The Photosensitized Oxygenation of N_b-Methyltryptamine[1]

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Abstract: Approaches to the synthesis of 3a-hydroxypyrroloindole (**4**) by the reaction of N_b-methyltryptamine (**6**) with singlet oxygen have been studied as a model reaction for the formation of **4** by the oxygenation of tryptophan catalyzed by dioxygenase. The reaction of **6** with singlet oxygen in nonaqueous solvents gave 4a-hydroxyoxazinoindole (**7**) and 3a-hydroxypyrroloindole (**8**) via 3a-hydroperoxyindole (**15**). The successful isolation of **15** provides strong evidence for participation of ethylamino side chain in **2**. Interconversion between **7** and **8** by oxidation-reduction was carried out, and mechanism of formation of **7** and **8** is discussed.

Biological hydroxylation of an aromatic ring by the monooxygenase, which is accompanied by the 1,2-hydride migration (the NIH shift), is now well documented[2] and is known to proceed via arene oxides as important intermediates.[3]

We have recently found[4] a model reaction for the oxidation of tryptophan by monooxygenase, viz., the conversion of N_a,N_b-dimethyltryptamine to 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrroloindole (**1**) by photolysis with pyridine-1-oxide (path A). It has been known that 2,3-disubstituted indoles are very sensitive to cleavage of the pyrrole ring in nonenzymatic oxidations, and usually *o*-acylformanilides are formed.[5] An analogous oxidation is operating in the metabolic transformation of tryptophan to kynurenine catalyzed by tryptophan-2,3-dioxygenase[6] and the reaction has been suggested[7] to involve the 3-hydroperoxyindolenine **2** as a primary intermediate, which collapses to the formylkynurenine via dioxetane intermediate **5** derived by cyclization of **2** (path B).

The oxidation of tryptophan to formylkynurenine has been accomplished by several methods, e.g., O_3 oxidation,[8] photooxidation,[9] and transition metal complex catalyzed oxidation.[10] Dye-sensitized photooxidation has been developed as a tool for the elucidation of the active site in enzymes, and the conversion of tryptophan to formylkynurenine by photosensitized oxygenation[11] provides a model reaction for the dioxygenase oxidation. The reaction is believed to proceed via dioxetane intermediate **5** derived from **2**. However, there appears to be no successful example of isolating the hydroperoxide **2**, although numerous reports of the hydroperoxyindolenine **2** or dioxetane **5** as the reaction intermediate in photochemical oxygenation of tryptophan can be cited.[11]

Considering the reactivity of the hydroperoxyindolenine **2**, there may be another reaction path (C) in which the ethylamino side chain participates, leading to the formation of 3a-hydroperoxypyrroloindole (**3**), which may further be reduced to the 3a-hydroxypyrroloindole ring system found in sporidesmins,[12] brevianamide E,[13] and hunteracine bromide.[14] Therefore, we were interested in exploring the possibility of preparing the ring system of **4** by the reaction of tryptophan derivatives with singlet oxygen. This conversion may also provide a model for the formation of hydroxypyrroloindole **4** by the oxygenation of tryptophan catalyzed by dioxygenase.

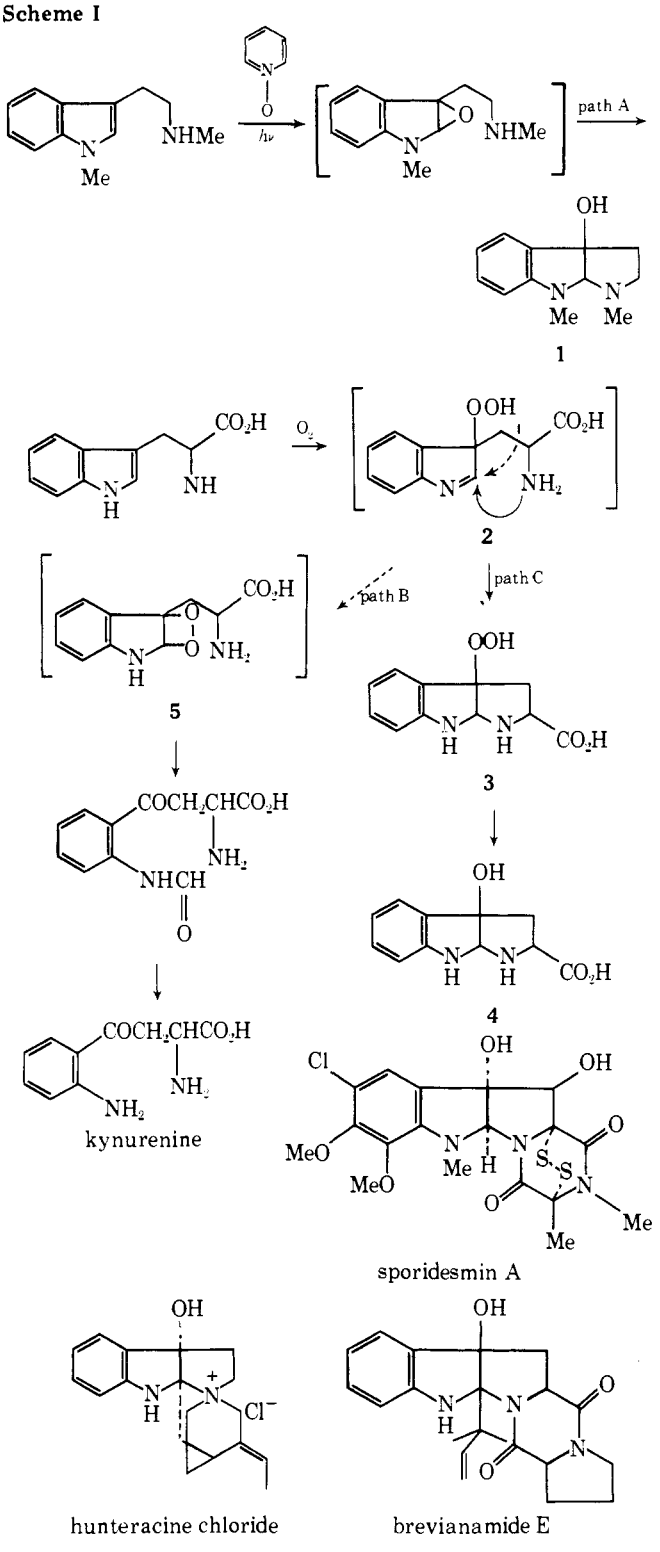
We now report the first successful isolation of the 3a-hydroperoxypyrroloindole (**15**) by the dye-sensitized photooxygenation of N_b-methyltryptamine (**6**) and from which we obtained 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**8**) and 4a-hydroxy-2-methyl-2,3,4,4a-9,9a-hexahydro-1,2-oxazino[6,5-*b*]indole (**7**).

Results and Discussion

Singlet oxygen was generated in situ by irradiation of the reaction mixture containing N_b-methyltryptamine (**6**) and Rose Bengal as sensitizer, while oxygen was bubbled through the solution. When a 28.5 m*M* solution of **6** in benzene was irradiated until all the starting material exhausted, no desired product **8** was detected and instead a new indoline derivative **7** was obtained as the main product. In addition, 3-formylindole (3-4%) and N_b-formyl-N_b-methyltryptamine (5-7%) were formed. The reaction was sensitive to the light source used and the reaction time and was best carried out by using a 200-W halogen lamp, giving 25-34% yield of **7**, as shown in Table I. Other light sources such as 650-W lamp have also been used but led to a decreased yield of **7** and an increased yield of tar. Likewise, photooxygenation of **6** was run in a 46 m*M* benzene solution for 13 hr; **7** was obtained in 23% yield. However, irradiation of this reaction for 8 hr gave rise to the desired product, 3a-hydroxypyrroloindole (**8**) in 7% yield after chromatographic separations, in addition to **7** in 9% yield, and considerable starting material **6** (31%) was recovered. As a further survey of the solvent effects existing in photooxygenation of **6**, irradiation was performed in other solvents as summarized in Table II. However, the solvent variations in this range did not measurably affect the product distributions. Nonetheless, of particular note is that the TLC of the reaction mixtures both in methanol and 2% pyridine in methanol showed a new spot indicative of the presence of an appreciable amount of an intermediate. 3-Formylindole, however, was formed in 3-4% yield irrespective of the kind of solvent used.

Structural assignments to the oxygenation products were made on the basis of elemental analysis, spectral data, and chemical reactions. These data are consistent with the structures of **7** and **8**. Crystalline compound 4a-hydroxy-2-methyl-2,3,4,4a,9,9a-hexahydro-1,2-oxazino[5,6-*b*]indole (**7**), obtained directly from the reaction mixture, showed a typical indoline chromophore in its ultraviolet spectrum having maxima at 242 and 297 nm, and the hypsochromic shift (236 and 293 nm) for both bands was observed on addition of acid. The mass spectrum exhibited a strong molecular ion peak corresponding to incorporation of two oxygens and the characteristic fragment peaks at M − 16, M − 17, *m/e* 147, and 146.[14] The ir spectrum contained a sharp band at 3300 cm^{-1} and a broad band at 3150 cm^{-1}, assigned to the OH and NH stretching. In accord with the favored structure **7**, the NMR spectrum in pyridine-d_5 showed the presence of a methine proton N-CH-O at δ 5.37[15] as a singlet which experiences a significant downfield shift (49 Hz) compared with the corresponding proton

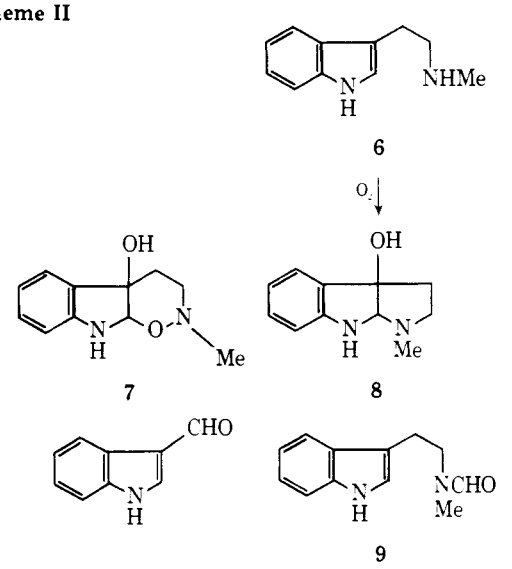
Scheme I



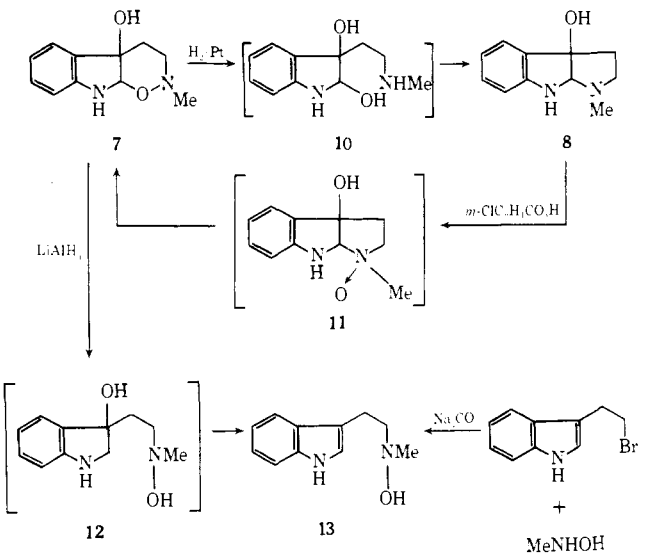
in **8**, indicative of a proton attached to carbon atom flanked by an oxygen and nitrogen atom.[16]

The properties of the second product **8** are in good agreement with expectations, and with the known properties of **1** from our earlier work.[4] The NMR spectrum in $CDCl_3$ contained a methine singlet at δ 4.38 which shifts to δ 4.88 in pyridine-d_5. The uv spectrum was similar to that of **1**, displaying λ_{max} at 243 and 303 nm which undergoes a hypsochromic shift of 8 nm in dilute acidic solution.[17] The mass spectrum of **8** displayed a strong molecular ion peak and the peaks at *m/e* 173, 172, 147, and 146, expected by analogy with **1**. The ir spectrum indicated the presence of NH and

Scheme II



Scheme III



OH groups (3300 and 3090 cm^{-1}) and PhNC moiety (1620 cm^{-1}).[18]

Catalytic hydrogenation of **7** in methanol in the presence of HCl gave **8** in 87% yield. On the other hand, **8** reacted with *m*-chloroperbenzoic acid in $CHCl_3$ to give **7** as the major product, instead of the expected N_b-oxide **11**. In view of these results, we propose that, on catalytic hydrogenation, **7** undergoes hydrogenolysis to give unstable intermediate diol **10** which then recyclizes to give **8** directly or after elimination of water, forming indolenine derivative. The oxidation of **8** to give **7** in place of **11** is probably influenced by unusual instability of **11** at room temperature, which rapidly undergoes Meisenheimer type rearrangement to give **7**. Of interest is that the present example provides a new system for Meisenheimer rearrangement since a requirement for the group migration from N to O in the rearrangement of *N*-oxides has been suggested to be benzylic or allylic type.[19] The oxidation of physostigmine by hydrogen peroxide and rearrangement to geneserine has been reported.[20] For comparison, we carried out the *m*-chloroperbenzoic acid oxidation of physostigmine in $CHCl_3$ at room temperature, and geneserine was obtained in nearly quantitative yield, suggesting that a similar process takes place. The stereochemistry of **7**, at present, is not certain but presumed to be the cis fused B/C ring on the basis that the oxygen attack at 9a-carbon from the opposite side to 4a-

Table I. Photosensitized Oxygenation of 6 in Benzene in the Presence of Rose Bengal (A Minimum Amount of Methanol Was Used to Dissolve Rose Bengal in Benzene)

Light source	N_b-Methyltryptamine	Reaction Time, hr	Yield, % 7	8	Recovery, % 6
300 W flood lamp[a]	1 g (5.7 mmol)	10	20		
100 W halogen lamp[b]	1 g (5.7 mmol)	7	24		
200 W halogen lamp[b]	1 g (5.7 mmol)	7	25–34		
650 W halogen lamp[b]	1 g (5.7 mmol)	4	14		
200 W halogen lamp[b]	2 g (11.5 mmol)	13	23		Trace
200 W halogen lamp[b]	2 g (11.5 mmol)	8	9	7	31

[a] External irradiation. [b] Internal irradiation. Ushio halogen lamp. JCV-100-100 CS, JCV-100-200CS, and JPD-100-650C are used for 100, 200, and 650 W lamps, respectively.

Table II. Photosensitized Oxygenation of 6 in the Presence of Rose Bengal[a]

6	Solvent	Reaction time, hr	Yield, % 7	8	3-Formylindole
1 g (5.7 mmol)	CH_3OH	5	22	3	4.3
2 g (11.5 mmol)	t-BuOH[b]	12	12	0	3.5
2 g (11.5 mmol)	2% pyridine in CH_3OH	9	17	3.9	3.9

[a] All the reactions were carried out until the starting material disappeared. [b] Methanol (10 ml) was used to dissolve Rose Bengal in t-BuOH.

Table III. Photosensitized Oxygenation of 6 in Various Conditions

6	Irradiation, hr		Yield, % 7	8	Recovery, % 6
11.5 mmol	8		9	7	31
11.5 mmol	13		23	None	Trace
11.5 mmol	8	$NaBH_4$	6	12	30
11.5 mmol	13	$NaBH_4$	19	4	
11.5 mmol	8	Ph_3P	3	15	
11.5 mmol	13	2,6-Di-*tert*-butylphenol	23	8	17

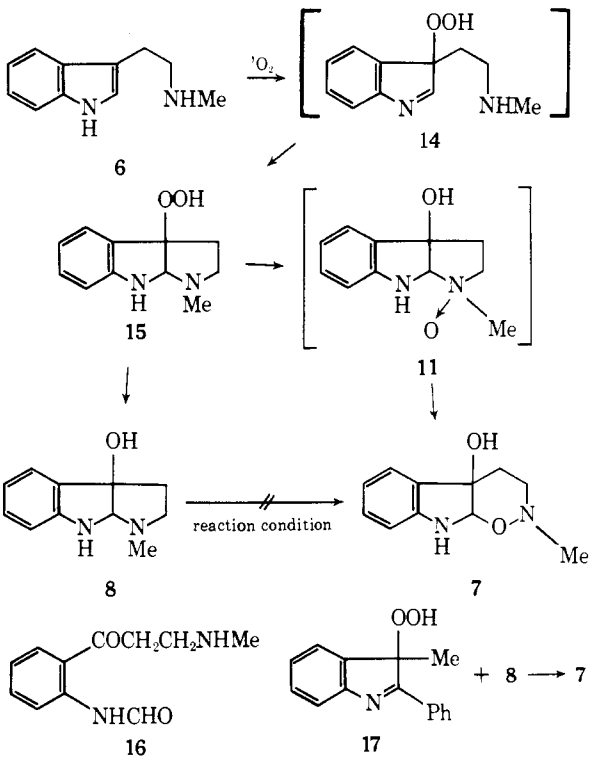
hydroxyl group is kinetically favored and that the oxidative conversion of physostigmine to geneserine has been known to proceed with retention of configuration.[21] Further support for structure of **7** was provided by lithium aluminum hydride reduction in tetrahydrofuran, which led to the formation of a hydroxylamine derivative **13**. As shown in Scheme III, **13** can be formed by hydride attack at the 9a-carbon to give **12**, followed by dehydration. Unambiguous proof of the structure for **13** rested upon an alternate synthesis involving the reaction of methylhydroxylamine with 3-(2-bromoethyl)indole in aqueous alcohol. In this regard, essentially the same reaction has been found to occur in $LiAlH_4$ reduction of quinamine to chinconamine.[22]

Reaction Mechanism

Control experiments demonstrated that both sensitizer and light were essential for the formation of **7** and **8**. Compound **8** rapidly decomposed when irradiated under the reaction conditions for 8 hr. This excludes the possible formation of **7** via **8**. In contrast, **7** was completely unreactive when subjected to the identical conditions required for the formation of **7** and was recovered substantially unchanged. Therefore, in prolonged reaction conditions (13 hr), apparently **7** became the sole product, and the complete absence of **8** in the reaction mixture was consistent with the experimental data. When $NaBH_4$ was added to the reaction mixture immediately after 8 hr irradiation, an increased yield of **8** was observed and the yield of **7** was decreased. Furthermore, it was found that **8** can be obtained by addition of $NaBH_4$ even after prolonged irradiation as shown in Table III. These experiments suggested the existence of an unstable hydroperoxyindole **15** as the common intermediate, which largely survives the reaction conditions and is reduced to the alcohol **8** by addition of $NaBH_4$. Therefore, when the reaction mixture was allowed to stand overnight in absence of reductant, **15** converted to **11** probably intramolecularly, which then spontaneously rearranged to **7** at room temperature. Aforementioned short-time experiments suggested that **15** also breaks down to **8** during irradiation to some extent. Further evidence on the involvement of the key intermediate **15** was obtained by the isolation of **8** after reduction of labile hydroperoxide intermediate with triphenylphosphine. The possibility that radical reactions were responsible for the oxygenated products **7** and **8** was discounted by the observation that, in the reaction of **6**, the presence of a free radical inhibitor, 2,6-di-*tert*-butylphenol, had no effect on the formation of **7** and **8**. Furthermore, the isolation of **8** in the presence of a radical inhibitor suggested that triplet oxygen may participate in the destruction of **8**.

For the dye-sensitized oxygenation of N_b-methyltryptamine (**6**), a likely reaction pathway consistent with the results presented in this study is outlined in Scheme IV. In the initial step, the reaction of singlet oxygen with **6** to yield **14** was followed by cyclization of the ethylamino side chain

Scheme IV



forming **15**,[23] which then collapsed to either **7**, probably intramolecularly but this is as yet by no means certain, or **8**. Thus our result appears to be the first example of the anticipated third pathway (C). Previous photosensitized oxidations of tryptophan have been conducted in either water[11b,24] or organic acids such as HCO_2H[25] or CH_3CO_2H,[26] where participation of the ethylamino side chain is unfavorable and the reaction consequently proceeds via path B. Of particular note is that the dicarbonyl compound **16** has not been isolated from our reaction mixture. However, this may have been caused by the unusual instability of **16** since attempts to synthesize **16** by ozonization of **6** failed. Therefore, we can not exclude path B operating competitively. Finally, we were able to isolate the key compound **15** in a separate experiment which was performed at lower temperature (1-0°C) and followed by rapid work-up as follows: evaporation of the solvent at 0-5°C (2mm) and filtration of the residue through alumina to remove the sensitizer, followed by preparative TLC (silica gel-10% methanol in CH_2Cl_2). The signals and integrated area of the NMR spectrum in $CDCl_3$ were consistent with structure **15**, showing a sharp singlet at δ 4.88 attributable to the methine proton, which exhibited a down field shift to 5.21 in pyridine-d_5. The ultraviolet spectrum of **15** resembles that of **8**, displaying two absorption maxima at 242.5 and 300.5 nm while, in dilute acidic solution, both bands were shifted to 236 and 294 nm, respectively, indicating the presence of a PhNCN chromophore.[17] The mass spectral behavior of **15** has many similarities to that of **7**. However, in addition to the parent ion at *m/e* 206 (28%), strong M − O (40%) and M − OH (22%) ions are quite important and support the structure of **15** since the ions formed by losses of O and OH from **7** and **8** were weaker than their parent peaks as indicated in the Experimental Section. Furthermore, the structure was confirmed by the following chemical properties. Compound **15**, which gave a positive test with KI-starch, was found to be rather stable and, on standing in $CHCl_3$-pyridine-4% methanol in benzene at room temperature, was gradually converted to **7** during 24 hr, whereas reduction with $NaBH_4$ in methanol provided **8** in high yield.

In light of the above results, we carried out the reaction of 3-hydroperoxy-3-methyl-2-phenylindolenine **17** with **8** in order to know the reactivity of a hydroperoxide[27] toward tertiary amine **8**, which may support significantly our proposed reaction mechanism. In fact, the reaction proceeded at room temperature, and the oxazinoindole **7** was obtained in 87% yield, giving an additional support for the proposed pathway.

At present, the mechanisms which account for the formation of 3-formylindole and N_b-formyl-N_b-methyltryptamine remain unknown. The newly discovered facile conversion of N_b-methyltryptamine (**6**) to 3a-hydroxypyrroloindole (**8**) and 4a-hydroxyoxazinoindole (**7**) via 3a-hydroperoxyindole (**15**) may have important implications for the biosynthesis of sporidesmins, brevianamide E, and huteracine chloride.

Experimental Section

Melting points were taken on a Yamato melting point apparatus and a Yanagimoto micro hot-stage apparatus and are uncorrected. Ultraviolet spectra were taken on Hitachi 323 spectrophotometers. Infrared spectra were recorded on Hitachi Model G-3 and 215 spectrometers. The proton NMR spectra were taken in $CDCl_3$, except where otherwise indicated with JEOL(JMM)4H-100 and JEOL JMH-100 and measured at 100 MHz. Chemical shift data are reported in part per million (δ) downfield from tetramethylsilane as an internal standard. Mass spectra were run on a Hitachi RMU-6E mass spectrometer and are expressed in percent relative to the most intense peak.

Photooxygenation of N_b-Methyltryptamine (6) in Benzene. (1) Long-Term Irradiation. In a 300-ml water-cooled Pyrex immersion apparatus, **6**[28] (1 g, 5.7 mmol) was dissolved in benzene (200 ml) and mixed with Rose Bengal (50 mg) in methanol (10 ml). The vessel was placed in an ice-bath and irradiated by 200-W halogen lamp for 7 hr, while a stream of oxygen was bubbled through the reaction vessel. The reaction mixture was left overnight at room temperature. The solvent was evaporated. The residue (1.2 g) was mixed with a small amount of dichloromethane-benzene, and the precipitate **7** was collected, 400 mg (34%). Recrystallization from methanol gave colorless needles: mp 197-198°; uv_{max} (95% ethanol) 242 nm (ϵ 7460), 297 (2300); max (95% ethanol-HCl) 236 nm (ϵ 7590), 293 (2050); ir (KBr) 3300, 3150 (OH, NH), 1620 (PhNC), 990 cm^{-1} (N-O);[29] NMR (C_5D_5N) 2.50 (s, N_b-Me), 2.20-2.90 (m, CH_2CH_2), 4.70 (broad s, OH, NH, exchangeable), 5.37 (s, N-CH-O), 6.60-6.90, 7.00-7.50 (m, aromatic H); mass spectrum 206 (40) M^+, 189 (20) M-OH, 173 (8), 160 (5), 147 (100), 147 (76), 133 (30), 130 (18), 60 (75), 44 (57).

Anal. Calcd for $C_{11}H_{14}O_2N_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.97; H, 6.92; N, 13.57.

3-Formylindole and N_b-formyl-N_b-methyltryptamine were obtained as follows. The above mother liquor was evaporated. The residue was chromatographed on silica gel, and elution with dichloromethane gave 3-formylindole, 3-4% yield, mp 191-197°, identical (ir, TLC, mmp, uv, mass spectrum) with an authentic sample. Further elution with dichloromethane gave an oil which was subjected to preparative TLC (silica gel-5% methanol-dichloromethane). Extraction of the middle band (R_f v 0.5) with dichloromethane gave N_b-formyl-N_b-methyltryptamine as an oil, 5-7% yield, identical (ir, TLC, uv, mass spectrum) with the specimen[4b] prepared by the reaction of N_b-methyltryptamine with ethyl formate.

(2) Short-Term Irradiation. A solution of **6** (2 g, 11.5 mmol) in benzene (250 ml) was mixed with Rose Bengal (100 mg) in methanol (10 ml) and was irradiated for 8 hr under identical condition described above, at which time the starting material **6** still remained. The reaction mixture was left overnight, and the precipitates were filtered to give **7** (80 mg). The mother liquor was evaporated. The residue was treated with dichloromethane-benzene to give **7** as precipitate, 132 mg, totaling 212 mg, 9% yield. The mother liquor was concentrated to give a residue (1.94 g) which was chromatographed on alumina (24 g). The first elution with 2-3% methanol-dichloromethane gave an oil (865 mg) which showed many spots on TLC [silica gel—dichloromethane-methanol-triethylamine (40:3:2)]. The second elution with the same solvent gave an oil (555 mg). The further elution with 5-10% methanol-dichloromethane gave **6** (367 mg). The first and second elutes (1.42 g) were rechromatographed on silica gel (15 g). Elution with dichloromethane and 5% methanol-dichloromethane afforded an oil (887 mg), from which **6** (224 mg) was recovered after preparative TLC [silica gel—dichloromethane-methanol-triethylamine (40:3:2)]. Elution with 5-10% methanol-dichloromethane afforded an oil (270 mg) which was thick layer chromatographed [silica gel—dichloromethane-methanol-triethylamine (40:3:2)]. Extraction of the lower band with 10% methanol-dichloromethane provided **8** as pale yellow crystals (144 mg, 7%). Extraction of the more polar band with the same solvent gave **6** (34 mg), total recovery, 625 mg (31%). Recrystallization of **8** from acetone gave colorless prisms, mp 151°; uv_{max} (95% ethanol) 243 nm (ϵ 8740), 302 (2470); max (95% ethanol-HCl) 236.5 nm (ϵ 7980), 294.5 (2280); ir(KBr) 3300, 3080 (NH, OH), 1620 cm^{-1}; NMR 2.1-2.90 (m, CH_2CH_2), 2.35 (s, N_b-Me), 3.45 (broad s, OH, NH, exchangeable), 4.10 (broad s, OH or NH, exchangeable), 4.38 (s, NCHN), 6.50-7.35 (m, aromatic H); (C_5D_5N) 2.1-3.0 (m, CH_2CH_2), 2.46 (s, N_b-Me), 4.70 (broad s, OH or NH, exchangeable), 4.88 (s, NCHN), 6.18 (s, OH or NH, exchangeable), 6.60-7.60 (m, aromatic H); mass spectrum 190 (100) M^+, 173 (20) M − OH, 172 (13) M − H_2O, 147 (40), 146 (57), 133 (25), 132 (38), 131 (10), 130 (33), 44 (25), 42 (22).

Anal. Calcd for $C_{11}H_{14}ON_2$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.36; H, 7.42; N, 14.62.

(3) Control Experiment without Sensitizer. N_b-Methyltryptamine (**6**) (1 g, 5.7 mmol) in benzene (250 ml) and methanol (10 ml) was oxygenated and irradiated as above (8 hr) except that the sensitizer was omitted. Work-up gave a nearly quantitative recovery of the starting material, 986 mg, mp 81-83°, which was identified

by comparison of ir spectrum and R_f value on TLC as well as mixture melting point.

(4) In the Presence of a Radical Inhibitor. A solution of **6** (2 g, 11.5 mmol), 2,6-di-*tert*-butylphenol (530 mg, 2.6 mmol), and Rose Bengal (100 mg in 10 ml of methanol) in benzene (250 ml) was irradiated for 13 hr as above. Work-up as described above (1) gave **7** (534 mg, 23%), mp 196–198°. The mother liquor was concentrated. The residue (2.46 g) was subjected to chromatography on alumina and silica gel followed by preparative TLC described as above to give **8** (180 mg, 8.2%), mp 148–150°. From column chromatography on alumina, 4,4′-dihydroxy-3,3′5,5′-tetra-*tert*-butyldiphenyl (161 mg), mp 185–189°,[30] was obtained, and 2,6-di-*tert*-butylphenol (80 mg, 15%) was recovered.

(5) Addition of Ph_3P. Oxygenation of **6** (2 g, 11.5 mmol) was carried out for 8 hr as described above. When the irradiation was stopped, Ph_3P (2.41 g, 9.2 mmol) was quickly added to the reaction mixture which then was stirred overnight at room temperature. The solvent was evaporated, and the residue was mixed with a small amount of dichloromethane to give **7** as precipitate, 61 mg, 3%, mp 196–198°. The mother liquor was evaporated, and the residue (4.9 g) was chromatographed on alumina (60 g). Elution with benzene–hexane (1:1) gave Ph_3P as colorless crystals, 1.074 g. Elution with benzene–hexane (1:1) and dichloromethane gave Ph_3PO (1.39 g) as colorless crystals. Elutions with 1–5% methanol–dichloromethane gave a caramel (870 mg) which was rechromatographed on silica gel (15 g) prepared in dichloromethane. Elution with 3–10% methanol–dichloromethane afforded **8** as a pale yellow solid, 337 mg, 15.5%.

A control experiment was carried out as above for 1 hr except that **6** was omitted and Ph_3P (2.4 g, 9.2 mmol) was added to the reaction mixture. Work-up gave Ph_3PO (555 mg, 23%), and 77% of Ph_3P (1.86 g) was recovered.

Sodium borohydride reduction of the reaction mixture was carried out in a similar manner, and the results are listed in Table III.

(6) In Other Solvents.[31] The photooxygenation of **6** in other solvents was performed in a similar manner, and Table II provides a summary of these results.

Isolation of 3a-Hydroperoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (15). (1) A solution of **6** (1 g, 5.7 mmol) and Rose Bengal (50 mg) in anhydrous methanol (260 ml) was cooled with ice–Dry Ice to 1–0°C and irradiated for 3.5 hr as above. The TLC [silica gel—dichloromethane–methanol–triethylamine (40:3:2)] of the reaction mixture showed a new spot (R_f 0.5) which gave negative test with Ehrlich reagent. The spots corresponding to **7** (R_f 0.55) and **8** (R_f 0.3) were not observed. The solvent was distilled at 2 mm with a bath temperature of 0–5° C. The residue was dissolved in dichloromethane and filtered through alumina (25 g) to remove the sensitizer. The eluent obtained with dichloromethane and 5% methanol–dichloromethane was subjected to preparative TLC (silica gel—10% methanol–dichloromethane). Extraction of the middle band (R_f 0.3) with 10% methanol–dichloromethane provided **15** as an oil which showed one spot on TLC and gave a positive test with potassium iodide–starch: uv_{max} (95% ethanol) 242.5 nm, 300.5; max (95% ethanol–HCl) 236, 294 nm; NMR 2.0–3.40 (m, CH_2CH_2), 2.40 (s, CH_3N), 4.70 (broad s, NH, OOH), 4.88 (s, NCHN), 6.40–7.40 (m, aromatic H, C_5D_5N), 2.20–3.00 (m, CH_2CH_2), 2.49 (s, CH_3N), 5.00 (broad s, NH, OOH), 5.21 (s, NCHN), 6.6–7.00, 7.00–7.20, 7.20–7.60 (m, aromatic H); mass spectrum 206 (28) M^+, 190 (40) M − O, 189 (22) M − OH, 188 (2), M − H_2O, 173 (13) M − OOH, 160 (16), 147 (100), 146 (97), 133 (32), 132 (37), 130 (42), 60 (58), 44 (47), 42 (33). The solutions of **15** in $CDCl_3$ or pyridine-d_5 used for taking the NMR spectrum resulted in precipitation of **7** upon standing for 15 hr at room temperature. Furthermore, **7** was obtained when **15** was allowed to stand in 4% methanol–benzene. (2) The photooxygenation of **6** (1 g, 5.7 mmol) was carried out under identical conditions described above (1) and followed by a similar work-up. Extraction of **15** from preparative TLC was performed with methanol. To the methanol extract was added $NaBH_4$ (2 g), and the reaction mixture was left overnight. The methanol was evaporated, and the residue was extracted with dichloromethane, washed, dried, and evaporated. The residue was thick layer chromatographed on silica gel (dichloromethane–methanol–triethylamine 40:3:2). Extraction of the lower band with 10% methanol–dichloromethane furnished **8** (240 mg, 22%), mp 147–149°.

Irradiation of 7 under the Reaction Conditions. To a solution of **7** (120 mg) in benzene (250 ml) was added Rose Bengal (6 mg) in methanol (6 ml). The reaction mixture was irradiated under identical conditions as described above for 8 hr. TLC examination of the reaction mixture showed a spot corresponding to **7**, and no other significant spot was observed. Work-up gave a nearly quantitative recovery of **7** (124 mg, mp 180°). Recrystallization from methanol gave product, mp 192–196°, which showed an ir spectrum identical with that of the starting material.

Irradiation of 8 under the Reaction Conditions. A solution of **8** (114 mg) in benzene (250 ml) was mixed with Rose Bengal (6 mg) in methanol (6 ml) and irradiated under identical condition as described above for 7 hr by which time the spot corresponding to **8** on TLC was completely decomposed to many spots. However, none of the spots corresponded to **7**. These spots were separated by preparative TLC [silica gel—dichloromethane–methanol–triethylamine (40:3:2)], and minor unidentified tarry compounds were obtained.

An Attempted Reduction of 7 with $NaBH_4$. A mixture of **7** (152 mg, 7.5 mmol) and $NaBH_4$ (143 mg, 38 mmol) in methanol (20 ml) was refluxed for 5 hr. Work-up in the usual way gave colorless crystals, 113 mg, mp 169–176°, which were crystallized from methanol to give **7** as colorless needles, mp 195–198°.

$LiAlH_4$ Reduction of 7. To a boiling solution of $LiAlH_4$ (190 mg, 5 mmol) in anhydrous dioxane (50 ml) was added **7** (344 mg, 1.7 mmol) in anhydrous dioxane (50 ml). The reaction mixture was refluxed for 1.5 hr, and the excess hydride was destroyed by addition of 10% NaOH. The dioxane layer was filtered and evaporated to give a residue (306 mg) which was subjected to preparative TLC [silica gel—dichloromethane–methanol–triethylamine (40:3:2)]. The upper band afforded, upon extraction with 10% methanol in dichloromethane, **13** (177 mg, 56%), mp 48–65°. Recrystallization from benzene gave colorless prisms, mp 95–98°, which were identified by direct comparison of the spectral data (ir, NMR, mass, uv) and R_f value with the specimen prepared by the following procedure. The more polar band, extracted with the same solvent, gave **6** (30 mg, 10%).

***N*b-Hydroxy-*N*b-methyltryptamine (13).** To a solution of 3-(2-bromoethyl)indole, prepared by the known method[32] from tryptophol (4.72 g, 29 mmol) in 70% ethanol (150 ml), was added Na_2CO_3 (6.4 g, 6 mmol) and *N*-methylhydroxylamine hydrochloride (2.5 g, 30 mmol). The reaction mixture was refluxed for 4 hr, and the solvent was evaporated. The residue was extracted with dichloromethane. The extracts were washed, dried, and evaporated to give a dark brown oil (4.6 g) which was chromatographed on silica gel and rechromatographed on alumina and followed by preparative TLC [silica gel—dichloromethane–acetone (20:1)] to give tryptophol, 1.15 g, 24%, and **13**, 680 mg, 12% as crystals. Recrystallization from benzene gave colorless prisms: mp 100–101°; uv_{max} (95% ethanol) 222.5 nm (ϵ 37,600), 275 (5840), 282 (6230), and 290 (5340); ir (KBr) 3410 and 3220 cm^{-1} (NH, OH); ^1H NMR 2.34 (s, 3 H, Me), 3.03 (s, 4 H, CH_2CH_2), 6.95–7.70 (m, aromatic H), 7.99 (s, 1 H, NH); mass spectrum 190 (6) M^+, 172 (4), 149 (5), 131 (100), 115 (5), 60 (22), 42 (13).

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.27; H, 7.36; N, 14.69.

Catalytic Hydrogenation of 8 to 7. A solution of **7** (100 mg, 0.5 mmol) in methanol (15 ml) was hydrogenated over PtO_2 (50 mg) at room temperature. One equivalent of H_2 was taken up in 280 min. The solvent was evaporated after filtration of the reaction mixture to give a crystalline solid (98 mg), which was purified by preparative TLC [silica gel—dichloromethane–methanol–triethylamine (40:3:2)]. Extraction of a middle band with 10% methanol–dichloromethane gave **8** as colorless crystals (54 mg, 59%). Recrystallization from acetone gave a compound, mp 151°, identical (ir, uv, NMR, mass, TLC, mmp) with the compound obtained by photooxygenation of **6**.

The same reaction of **7** (206 mg, 1 mmol) in the presence of concentrated HCl (104 mg) was carried out to give **8** (165 mg) in 87% yield.

Oxidation of 8 with *m*-Chloroperbenzoic Acid. To a stirred solution of **8** (100 mg, 0.5 mmol) in chloroform (15 ml) was added dropwise a solution of *m*-chloroperbenzoic acid (130 mg, 0.5 mmol equiv as 70% purity) at 0–5°. The reaction mixture was stirred for further 3 hr at room temperature and chromatographed on alumina (10 g). Elution with dichloromethane gave **7**, 180–185°, 101 mg, 93%.

Oxidation of Physostigmine by *m*-Chloroperbenzoic Acid. To a

stirred solution of physostigmine (500 mg, 1.8 mmol) in chloroform (50 ml) was added dropwise *m*-chloroperbenzoic acid (450 mg, 1.8 mmol as 70% purity) in chloroform (10 ml) at 0–5°, and the reaction mixture was stirred for 3 hr at room temperature. The solution was passed through a column of alkaline alumina (50 g). Elution with dichloromethane gave geneserine (503 mg, 95%) which was converted to its picrate, mp 174–175.5° (EtOH) (lit.[20b] mp 174–175°).

Oxidation of 8 with 3-Hydroperoxy-3-methyl-2-phenylindolenine (17) to 7. A solution of **8** (50 mg, 0.24 mmol) and **17** (63 mg, 0.24 mmol) in dichloromethane (30 ml) was stirred for 96 hr at room temperature, and the solvent was evaporated. The residue was mixed with a 1:1 dichloromethane–benzene (20 ml) to give **7** (47 mg, 87%), mp 180–185°, identical (ir, TLC, uv) with the specimen prepared by photooxygenation of **6**.

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References and Notes

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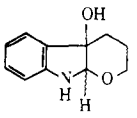

i

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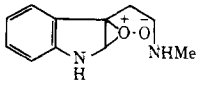
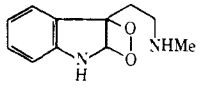


ii



iii

which the ethylamino side chain participates to give **15,** can also be considered. But nucleophilic displacement of the dioxetane by an amine has not been reported. Furthermore, it is known[33] that the enamine system >C=C—NH– undergoes "ene" reaction with singlet oxygen to give >C(OOH)—C=N–, whereas tertiary enamines undergo 1,2-cycloaddition to give dioxetanes.
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