (**1a–b**) to the 2-acetyl derivatives (**2a–b**) was observed.

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The α -methylene carbon of **1** is (i) at the β -position of enamine-imine system involving the nitrogen atom of 3*H*-indole, and (ii) at an allylic position of styrene-type conjugation system of 3*H*-indole. The marked reactivity of the carbon for autoxidation is obviously due to this polarized allylic character of this 2-substituted 3*H*-indole system.⁶⁾ A precedent of non-cyclic analogue of this system may be found in the air-oxidation of anils **3** early reported by Witkop.⁷⁾ Furthermore, analogous autoxidation of Schiff bases of α,β -unsaturated ketones **4** was recently reported.⁸⁾ Related oxygenation of enamine systems⁹⁾ may also be cited here.

Although **1a** and **1b** were rapidly oxidized at room temperature during the course of working-up, if purified through picrate, they are somewhat stable and oxidized more slowly. When a solution of **1a** in hexane was bubbled with a stream of air at room temperature, oxidation proceeded very slowly after an induction period of several days and completed after eleven days.⁶⁾ In order to elucidate more detailed aspects of the autoxidation, photo- and peroxide-induced oxygenation of these substrates was now examined.

A solution of **1a** in cyclohexane was bubbled with a stream of oxygen under irradiation with a 100-W high pressure mercury lamp at room temperature for 8 hr. Forty nine % of the oxidized product **2a** was isolated. In a similar experiment, **1b** was converted into **2b** in 38% yield after 5 hr of irradiation.

In an attempt to clarify the mechanism of this photo-oxidation, effects of sensitizers on this reaction was examined. Addition of common sensitizer such as methylene blue or benzophenone showed no appreciable effect on the rate of this oxidation suggesting that singlet oxygen may not, if any, be largely involved in this photo-induced process.¹⁰⁾ Probably direct photo-oxidation mechanism involving triplet oxygen¹⁰⁾ may operate in this reaction. However, more evidence must be needed to reach the final conclusion.

The effect of radical initiators on the oxidation was next examined. Bubbling a stream of oxygen through a cyclohexane solution of **1a** and **1b** in the presence of benzoyl peroxide under refluxing for 60–80 min gave rise to formation of **2a** and **2b**, respectively. Under similar conditions, without the peroxide, no appreciable oxidation took place. Preparative oxygenation of **1a** using benzoyl peroxide (0.1 molar equivalent) as an initiator gave **2a** in 71% yield. The fact that this oxygenation reaction is considerably accelerated by such a typical radical initiator suggests that the autoxidation of 2-ethyl-3*H*-indole system is likely a free radical chain process. A tentative mechanism for the formation of **2** from **1** is outlined in Chart 1.

Thus the reaction may be a radical chain process proceeding *via* a propagation step involving a 3*H*-indole radical **5** and a hydroperoxide radical **6**. Alternatively, the process may proceed *via* the enamine form **8**, which gives rise to a radical cation **9** and a peroxide radical cation **10**.⁸⁾ Both of the above paths may lead to the hydroperoxide **7** and its ionic form **11**, respec-

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Chart 1. Apossible Radical Mechanism

tively, as generally accepted in radical oxidation mechanism,¹¹⁾ which then will transform to give the final product **2** through a known sequence of reactions of peroxides.¹²⁾

When subjected to both the photo- and peroxide-induced reaction, neither 2-methyl-3*H*-indoles, nor tricyclic 3*H*-indole such as 2,3-tetramethylene-3-methyl-3*H*-indole underwent autoxidation indicating that requirement for occurrence of the reaction is restricted to the 2-methylene carbon of non-cyclic side chain at the C-2 position of the system. Studies along these lines are in progress.

Experimental

NMR spectra were determined on a NMR Hitachi H-60 spectrophotometer; chemical shifts are in ppm(δ) from TMS as internal standard. UV spectra were taken on a Hitachi EPS-3T spectrophotometer. For TLC, SiO₂ (E. Merck), GF₂₅₄ and G were used.

2-Acetyl-3,3-dimethyl-3H-indole 2a—a) Autoxidation: A soln. of **1a** (200 mg) in *n*-hexane (100 ml) was bubbled with a stream of air at room temp. for 12 days. After the reaction the solvent was removed *in vacuo* at room temp., **2a** was obtained as colorless long needles from EtOH; yield, 120 mg. The physical constants were previously described.⁶⁾

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b) Photo-induced: A soln. of **1a** (177 mg) in cyclohexane (150 ml) was bubbled with a stream of oxygen for 8 hr under irradiation with a 100-W high pressure mercury lamp and worked up as usual. **2a** was recrystallized from EtOH; 94 mg.

c) Radical-initiated: A soln. of **1a** (180 mg, 1 mmole) and benzoyl peroxide (23.4 mg, 0.1 mmole) in cyclohexane (50 ml) were bubbled with a stream of oxygen under reflux for 80 min and worked up as usual. **2a** was recrystallized from EtOH; 136 mg.

2-Acetyl-3,3-tetramethylene-3H-indole 2b—a) Photo-induced: A soln. of **1b** (100 mg) in cyclohexane (150 ml) was bubbled with a stream of oxygen under irradiation with a 100-W high pressure mercury lamp for 5 hr at room temp. After removal of the solvent *in vacuo* at room temp. the residue was applied to a preparative thin-layer chromatography (TLC) (silica gel), developed with benzene, separated an upper portion of this TLC, eluted with ether. The crude **2b** was obtained on evaporation of the solvent; 41 mg. The UV spectrum was previously described. NMR (CCl₄): 8.20—6.80 δ (m, 4H, aromatic), 2.55 (s, 3H, 2-COCH₃), 2.40—1.50 (m, 8H, 3,3-(CH₂)₄).

b) Radical-initiated: A soln. of **1b** (13 mg; 6.5×10^{-5} mole) and benzoyl peroxide (7.8 mg; 3.3×10^{-5} mole) in cyclohexane (15 ml) was bubbled with a stream of oxygen under reflux for 1 hr. After removal of the solvent *in vacuo* at room temp. the residue was applied to a silica gel TLC to give 9 mg of crude **2b**.

Attempted Oxygenation of 3,3-Dimethyl-3H-indole with Photosensitizer—a) Methylene blue: A soln. of **1a** (5.6 mg; 2.3×10^{-5} mole) and methylene blue (0.75 mg; 2.0×10^{-5} mole) in MeOH (25 ml) saturated with O₂ was irradiated with a 100-W high pressure mercury lamp for 4 hr. No appreciable oxidation took place as measured by UV.

b) Benzophenone: A soln. of **1a** (1.00 mg; 5.7×10^{-6} mole) in cyclohexane (4 ml) saturated with O₂ with or without benzophenone (0.01 mg; 5.2×10^{-8} mole) was irradiated as above for 30 min. In both cases no appreciable reaction took place as measured by UV. Experiment in benzene soln. gave the same result.

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A Further Investigation on Oxidative Coupling of *dl*-2-Methylisosalsole

OSAMU HOSHINO, HIROSHI HARA, MORITAKA WADA
and BUNSUKE UMEZAWA

Faculty of Pharmaceutical Sciences, Science University of Tokyo¹⁾

(Received October 6, 1969)

In a previous paper,²⁾ oxidative coupling of *dl*-2-methylisosalsole (*dl*-1,2-dimethyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline) (I)³⁾ with potassium ferricyanide in a mixture of 2.8% ammonia solution and dioxane has shown to give *dl*-1,1',2,2'-tetramethyl-6,6'-dimethoxy-7,7'-dihydroxy-1,1',2,2',3,3',4,4'-octahydro-8,8'-bisisoquinoline (C-C dehydrodimer) (II)^{4,5)} and *dl*-1,1',2,2'-tetramethyl-6,6'-dimethoxy-7'-hydroxy-1,1',2,2',3,3',4,4'-octahydro-7,8'-bisisoquinolyl ether (C-O dehydrodimer) (III)^{4,5)} in 10.5 and 2.1% yield (as each dihydrochloride), respectively. Compared with the case of corypalline (2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline) (IV), in which 8,8'-bicorypallyl (C-C dehydrodimer) (V)⁶⁻⁸⁾ is only formed under the similar condition, the above formation of C-O dehydrodimer (III) suggested that this reaction might be largely dependent on both oxidants and solvents

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