[Chem. Pharm. Bull. 29(4)1013—1026(1981)]

# Dye-sensitized Photooxygenation of Tyrptophan: 3a-Hydroperoxypyrroloindole as a Labile Precursor of Formylkynurenine

Masako Nakagawa,*,[a] Shiro Kato,[a] Shigehiro Kataoka,[a] Shinichi Kodato,[a] Hideyuki Watanabe,[a] Haruo Okajima,[a] Tohru Hino,[a] and Bernhard Witkop[b]

*Faculty of Pharmaceutical Sciences, Chiba University,[a] Chiba, 260, Japan and Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health,[b] Bethesda, Maryland 20014, U.S.A*

(Received October 3, 1980)

The isolation, structure determination, and reactivity of the tricyclic labile hydroperoxides **10** and **2** obtained by dye-sensitized photooxygenation of L-, D-, and DL-tryptophan and Nb-methoxycarbonyltryptophan ester are reported. The tricyclic hydroperoxide **10**, under appropriate conditions, was easily convertible to formylkynurenine. Plausible mechanisms for these transformations are discussed.

**Keywords**——tryptophan and its derivatives; dye-sensitized photooxygenation; formylkynurenine; hydroperoxypyrroloindoles; 3-hydroperoxyindolenines; 1,3-benzoxazines; CD spectra; rearrangement; ring-chain tautomerism; biological oxidation

Tryptophan, one of the essential amino acids, is metabolized to NAD, melatonin, serotonin, and a number of other biologically important substances[1] and serves as an important precursor for the biosynthesis of indole alkaloids.[2] The oxidative cleavage of the 2,3-bond of L-tryptophan, catalyzed by tryptophan 2,3-dioxygenease, to formylkynurenine is the major oxidative and metabolic pathway of L-tryptophan and the first key step leading to the biosynthesis of coenzyme NAD as well as to the aromatic and quinoline pathways with complete degradation of tryptophan, in this respect a source of energy.[1]

The mechanism for this step has long been of interest, but has not been well understood. In 1931, Kotake, who first isolated kynurenine as a metabolite of tryptophan, suggested oxytryptophan (oxindolylalanine) as a likely intermediate for this conversion.[3] Oxindoles monosubstituted at the 3-position readily undergo air oxidation to give the corresponding dioxindole derivatives, and a mechanism involving the formation of dioxindoles from tryptophan was proposed.[4] Soon thereafter, it was shown that oxytryptophan was not metabolized to kunurenine.[5] Moreover, by the use of heavy oxygen, Hayaishi demonstrated that two oxygen atoms are incorporated into formylkynurenine.[6] In 1951, Witkop, on the basis of model studies, postulated 3-hydroperoxyindolenines as the intermediate in the oxidation or autoxidation of indoles, such as tetrahydrocarbazole.[7]

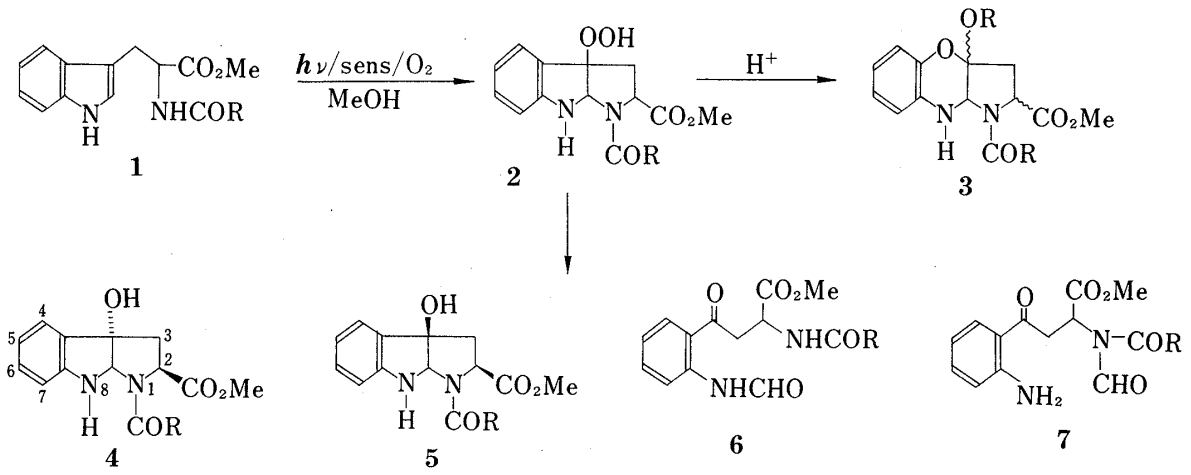
From this observation and related studies, Witkop originally proposed that, in the biological oxidation of tryptophan, the 3-hydroperoxyindolenine **9** or the ring tautomer **10** is the primary intermediate capable of rearranging to formylkynurenine **13**.[8] This concept of the primary intermediate, 3-hydroperoxyindolenine **9**, undergoing rearrangement to formylkynurenine **13**, possibly *via* the dioxetane **14**, has been widely accepted.[9] On the other hand, Hamilton proposed a similar mechanism which involves the hydrated indolenine **15** and its rearranged product **16** instead of the dioxetane **14**.[10]

The chemical conversion of tryptophan to formylkynurenine was first achieved by Witkop with ozone as the oxidizing agent.[11] Several modifications of this conversion by a variety of oxidants have been reported, but none led to the peroxidic intermediate postulated in the biological oxidation of tryptophan.[12]

Dye-sensitized photooxygenation of tryptophan became the method of choice in our mechanistic studies of the chemical and biochemical process in which molecular oxygen is used

as the oxidant; the reaction was expected to lead to the postulated intermediate hydroperoxide **9** under mild conditions. In preceding papers,[13] we reported the isolation and characterization of 3a-hydroxypyrroloindoles and their ready rearrangement to formylkynurenines. In an effort to understand further the mechanism of the transformation of tryptophan to formylkynurenine, we now present details of these dye-sensitized photooxygenations of tryptophan and Nb-acyltryptophan esters.[14]

The oxygenation of Nb-methoxycarbonyl-DL-tryptophan methyl ester **1a** was carried out under cooling by irradiation in methanol under a stream of oxygen with Rose Bengal as the sensitizer, followed by purification over silica gel to give the cleavage product **6a** (16%) accompanied by Nb-formylkynurenine **7a** (17%) together with the two diastereoisomers **4a** (12%) and **5a** (8%). When the reaction mixture was treated with dimethyl sulfide immediately after irradiation, the hydroxide was obtained as the sole product in 62% yield as a mixture of the two diastereoisomers **4a** and **5a**. On the other hand, removal of the solvent at low temperature followed by alumina coulmn chromatography and preparative thin layer chromatography (TLC) gave the 3a-hydroperoxypyrroloindole **2a** in 40% yield as a mixture of two diastereoisomers which were readily converted to **4a** (10%), **5a** (10%), **6a** (11%), and **7a** (18%) on treatment with silica gel in methylene chloride at ambient temperature.[14d] The hydroperoxide **2a** was further characterized by measurement of its spectra, iodometric titration, and reaction with dimethyl sulfide to give a mixture of diastereoisomers (**4a** and **5a**, 85% yield) which were readily separated by fractional crystallizations into the more polar isomer **4a**, mp 163—164° and the less polar isomer **5a**, mp 124—125°. The isomer **4a** was unequivocally determined by X-ray analysis to have the *trans* configuration with regard to the relative position of the hydroxyl and ester groups.[13a]




1 2 3 4 5 6 7

**a**: R=OMe DL
**b**: R=OMe L
**c**: R=OMe D (enantiomer of b)
**d**: R=Me DL

sens: sensitizer

Chart 1

Under similar conditions, photooxygenation of Nb-methoxycarbonyl-L-tryptophan ester **1b** (at −5°), followed by reduction with dimethyl sulfide, produced the hydroxides **4b** and **5b** in 24% and 31% yields, respectively, and small quantities of **6b** (4%). The analogous reaction at elevated temperature (17—20°), followed by reduction with dimethyl sulfide similarly afforded **4b** and **5b** in 27% and 33% yields, respectively, accompanied, however, by the ketoamide **6b** in 27% yield. Variation of the reaction temperature effected similar changes in product distributions in the oxygenation of Nb-acetyl-DL-tryptophan methyl ester **1d**. The reaction of **1d** at 0°, followed by dimethyl sulfide reduction, gave the *trans* alcohol **4d** (41%)

and the *cis* isomer **5d** (34%), accompanied by minor amounts of **6d** (6.4%). In contrast, room temperature (20°) oxygenation of **1d** proceeded to give **6d** in 22% yield besides **4d** (27%) and **5d** (34%).[15] This temperature dependence indicates that at higher temperature the oxygenation of tryptophan carbamate ester **1** to the formylkynurenine analog **6**[12,14d] competes with the formation of the tricyclic hydroperoxide (*vide infra*). In these reactions, only a trace amount of the Nb-formyl derivative **7** was obtained.

The L-isomers **4b** and **5b** were not crystallized but their stereochemistry was determined by analogy to the DL-series and we found the more polar isomer **4b** to be the *trans*, and the less polar isomer **5b** to be the *cis* alcohol. The $^1$H NMR spectrum of the *trans* isomer **4a** shows peaks peaks at $\delta$ 5.15 and 5.17 for the **8a** proton and at $\delta$ 4.55 for the C-2 proton, whereas the *cis* isomer **5a** shows resonance at lower field, $\delta$ 5.40, for the **8a** proton, and at higher field, $\delta$ 4.38, for the C-2 proton. The methyl protons of the ester and carbamate groups of **5a** show peaks at $\delta$ 3.65 and 3.78, but 4a showed split signals at $\delta$ 3.18 and 3.21 for the ester group and split signals at $\delta$ 3.65 and 3.78 for the carbamate group[16] as shown in Table I. A comparison of data obtained for **4a** and **5a** revealed that the protons of the ester group were shifted upfield in the *trans* isomer **4a**. Inspection of Dreiding models of **4a** indicates that the ester group is close to the mid-point of the benzene ring and therefore is subject to a strong upfield shift.

TABLE I. $^1$H-NMR Spectra of **4a**, **5a**, and **2a** in $CDCl_3$

| | $\delta$ ppm | | | | |
|---|---|---|---|---|---|
| | $CH_2$ | 1-$CO_2CH_3$ | 2-$CO_2CH_3$ | 2-H | 8a-H |
| **4a** | 2.71(d-like) | 3.65, 3.78(s) | 3.18, 3.21(s) | 4.55(m) | 5.15, 5.17(s) |
| **5a** | 2.40—2.70(m) | 3.65, 3.78(s, 6H) | | 4.38(m) | 5.40(s) |
| **2a** | 2.40—2.80(m) | 3.24, 3.64, 3.74, 3.76(s, 6H) | | 4.40(m, 0.6H, *cis*)<br>4.60(m, 0.4H, *trans*) | 5.64(s, 0.4H, *trans*)<br>5.76, 5.82(s, 0.6H, *cis*) |

The circular dichroism (CD) spectra of the two isomers **4b** and **5b** show that a positive Cotton effect at 240 nm must be associated with the strong UV chromophore of the PhNCNCO moiety and indicates a *trans* relationship between the hydroxyl and the ester groups, whereas a negative Cotton effect at 240 nm indicates a *cis* relationship. The Cotton effect at 300 nm of both isomers is negative. The alcohols of the D-series, **4c** and **5c**, obtained by analogous oxygenation of the D-tryptophan derivative **1c**, gave commensurate antipodal CD spectra.

Different reactivity towards acetylation with acetic anhydride-pyridine has been observed for **4** and **5**. After 20 hr at 16°, the *trans* **4a** and **4d** easily formed the N,O-diacetyl derivatives in high yields, while the reaction with the *cis* isomer **5a** was slow and incomplete even after 45 hr; the diacetate was obtained only by further stirring at 70—90° for 8 hr. When the acetylation of **5d** was carried out at 15° for 26 hr, the monoacetate (O-acetyl, 20%) was obtained besides the diacetate (77%). Treatment of **2** with an acid provided the corresponding rearranged product **3**.[12,14c,d]

Our foregoing results encouraged us to inverstigate the dye-sensitized photooxygenation of tryptophan iself. The corresponding tricyclic hydroperoxide has long been sought after as the primary oxidative metabolite of tryptophan, whose oxygenation in this case had to be carried out in water. Accordingly, the oxygenation of an aqueous solution of DL-tryptophan **8a** was carried out by irradiation ($\lambda$>490 nm) at 0—5° for 3—4 hr in the presence of a sensitizer, and oxygen was bubbled through the solution followed by reduction as summarized in Table II. Removal of the solvent by evaporation gave 3a-hydroxypyrroloindoles in about 85% yield as a mixture of two isomers (**11a** and **12a**), which were readily separated by fractional crystallization from water into a lower melting (**11a**) and a higher melting (**12a**) diastereoisomer. Neither formylkynurenine **13** nor Nb-formylkynurenine **18** has so far been detected (TLC) in the

reaction mixture. The melting point and the spectral properties of the alcohols **11a** and **12a** are in agreement with those reported by Savige, who obtained them by oxidation of DL-tryptophan with peracetic acid.[17] However, the stereochemistry of the isomers has not been determined yet. Therefore, alkaline hydrolysis of the carbamate esters **4a** and **5a** was carried out. Treatment of the *trans* isomer **4a** in aqueous ethanol with NaOH gave the lower melting isomer **11a** in 88% yield, in addition to trace amounts of **12a** (detected on TLC), whereas the *cis* isomer **5a** gave **12a** as a single product in 84% yield. Accordingly, **11a** has a *trans* relationship with regard to the hydroxyl and ester groups, while **12a** is the *cis* isomer.

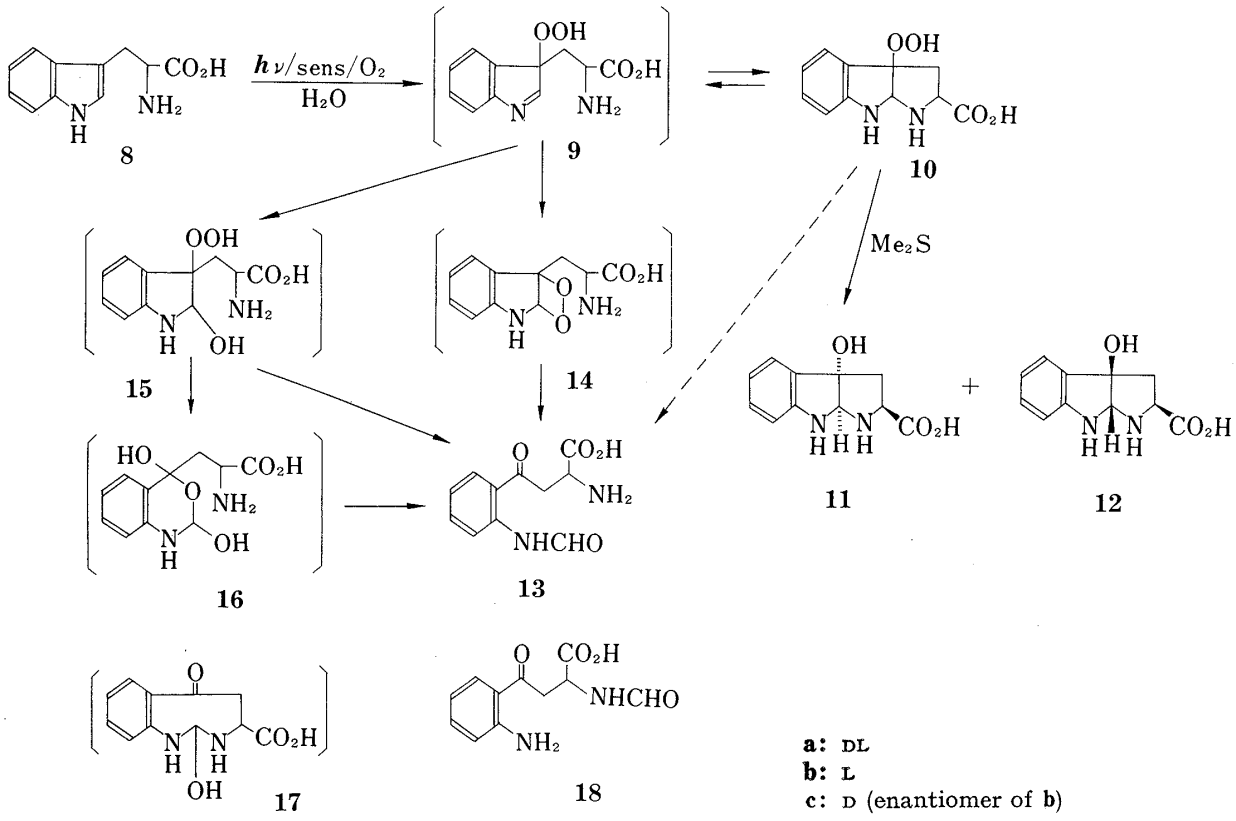



Chart 2

TABLE II. Sensitized Photooxygenation of L-Tryptophan **8b**[a]

| Sensitizer | mg (mM) molar equivalent | Reaction time (hr) | **11b**+**12b** (%) | Recovery (%) |
|---|---|---|---|---|
| Rose Bengal | 100(1.1)1/50 | 3.5 | 81 | |
| | 50(0.05)1/100 | 3.5 | 86 | |
| | 25(0.025)1/200 | 3.5 | 84 | |
| | 15(0.015)1/300 | 3.5 | 85 | |
| | 5(0.005)1/1000 | 6.5 | 82 | |
| | 0 | 3.5 | | 99 |
| Methylene Blue | 6(0.016)1/300 | 1.6 | 86 | |

a) An aqueous solution (300 ml) of **8b** (1.02 g, 5 mM) containing 5% EtOH was oxygenated, followed by reduction with dimethyl sulfide.

These results show that the ethylamino side chain in **9**, participates, even in water, leading to the formation of the tricyclic hydroperoxide **10**. Encouraged by these results, we attempted the direct isolation of the tricyclic hydroperoxide **10**. An aqueous solution of L-tryptophan **8b** and Rose Bengal was oxygenated at 0—5° followed by extraction of the sensitizer after acidification with acetic acid. Lyophilization of the aqueous solution led to the first successful isolation

of the tricyclic hydroperoxide **10b** as a powder in about 85% yield (iodometry); it could be further purified on a Sephadex G-10 column to give an almost colorless powder. The hydroperoxide **10b** was not stable at room temperature and decomposed to a tar within 24 hr, but could be stored at −70° for 2 months without extensive decomposition. Chromatographic analysis on silica gel as well as the $^1$H nuclear magnetic resonance (NMR) spectrum revealed **10b** to be a mixture of *trans* and *cis* isomers, in a ratio of about 6:4, which on reduction with dimethyl sulfide furnished a mixture of the alcohols **11b** and **12b**. The structure of **10b** was confirmed by its spectral data, with an IR band at 1615 cm$^{-1}$ for the carboxylate, a typical PhNCN$^+$ UV absorption at 235, 294.5 nm, and a molecular ion at *m/e* 236 in the mass spectrum. The upfield and aromatic segments of the $^1$H NMR spectrum of **10b** in $D_2O$ were nearly identical with those of a mixture of **11b** and **12b**, except for two methine protons at positions 2 and 8a. Two triplets appear at $\delta$ 4.01 and 4.39 corresponding to the protons at the 2 position of the *cis* and *trans* isomers. Sharp singlets at $\delta$ 5.64 and 5.75 can be assigned to the 8a methine proton of the *trans* and *cis* isomers of **10b** by comparison with the spectra of **11b** and **12b**. Table III summarizes the $^1$H NMR chemical shifts observed for the various protons in the 3a-hydroxy- and hydroperoxy-pyr-

Table III. $^1$H-NMR Spectra of **11b**, **12b**, and **10b** in $D_2O$

| | $\delta$ ppm | | | |
|---|---|---|---|---|
| | $CH_2$ ABX | 2-H ABX | 8a-H | Aromatic protons |
| **11b** | 2.85(d-like, 2H, $J$=7 Hz) | 4.34(t, $J$=7 Hz) | 5.31(s) | 6.80(d, 7-H)<br>6.97(t, 5-H)<br>7.28(t, 6-H)<br>7.36(d, 4-H) |
| **12b** | 2.55(t, 1H, $J$=12, 12 Hz)<br>2.92(q, 1H, $J$=12, 7 Hz) | 3.86(q, $J$=12,7 Hz) | 5.40(s) | 6.86(d, 7-H)<br>6.98(t, 5-H)<br>7.30(t, 6-H)<br>7.40(d, 4-H) |
| **10b** | 2.50—3.25(m) | 4.01(t, 0.6H, $J$=8 Hz, *cis*)<br>4.39(t, 0.4H, $J$=8 Hz, *trans*) | 5.64(s, 0.4H. *trans*)<br>5.75(s, 0.6H, *cis*) | 6.70—7.15(m, 2H)<br>7.15—7.60(m, 2H) |

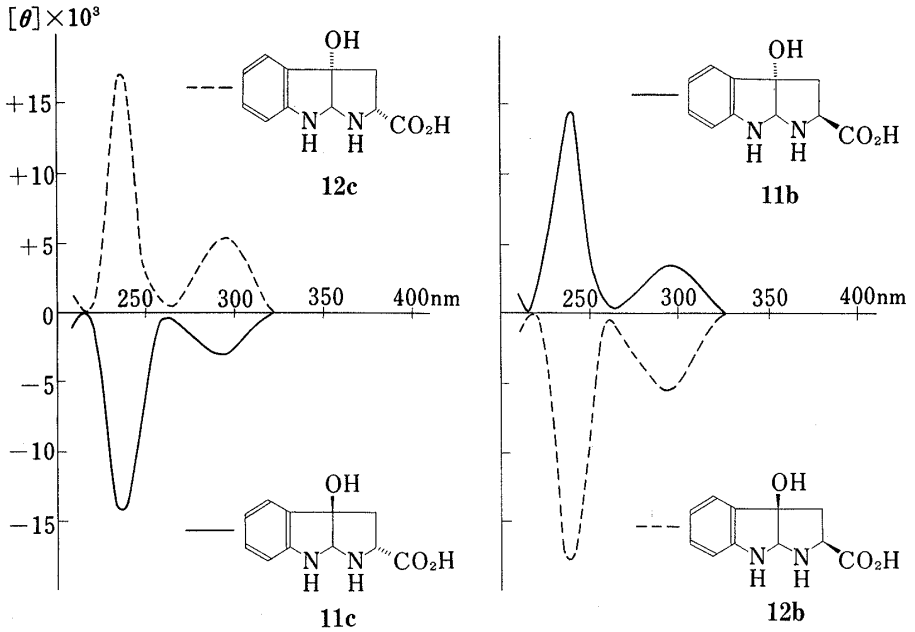


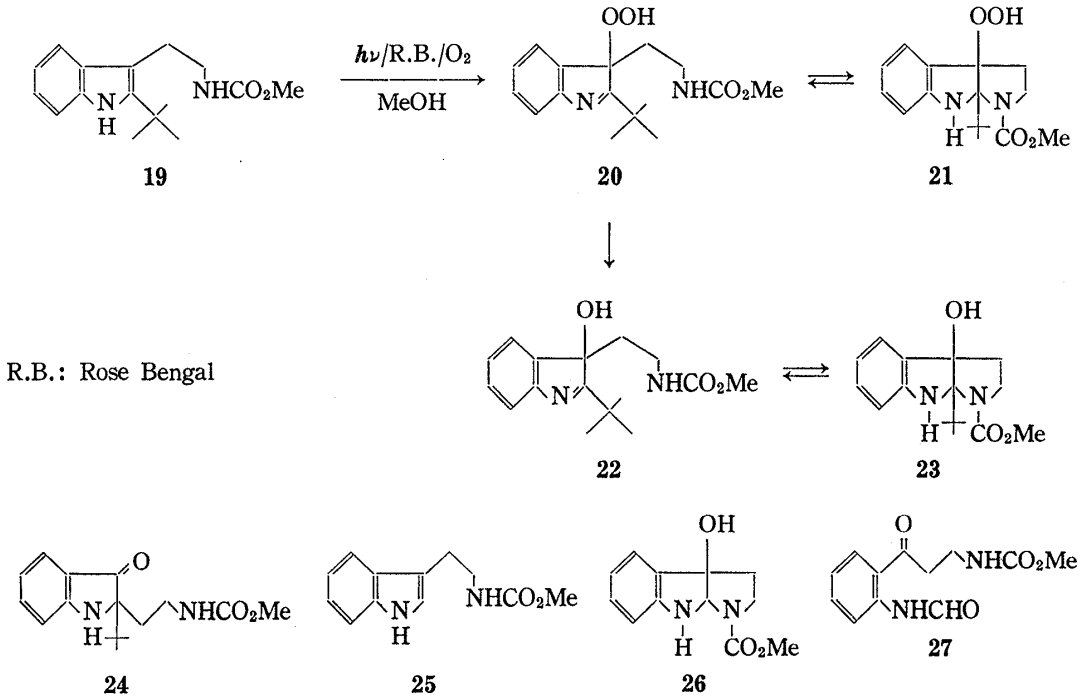

Fig. 1. CD Spectra of Hydroxypyrroloindoles

roloindoles and shows that **10b** displays its absorption 33—35 ppm downfield from the corresponding absorption of the methine proton in the **8a** position in **11a** and **12a**. D-Tryptophan **1c** also gave **11c** and **12c** upon analogous oxygenation and reduction. Antipodal CD spectra were obtained from the D-and L-series of the alcohols **11** and **12** as shown in Figure 1.

In order to elucidate the mechanistic aspects of the dye-sensitized photooxygenation of tryptophan, the reactivity of the hydroperoxide was investigated. An aqueous solution of **10b** was found to decompose gradually to formylkynurenine **13** in 6% yield and a mixture of **11b** and **12b** in 71% yield upon standing for one week at room temperature. However, one of the most important reactions of this hydroperoxide is its facile transformation into formylkynurenine **13** (10—30%) as well as to the alcohols (**11b** and **12b**, 40—50%) when the aqueous solution of **10b** is heated at 100° for 10—20 min. In contrast to **2**, no Nb-formylkynurenine **18** was detected in these reaction mixtures.

The rearrangement of the hydroperoxide **10** to formylkynurenine **13** could be explained by assuming the intermediate eight-membered hydroxyketone **17**, as previously proposed.[12] However, the alternative mechanism involving the decomposition of the dioxetane **14** formed from the indolenine **9** could be considered, provided that the equilibrium between these two compounds **9** and **10** is significant. Although such a ring-chain tautomerism **10**⇄**9** is probably negligible at room temperature, the reaction might attain equilibrium fairly rapidly at elevated temperature. The possibility that the tricyclic hydroperoxide **10** might be in equilibrium with the indolenine **9** was supported by the reaction of 3a-hydroxypyrroloindole with methyl thioglycolate to give 2-sulfur substituted indoles in high yields.[13a]

Additional evidence was obtained by the introduction of a *tert*-butyl group into the 2-position of the indole nucleus, which made it possible to isolate the hydroperoxyindolenine **20**. When **19** was oxygenated in a similar manner, the 3-hydroperoxyindolenine **20**, corresponding to the hypothetical primary intermediate **9** of the dye-sensitized photooxygenation as well as of the biological oxygenation of tryptophan to formylkynureine, was isolated in 90% yield as a powder. Direct observation of the equilibrium between the hydroperoxyindolenine **20** and its cyclic tautomer **21** was possible by observing the NMR spectrum of **20** as well as its behavior on TLC. The NMR spectrum of **20** in $CDCl_3$ showed that **20** exists as a tautomeric mixture of




**19** **20** **21**

**22** **23**

**24** **25** **26** **27**

Chart 3

**20** and **21** in a 3:2 ratio; this was demonstrated by following a peak at $\delta$ 1.44 assigned to the *tert*-butyl proton of **20** and a new peak at $\delta$ 1.20 assigned to that of **21** after 3 days at 25°. The cyclic hydroperoxide **21**, isolated by preparative TLC, had the expected IR, UV, and NMR spectra and gave a molecular ion peak at *m/e* 306. The reduction of **20** with dimethyl sulfide provided the corresponding hydroxyindolenine **22**. The $^1$H NMR spectrum of **22** in $CDCl_3$ gradually changed to that of a tautomeric mixture (15:85) of **22** and **23** after 6 days at 25°, whereas in $CD_3OD$ a 3:1 mixture of **22** and **23** was obtained after 13 days. Accordingly, when **22** was refluxed in $CH_2Cl_2$ for 11 hr, followed by crystallization from methylene chloride-hexane, the corresponding cyclic tautomer **23** was obtained in 72% yield together with the rearranged indoxyl **24** in 17% yield. On the other hand, the analogous equilibration mixture (**22**: **23**=15:85) was obtained by dissolving **23** in $CDCl_3$ and letting it stand for 3 days at 25°, while in $CD_3OD$, **23** slowly equilibrated with **22** to provide a 3:1 mixture after 13 days.

These results suggest the existence of an equilibrium between **9** and **10** under suitable conditions, although the tautomerization may occur only slowly at room temperature.

Our present results on the dye-sensitized photooxygenation of tryptophan in aqueous solution show that the ethylamino side chain of the primary intermediate **9** undergoes intramolecular addition to the azomethine unsaturation even in water, leading to the formation of the tricyclic hydroperoxide, which undergoes thermal rearragement to formylkynurenine. Furthermore, similar Rose Bengal-sensitized photooxygenation of Nb-methoxycarbonyltryptamine **25** at 0° in methanol and in 5% $H_2O$-methanol followed by reduction gave **26** in 62% and 51% yields, together with the formylkynurenine derivative **27** in 4% and 2% yields, respectively, eliminating the possible formation of formylkynurenine *via* the hydrate **15**.

Another characteristic reaction of **10** is its facile conversion to *o*-aminophenol at ambient temperature in 40% yield upon addition of concentrated hydrochloric acid to its aqueous solution, indicating that **10** undergoes a facile Baeyer–Villiger type rearrangement followed by spontaneous hydrolysis to *o*-aminophenol. *o*-Aminophenol is known to arise from 3-hydroxyanthranilic acid derived from kynurenine *in vivo*. Our results provide an alternative route for the formation of *o*-aminophenol from tryptophan. The hydroperoxides **10** and **20** showed visible light emission when heated in DMSO to 170°. The chemiluminescence may be derived from the decomposition of the intermediate dioxetane **14**,[18] and suggests the ring opening of **10** to **9** at higher temperature.

The evidence presented here illuminates the multiplicity of possible pathways, the steric course of oxygenation and the possibilities for various ring-chain tautomerisms. Detailed knowledge of these model reactions should create a basis for understanding the nature and mechanism of the enzyme-catalyzed oxygenation of tryptophan to formylkynurenine *in vitro* or *in vivo*, and should also cast light on possible pathways for the biosynthesis of natural products, such as sporidesmins, brevianamide E, and related compounds.

These photooxygenations also provide access to a whole new group of synthetic 3a-hydroxypyrroloindole derivatives.

## Experimental

$^1$H-NMR spectra were recorded with a JEOL MH-100 instrument in $CDCl_3$ using $Me_4Si$ as an internal standard, except where otherwise indicated; chemical shifts are expressed in $\delta$ (ppm). IR spectra were run on Hitachi EPI-G 3, IR-215, and IR-295 instruments. Mass spectra were recorded on a Hitachi RMU-6 instrument. Microanalyses were performed on a Perkin-Elmer 240 C, H, and N analyzer. UV-visible absorption spectra were obtained on Hitachi 323 and 340 spectrophotometers. CD spectra were taken with a JASCO J-20 polarimeter. All melting points (Yamato melting point apparatus and Yanagimoto micro hot-stage apparatus) reported are uncorrected. All photooxygenations were carried out in a Pyrex immersion apparatus using Ushio tungsten halogen JCV 500W, 300W, 200W lamps with or without Pyrex cooling, vacuum jackets and an aqueous $CuCl_2$–$CaCl_2$ filter solution.

**General Procedure for the Preparation of Nb-Methoxycarbonyltryptophan Methyl Ester 1 (a, b, c)**—— Nb-Methoxycarbonyltryptophan methyl ester **1** was synthesized by dissolving tryptophan methyl ester in

methylene chloride to which was added, with stirring under ice-cooling, a solution of methyl chloroformate (2 mol equivalents) in methylene chloride and an aqueous sodium hydroxide solution (2 mol equivalents). The methylene chloride extracts were washed, dried, and concentrated to give crude **1** which was crystallized directly or after chromatography on silica gel. **1a**: mp 111—112° (methanol–ether) prisms; $\nu_{max}^{KBr}$ 3372, 3300 (NH), 1737 ($CO_2CH_3$), 1710 ($NHCO_2CH_3$), 1550 (NHCO), 1282, 1230 $cm^{-1}$; $\delta$ 3.26 (d, 2H, $J$=6 Hz, $CH_2$), 3.63 (s, 6H, $2CH_3$), 4.65 (m, 1H, CH), 5.24 (m, 1H, NH, exchangeable), 6.90 (d, 1H, $J$=2 Hz, $\alpha$-H), 7.00—7.40, 7.40—7.60 (m, 4H, aromatic H), 8.26 (broad s, 1H, NH, exchangeable); *m/e* (rel intensity) 276 (32) $M^+$, 217 (13), 245 (7), 130 (100). *Anal.* Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.76; H, 5.85; N, 10.05. **1b**: mp 101.5—102° (methanol–ether) colorless prisms; $\lambda_{max}^{EtOH}$ nm ($\varepsilon$) 221.5 (37000), 274.5 (6200), 282 (6600), 290 (5700); $[\alpha]_D^{28}$ −2.0 ($c$=2, MeOH). **1c**: mp 101.5—102°; $[\alpha]_D^{28}$ +1.4 ($c$=2, MeOH). *Anal.* Found: C, 60.93; H, 5.85; N, 10.20.

**Dye-sensitized Photooxygenation of Nb-Methoxycarbonyltryptophan Methyl Ester 1**——1) A solution of **1a** (1.0 g, 3.6 mM) and Rose Bengal (450 mg, 0.46 mM) in 5% pyridine–methanol (300 ml) was cooled in an ice-salt bath and then irradiated with a 200W halogen lamp for 5 hr while oxygen was bubbled through. Removal of the solvent under reduced pressure gave a viscous material (1.6 g), which was chromatographed over alumina (15 g) to remove the dye. Elution with 2% methanol–methylene chloride gave an oil (1.1 g) which was rechromatographed on silica gel (30 g). Elution with methylene chloride gave **7a** (124 mg), a mixture of **7a** and **1a** (186 mg), and a mixture of **1a** and **6a** (67 mg). Continued elution with 1% methanol–methylene chloride afforded crystalline **6a** (15 mg), **5a** (43 mg), a mixture of **5a** and **4a** (128 mg, crystals), and **4a** (66 mg). The mixture of **7a**, **1a**, and **6a** was subjected to preparative TLC in a mixture of acetone–methylene chloride (1: 7) to give **7a** (66 mg), **1a** (84 mg), and **6a** (28 mg). The mixture of **5a** and **4a** was subjected to preparative TLC with a mixture of acetone–methylene chloride (1: 4) to give **5a** (44 mg) and **4a** (56 mg). Total yields: **4a** (122 mg, 12%), **6a** (187 mg, 16%), **7a** (196 mg, 17%), recovery of **1a** (84 mg, 18%). **4a**: mp 163—164° (methanol–ether), colorless prisms; $\lambda_{max}^{EtOH}$ nm ($\varepsilon$) 243 (8140), 302 (2370); $\lambda_{min}^{KBr}$ 224 (3690), 267 (500); $\nu_{max}^{KBr}$ $cm^{-1}$ 3350 (NH, OH), 1740, 1695 ($CO_2CH_3$, $NCO_2CH_3$), 1618 (PhNCN); $\delta$ 2.30—3.00 (m, 2H, $CH_2$), 3.18 and 3.21 (2s, 3H, $CO_2CH_3$), 3.65 and 3.78 (2s, 3H, $NCO_2CH_3$), 4.55 (m, 1H, $C_2$–H), 5.15 and 5.17 (2s, 1H, NCHN), 6.50—6.90, 7.00—7.50 (m, 4H, aromatic H); $\delta$ (pyridine-$d_5$) 3.00 (m, 2H, $CH_2$), 3.25 (s, 3H, $CO_2CH_3$), 3.54 and 3.63 (2s, 3H, $NCO_2CH_3$), 4.90 (m, 1H, $C_2$–H), 5.59 and 5.70 (2s, 1H, NCHN), 6.60—7.60 (m, 4H, aromatic H); *m/e* (rel intensity) 292 (10) $M^+$, 274 (3) M–$H_2O$, 233 (13), 173 (7), 158 (12), 149 (7), 147 (12), 146 (34), 133 (21), 132 (100), 130 (22). *Anal.* Calcd for $C_{14}H_{16}N_2O_5$: C, 57.45; H, 5.56; N, 9.54. Found: C, 57.53; H, 5.52; N, 9.59. A sample of this material was crystallized from methanol–ether for X-ray crystallographic analysis.[13a] **5a**: mp 124—125° (benzene–hexane) colorless powder; $\lambda_{max}^{EtOH}$ nm ($\varepsilon$) 240.5 (8150), 296 (2490); $\lambda_{max}^{KBr}$ $cm^{-1}$ 3460, 3340 (NH, OH), 1750 sh, 1705 (CO), 1615 (PhNCN); $\delta$ 2.50 (m, 2H, $CH_2$), 3.06 and 3.36 (s, 1H, NH or OH, exchangeable), 3.65 and 3.78 (s, 6H, $CO_2CH_3$), 4.38 (q, 1H, $C_2$–H), 4.80 and 5.15 (2s, 1H, OH or NH, exchangeable), 5.44 (s, 1H, NCHN), 6.50—6.90, 7.00—7.40 (m, 4H, aromatic H); $\delta$ (pyridine-$d_5$) 2.65—3.10 (m, 2H, $CH_2$), 3.59, 3.65, and 3.70 (3s, 6H, $CH_3$), 4.70 (m, 1H, $C_2$–H), 5.90 and 6.00 (2s, 1H, NCHN), 6.70—7.60 (m, 4H, aromatic H), 7.80 (broad s, 1H, NH or OH, exchangeable); *m/e* 292 (27) $M^+$, 274 (6), 233 (12), 173 (12), 149 (18), 146 (30), 132 (100). *Anal.* Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.59. Found: C, 57.90; H, 5.57; N, 9.47. **6a**: mp 128—129° (methanol–ether) colorless prisms; $\lambda_{max}^{EtOH}$ nm ($\varepsilon$) 231 (25700), 235.5 (25100), 261 (11700), 268 (10400), 324 (4240); $\nu_{max}^{KBr}$ $cm^{-1}$ 3290 (NH), 1762, 1705, 1690, 1675 (CO), 1520 (CONH); $\delta$ 3.40—4.00 (m, 2H, $CH_2$), 3.68 (s, 3H, $CH_3$), 3.74 (s, 3H, $CH_3$), 4.70 (m, 1H, CH), 5.75 (d, 1H, $J$=8 Hz, NHCH, exchangeable), 7.16 (t, 1H, $J$=8 Hz, $C_5$–H), 7.58 (t, 1H, $J$=8 Hz, $C_4$–H), 7.90 (d, 1H, $J$=8 Hz, $C_3$–H), 8.46 (s, 1H, NCHO), 8.72 (d, 1H, $J$=8 Hz, $C_6$–H), 11.32 (broad s, NHCHO, exchangeable); *m/e* 308 (18) $M^+$, 290 (11), 249 (12), 173 (43), 148 (100), 146 (35), 120 (30), 92 (13), 65 (13). *Anal.* Calcd for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.09. Found: C, 54.49; H, 5.27; N, 9.11. **7a**: mp 115—116° (benzene–hexane) colorless powder; $\lambda_{max}^{EtOH}$ nm ($\varepsilon$) 228 (24800), 257 (6850), 364 (5960); $\nu_{max}^{KBr}$ $cm^{-1}$ 3480, 3370 ($NH_2$), 1750, 1690, 1654 (CO), 1620, 1590, 1555, 1205; $\delta$ 3.25—4.20 (m, 2H, $CH_2$), 3.74 (s, 3H, $CH_3$), 3.92 (s, 3H, $CH_3$), 5.84 (t, 1H, $J$=6 Hz, CH), 6.20 (s, 2H, $NH_2$, exchangeable), 6.60 (m, 2H, $C_3$– and $C_5$–H), 7.25 (t, 1H, $C_4$–H), 7.70 (d, 1H, $J$=8 Hz, $C_6$–H), 9.15 (s, 1H, CHO); *m/e* 308 (48) $M^+$, 277 (5), 276 (5), 205 (11), 189 (5), 174 (8), 147 (8), 146 (59), 134 (8), 133 (29), 120 (100), 93 (27), 92 (27), 65 (16). *Anal.* Calcd for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.09. Found: C, 54.64; H, 5.22; N, 9.05.

2) A solution of **1a** (3 g, 10.8 mM) and Rose Bengal (1.35 g, 1.4 mM) in 5% pyridine–methanol (500 ml) was oxygenated as described above for 4 hr followed by addition of dimethyl sulfide (15 ml), then the reaction mixture was stirred for 3 hr at room temperature. The photooxygenation was repeated again under identical conditions and the product mixtures were combined. Removal of the solvent under reduced pressure gave a viscous oil which was chromatographed on alumina followed by silica gel to give a mixture of **4a** and **5a** (3.93 g, 62%), **1a** (660 mg, 11%), and a mixture of **1a** and **6a** (370 mg, main part is **1a**). The mixture of **4a** and **5a** was rechromatographed on silica gel to give **4a** and **5a**, identified by IR spectroscopy and mixed melting point determinations. Similar results were obtained by using methanol as the reaction solvent and Rose Bengal (1/300—1/100 mol equivalent).

3) The analogous oxygenation of **1b** (1 g, 3.6 mM) and Rose Bengal (500 mg, 0.5 mM) in methanol (250 ml) was carried out twice at −5——6° (inner temperature) with a 500W halogen lamp using a liquid filter ($CuCl_2$–$CaCl_2$) for 5 hr. Work-up by the method described above gave **4b** (490 mg, 24%, amorphous), **5b**

(644 mg, 31%, amorphous), **6b** (88 mg, 4%), and a mixture of **6a** (trace), **7a** (trace), and **1b** (main, 130 mg). The structures of **4b**, **5b**, and **6b** were identified (TLC, and UV, NMR, and mass spectroscopy) by comparison with those of **4a**, **5a**, and **6a**, respectively. Crude **4b** and **5b** were further purified by preparative TLC (silica gel–methylene chloride and alumina–methylene chloride). **4b**: CD ($c=4.24\times10^{-4}$, methanol) [$\theta$] (nm) $+1.39\times10^{4}$ (241), $-0.60\times10^{3}$ (300). **5b**: CD ($c=4.47\times10^{-4}$, methanol) [$\theta$] (nm) $-2.37\times10^{4}$ (240), $-3.60\times10^{3}$ (295).

4) Nb-Methoxycarbonyl-D-tryptophan methyl ester **1c** (997 mg, 3.6 mM) and Rose Bengal (38 mg, 1/100 mol equivalent) were oxygenated in methanol for 6.5 hr at $-10°$ as described above, 3), followed by dimethyl sulfide reduction. Column chromatography of the reaction mixture on alumina (10 g, methylene chloride) and silica gel (20 g, methylene chloride) afforded **4c** (341 mg, 32%), **5c** (377 mg, 36%), and recovered **1c** (154 mg, 15.5%). **4c**: CD ($c=3.70\times10^{-4}$, methanol) [$\theta$] (nm) $-1.86\times10^{4}$ (241), $+0.80\times10^{3}$ (303). **5c**: CD ($c=3.70\times10^{-4}$, methanol) [$\theta$] (nm) $+1.95\times10^{4}$ (241), $+4.9\times10^{3}$ (296).

5) A solution of **1d** (1 g, 3.9 mM) and Rose Bengal (76 mg, 0.02 mol equivalent) in methanol (300 ml) was oxygenated as described above 3) at *ca.* 20° for 6 hr, followed by reduction with dimethyl sulfide (11.6 ml). The residue, obtained by evaporating off the solvent, was chromatographed on alumina (30 g, methylene chloride) followed silica gel chromatography (45 g). Elution with methylene chloride–acetone (13: 1) provided **7d** (15 mg, 1.3%, deduced from the UV peaks, 228, 257.5, 262 sh, 292, 369 nm) and **6d** (249 mg, 22%). Elution with methylene chloride–acetone (6: 1) provided **5d** (332 mg). Further elution with methylene chloride–acetone (6: 1) and (4: 1) gave a mixture of **5d** and **4d** (108 mg) which was subjected to preparative TLC (methylene chloride–acetone, 3: 1) to afford **5d** (28 mg, *Rf* 0.24) and **4d** (52 mg, *Rf* 0.17). Elution with methylene chloride–acetone (4: 1) and (3: 1) gave **4a** (231 mg). Total yields were: **4d** (283 mg, 27%), **5d** (360 mg, 34%). The *trans* hydroxide, **4d**: mp 156—156.5° (methylene chloride–hexane), prisms, more polar isomer; $\lambda_{max}^{EtOH}$ nm ($\varepsilon$) 243 (8160), 301 (2180): $\nu_{max}^{KBr}$ $cm^{-1}$ 3420, 3310 (NH, OH), 1740, 1620; $\delta$ 1.89 and 2.13 (2s, 3H, $COCH_3$), 2.60—3.00 (m, 2H, $CH_2$), 3.19 and 3.23 (2s, 3H, $CO_2CH_3$), 3.32 (broad s, 1H, NH or OH, exchangeable), 4.24 (m, 1H, CHCO), 4.80 (broad s, 1H, NH or OH, exchangeable), 5.26 (s, 1H, NCHN), 6.50—6.90 (m, 2H, aromatic H), 7.00—7.40 (m, 2H, aromatic H); *m/e* 276 (96) $M^+$, 190 (97), 175 (32), 174 (11), 173 (10), 172 (17), 158 (17), 157 (12), 149 (31), 148 (100), 147 (31), 146 (37), 132 (55), 130 (20). *Anal.* Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.86; N, 10.14. Found: C, 60.66; H, 5.84; N, 10.13.

The *cis*-Hydroxide, **5d**: mp 180.5—181.5° (methylene chloride–hexane) needles, less polar isomer; $\lambda_{max}^{EtOH}$ nm ($\varepsilon$) 239 (8370), 294 (2380); $\nu_{max}^{KBr}$ $cm^{-1}$ 3350, 3255 (NH, OH), 1745, 1625; $\delta$ 1.96 and 2.14 (2s, 3H, $COCH_3$), 2.40—2.80 (m, 2H, $CH_2$), 3.45 (broad s, 1H, NH or OH, exchangeable), 3.74 and 3.80 (2s, 3H, $CO_2CH_3$), 4.10 (broad s, 1H, NH or OH, exchangeable), 4.47 (m, 1H, $C_2$–H), 5.53 (s, 1H, NCHN), 6.50—7.00, 7.00—7.40 (m, 4H, aromatic H); *m/e* 276 (100) $M^+$, 190 (65), 175 (37), 149 (22), 148 (57), 147 (27), 146 (29), 132 (45), 84 (30). *Anal.* Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.84; H, 5.84; N, 10.15.

The Kynurenine Derivative **6d**: mp 161—162.5° (methanol), colorless prisms;[19] $\lambda_{max}^{EtOH}$ nm ($\varepsilon$) 231.5 (26200), 235.5 (25600), 261 (12000), 268.5 (1000), 324 (4600); $\nu_{max}^{KBr}$ $cm^{-1}$ 3250 (NH), 1760, 1700, 1660, 1640 (CO); $\delta$ 2.00 (s, 3H, $NCOCH_3$), 3.74 (s, 3H, $CO_2CH_3$), 3.40—4.00 (m, 2H, $COCH_2$), 4.95 (m, 1H, CHCO, changed to triplet after $D_2O$ addition, $J=4$ Hz), 6.67 (d, 1H, $NHCOCH_3$, exchangeable), 7.16 (t, 1H, $J=8$ Hz, $C_5$- or $C_4$–H), 7.57 (t, 1H, $J=8$ Hz, $C_4$- or $C_5$–H), 7.90 (d, 1H, $J=8$ Hz, $C_6$–H), 8.46 (s, 1H, NCHO), 8.72 (d, 1H, $J=8$ Hz, $C_3$–H), 11.30 (broad s, 1H, NHCHO, exchangeable); *m/e* 292 (9) $M^+$, 274 (16), 209 (27), 149 (19), 148 (100), 146 (42), 144 (27), 135 (27), 120 (41), 102 (19), 92 (21), 77 (17). *Anal.* Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.60; H, 5.55; N, 9.71.

**Isolation of 1,2-Dimethoxycarbonyl-3a-hydroperoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole 2a**——A solution of **1a** (300 mg, 1.1 mM) and Rose Bengal (150 mg, 0.15 mM) in 5% pyridine–methanol (150 ml) was cooled in an ice-salt bath and irradiated for 5 hr with a 200W halogen lamp as above; TLC (alumina/iso-$Pr_2O$) of the reaction mixture showed a new spot (*Rf* 0.3) together with those of **4a**, **5a**, and **6a** (trace). Romoval of the solvent *in vacuo* at room temperature furnished a dark-colored oil (485 mg). The mixture was placed upon a column containing 8 g of alumina and eluted with 2% methanol–methylene chloride to afford an oily residue (320 mg) which was purified by preparative TLC (iso-$Pr_2O$). The main segment, corresponding to *Rf* 0.3, was collected and extracted with 20% methanol in methylene chloride to give **2a** as a pale yellow oil (132 mg, 40%), which TLC and NMR spectroscopy indicated to be a mixture of *trans* and *cis* **2a**; $\lambda_{max}^{EtOH}$ 243, 304 nm; $\nu_{max}^{CDCl_3}$ $cm^{-1}$ 3640, 3390 (NH, OOH), 1740, 1700 (CO); $\delta$ 5.30 (broad s, 1H, NH or OOH, exchangeable), 6.50—6.90, 7.00—7.40 (m, 4H, aromatic H), 9.40 (broad s, 1H, NH or OOH). The data for the other protons are shown in Table I; *m/e* 308 (20) $M^+$, 292 (60) M–O, 291 (8) M–OH, 290 (43) $M-H_2O$, 233 (18), 231 (20), 146 (59), 145 (59), 132 (100), 131 (37), 130 (46).

Similar results were obtained by the use of Rose Bengal (1/100—1/300 mol equivalent) in anhydrous methanol.

**Dimethyl Sulfide Reduction of 2a to 4a and 5a**——Dimethyl sulfide (2 ml) was added to a solution of **2a** (80 mg, 0.26 mM) in methylene chloride (10 ml). The mixture was stirred for 1 hr and concentrated to leave an oil (89 mg), which was chromatographed on silica gel (3 g). Elution with methylene chloride gave a mixture of **4a** and **5a** (64 mg, 85%). The ratio of the two isomers was roughly 1: 1 as judged by the integration of the two **8a** protons in the NMR spectrum.

**Transformation of the Hydroperoxide 2a to 4a, 5a, 6a, and 7a**——The hydroperoxide **2a** (102 mg, 0.3 mM) was dissolved in a small amount of methylene chloride and put on a silica gel column (5 g) prepared in methylene chloride. The column was left for 14 hr then eluted with 2% methanol–methylene chloride to afford a mixture of **4a** and **5a** (18 mg, 19%), **6a** (11 mg, 11%), and **7a** (18 mg, 18%).

**Acetylation of 4 and 5**——1) *trans*-3a-Acetoxy-8-acetyl-1,2-dimethoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole: A solution of the *trans* isomer **4a** (180 mg, 0.62 mM) and pyridine (1.8 ml) in acetic anhydride (4.3 ml) was stirred for 26 hr at room temperature. TLC analysis of the reaction mixture showed quantitative acetylation. The solid obtained by evaporation under reduced pressure was taken up in methylene chloride, which was washed with water and dried. Removal of the solvent afforded an almost colorless solid, the Na, O-diacetate of **4a** (230 mg, 99%). Recrystalliization from methanol–ether gave the product, mp 162.5—163.5°, as colorless needles; $\lambda_{max}^{EtOH}$ nm ($\varepsilon$) 244.5 (11900), 281.5 (1500), 287 sh; $\nu_{max}^{KBr}$ $cm^{-1}$ 1745, 1720, 1685, 1675 (CO), 1245; $\delta$ 1.98 (s, 3H, $OCOCH_3$), 2.56 (s, 3H, $NCOCH_3$), 3.10 (s, 3H, $CO_2CH_3$), 3.72 (s, 3H, $NCO_2CH_3$), 2.65—3.50 (m, 2H, $CH_2$), 4.64 (d, 1H, $J=8$ Hz, $C_2$–H), 6.18 (s, 1H, NCHN), 7.04 (t, 1H, $J=8$ Hz, $C_5$- or $C_6$–H), 7.32 (t, 1H, $J=8$ Hz, $C_6$- or $C_5$–H), 7.43 (d, 1H, $J=8$ Hz, $C_4$–H), 7.90 (d, 1H, $J=8$ Hz, $C_7$–H); *m/e* 376 (35) $M^+$, 334 (81), 274 (100), 215 (37), 146 (16), 132 (16), 130 (25), 43 (35). *Anal.* Calcd for $C_{18}H_{20}N_2O_7$: C, 57.44; H, 5.36; N, 7.44. Found: C, 57.45; H, 5.33; N, 7.36.

2) *cis*-3a-Acetoxy-8-acetyl-1,2-dimethoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole and 8-Acetyl derivative: Analogous acetylation of the *cis* isomer **5a** (180 mg, 0.62 mM) yielded two spots on TLC after 26 hr. Work-up, followed by chromatography on silica gel (10 g) with methylene chloride and preparative TLC (silica gel, methylene chloride–acetone, 12: 1), gave the N,O-diacetate of **5a** (180 mg, 17%) and O-acetate of **5a** (43 mg, 21%). N,O-Diacetate of **5a**: mp 150—151° (methanol–ether) colorless plates; $\lambda_{max}^{EtOH}$ nm ($\varepsilon$) 243 (12300), 278.5 (1500), 285 sh; $\nu_{max}^{KBr}$ $cm^{-1}$ 1761, 1750, 1716, 1681 (CO), 1240, 1050; $\delta$ 1.97 (s, 3H, $OCOCH_3$), 2.54 (s, 3H, $NCOCH_3$), 3.64 and 3.76 (2s, 6H, $OCH_3$), 2.30—2.70, 3.30—3.80 (m, 2H, $CH_2$), 4.05 (m, 1H, $C_2$–H), 6.10 (s, 1H, NCHN), 7.15 (t, 1H, $J=8$ Hz, $C_5$– or $C_6$–H), 7.40 (t, 1H, $J=8$ Hz, $C_6$ or $C_5$–H), 7.64 (d, 1H, $J=8$ Hz), 7.99 (d, 1H, $J=8$ Hz, $C_7$–H); *m/e* 376 (13) $M^+$, 334 (16), 274 (100), 215 (20), 146 (8), 132 (9), 130 (12), 43 (32). *Anal.* Calcd for $C_{18}H_{20}N_2O_7$: C, 57.44; H, 5.36; N, 7.44. Found: C, 57.49; H, 5.35; N, 7.36.

The O-Acetate of **5a**: mp 121—122.5° (methanol–ether–hexane), colorless prisms; $\lambda_{max}^{EtOH}$ nm ($\varepsilon$) 241.5 (8400), 301 (2560); $\nu_{max}^{KBr}$ $cm^{-1}$ 3400 (NH), 1755, 1710 (CO), 1245, 1040; $\delta$ 2.00 (s, 3H, $OCOCH_3$), 2.60—3.40 (m, 2H, $CH_2$), 3.68, 3.76, and 3.80 (3s, 6H, $CO_2CH_3$ and $NCO_2CH_3$), 4.30 (m, 1H, $C_2$–H), 5.00 (0.5H) and 5.40 (0.5H) (broad s, NH, exchangeable), 5.74 (finely split s, 1H, NCHN, collapsed to 5.65 and 5.72 upon $D_2O$ addition), 6.64 (d, 1H, $J=8$ Hz, $C_7$– or $C_4$–H), 6.80 (d, 1H, $J=8$ Hz, $C_4$– or $C_7$–H), 7.17 (t, 1H, $J=8$ Hz, $C_5$– or $C_6$–H), 7.42 (t, 1H, $J=8$ Hz, $C_6$– or $C_5$–H); *m/e* 334 (18) $M^+$, 274 (100), 215 (33), 146 (11), 132 (16), 130 (20), 43 (12). *Anal.* Calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.42; H, 5.45; N, 8.24.

3) *trans*-3a-Acetoxy-1,8-diacetyl-2-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole: A solution of the *trans* isomer **4d** (185 mg, 0.67 mM) and pyridine (1.1 ml) in acetic anhydride (2.2 ml) was stirred for 25 hr at room temperature then concentrated under reduced pressure. The residue was dissolved in ethyl acetate and the solution was washed with water, dried, and concentrated to give the N,O-diacetate of **4d** as a solid (151 mg, 63%). Recrystallizations from methanol–ether–hexane gave the pure product, mp 173.5—174°, as colorless prisms; $\lambda_{max}^{EtOH}$ nm ($\varepsilon$) 244 (10000), 281.5 (1400), 287 sh; $\nu_{max}^{KBr}$ $cm^{-1}$ 1765, 1753, 1678 (CO), 1235; $\delta$ 2.00 (s, 3H, $OCOCH_3$), 2.20—3.60 (m, 2H, $CH_2$), 2.40 and 2.64 (2 broad s, 9H, $2NCOCH_3$, $CO_2CH_3$), 4.50 and 4.75 (2 broad s, 1H, $C_2$–H), 6.28 and 6.56 (2 broad s, 1H, NCHN), 6.80—8.10 (m, 4H, aromatic H); *m/e* 360 (34) $M^+$, 318 (81), 258 (78), 216 (100), 190 (27), 157 (34), 156 (31), 149 (24), 146 (15), 132 (14), 130 (31), 75 (12), 45 (51), 43 (68). *Anal.* Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.98; H, 5.51; N, 7.61.

4) *cis*-3a-Acetoxy-1,8-diacetyl-2-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole: Analogous acetylation of the *cis* isomer **5d** (180 mg, 0.66 mM) was carried out at room temperature for 45 hr (TLC, two spots) and then the mixture was heated at 70—90° for 8 hr (TLC, one spot). Work-up as above provided the N,O-diacetate of **5d** (147 mg, 59%). Recrystallization from ether–hexane gave the pure product, mp 152.5—153°, colorless fine needles; $\lambda_{max}^{EtOH}$ nm ($\varepsilon$) 242.5 (10300), 278 (1400), 285 sh (1200); $\nu_{max}^{KBr}$ $cm^{-1}$ 1760, 1750, 1680, 1660 (CO); $\delta$ 1.98 (s, 3H, $OCOCH_3$), 2.24 (s, 3H, $NCOCH_3$), 2.40 (s, 3H, $NCOCH_3$), 3.74 (s, 3H, $CO_2CH_3$), 2.60—3.60 (m, 2H, $CH_2$), 3.60—4.20 (m, 1H, $C_2$–H), 6.60 (finely split s, 1H, NCHN), 7.00—7.50 (m, 3H, aromatic H), 7.62 (d, 1H, $J=8$ Hz, $C_7$–H); *m/e* 360 (11) $M^+$, 318 (32), 258 (76), 216 (100), 199 (11), 157 (36), 156 (30), 149 (23), 146 (13), 132 (13), 130 (32), 129 (15), 43 (70). *Anal.* Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.86; H, 5.60; N, 7.77.

**Acid-catalyzed Rearrangement of the Hydroperoxide 2 to the Oxazine Derivative 3**——1) Formation of **3a**: Isolation of two diastereoisomers (**3a**-1) and (**3a**-2) Nb-methoxycarbonyl-DL-tryptopahn methyl ester **1a** (1.0 g, 3.6 mM) was oxygenated as described above. The reaction mixture was immediately acidified with 10% hydrochloric acid to pH 2—3, stirred for 1.5 hr at room temperature, neutralized with 10% NaOH and concentrated. The residue was chromatographed on alumina (15 g) to remove the dye. Elution with 2—3% methanol–methylene chloride gave an oily residue which was rechromatographed on silica gel (30 g). Elution with methylene chloride afforded the less polar benzoxazine derivative **3a**-1 (21 mg, fraction 1, pale

yellow crystals). Further elution with methylene chloride gave a mixture of **3a**-1 and the more polar benzoxazine derivative **3a**-2 (184 mg, fraction 2, solid), **3a**-2 (96 mg, fraction 3, yellow solid), a mixture of **3a**-2 and **5a** (29 mg, fraction), and a mixture of **4a** and **5a** (129 mg, fraction 5). Fraction 2 was subjected to preparative TLC (silica gel, methylene chloride–acetone, 7: 1) to give **3a**-1 (11 mg) and **3a**-2 (48 mg). Fraction 4 was separated in a similar manner to yield **3a**-1 (2 mg), **3a**-2 (4 mg), and a mixture of **4a** and **5a** (22 mg). Total yields, **3a**-1 (135 mg, 12%), **3a**-2 (148 mg, 13%), a mixture of **4a** and **5a** (151 mg, 14%). **3a**-1: mp 178—178.5° (methanol) colorless prisms; $\lambda_{max}^{EtOH}$ nm ($\varepsilon$) 240.5 (8800), 290.5 (3800); $\nu_{max}^{KBr}$ $cm^{-1}$ 3385 (NH), 1751, 1710 (CO), 1215, 1125, 1110, 1065; $\delta$ 2.07 (q, 1H, $J=12$ and 8 Hz, $C_3$–H), 2.75 (q, 1H, $J=12$ and 8 Hz, $C_3$–H), 3.40 (s, 3H, $OCH_3$), 3.58 and 3.72 (2s, 6H, $CO_2CH_3$, $NCO_2CH_3$), 4.34 (t, 1H, $J=8$ Hz, $C_2$–H), 5.16 (s, 1H, NCHN), 5.20 (broad s, 1H, NH, exchangeable), 6.50—6.90 (m, 4H, aromatic H); *m/e* 322 (100) $M^+$, 307 (21), 291 (10), 290 (8), 231 (20), 215 (52), 214 (74), 182 (37), 159 (91), 120 (18), 109 (31), 93 (20). *Anal.* Calcd for $C_{15}H_{18}N_2O_6$: C, 55.89; H, 5.63; N, 8.69. Found: C, 55.96; H, 5.64; N, 8.66.

**3a**-2: Amorphous; $\lambda_{max}^{EtOH}$ nm ($\varepsilon$) 240.5 (8100), 290.5 (3700); $\nu_{max}^{KBr}$ $cm^{-1}$ 3400 (NH), 1770, 1715 (CO), 1200, 1120, 1065; $\delta$ 2.33 (q, 1H, $J=13$ and 9 Hz, $C_3$–H), 2.84 (d, 1H, $J=13$ Hz, $C_3$–H), 3.42 (s, 3H, $OCH_3$), 3.54 and 3.75 (2s, 6H, $CO_2CH_3$, $NCO_2CH_3$), 4.50 (d, 1H, $J=9$ Hz, $C_2$–H), 5.12 (s, 1H, NCHN), 5.20 (broad s, 1H, NH, exchangeable), 6.50—7.00 (m, 4H, aromatic H); *m/e* 322 (100) $M^+$, 307 (31), 291 (4), 231 (13), 215 (30), 214 (21), 156 (43), 120 (9), 78 (40).

2) Formation of **3b**: Isolation of two diastereoisomers (**3b**-1) and (**3b**-2). Nb-Methoxycarbonyl-L-tryptophan methyl ester **1b** (1 g, 3.6 mM) was oxygenated and treated with 10% hydrochloric acid as above. Analogous work-up gave **3b**-1 (197 mg, 17%) as an amorphous solid, **3b**-2 (197 mg, 17%, amorphous), and recovered **1b** (92 mg, 9%). The structures of **3b**-1 and **3b**-2 were determined (TLC, and UV, NMR, and mass spectroscopy) by comparison with those of **3a**-1 and **3a**-2, respectively.

**Dye-sensitized Photooxygenation of Tryptophan: General Procedure**——Tryptophan (1.02 g, 5 mM) was dissolved in distilled water (200 ml) by brief heating and then cooled to room temperature. This solution was transferred into a reaction vessel and Rose Bengal (15 mg, 0.015 mM), water (85 ml), and ethanol (15 ml) were added. The reaction mixture was cooled with an ice-bath and irradiated with a 500 W halogen lamp through a liquid filter while oxygen was bubbled through. After 3.5 hr, TLC analysis (silica gel, *n*-PrOH–$H_2O$, 7: 3) and UV spectroscopy showed the reaction to be complete. Dimethyl sulfide (5 ml) was added and then the reaction mixture was stirred for 1 hr at room temperature until the starch-KI test became negative. Excess dimethyl sulfide and ethanol were removed under reduced pressure at 30—35°. The resulting aqueous solution was acidified with acetic acid (3 ml) and extracted with methylene chloride. The aqueous solution (300 ml) was lyophilized to give a powder, which was dissolved in water. The solution was filtered to remove insoluble material. The filtrate was chromatographed on an ion exchange column (Amberlite CG-50, COOH form, 4.7 $\phi \times 46$ cm) with water, followed by lyophilization to give a mixture of **11** and **12** in about 85% yield (see Table II). The NMR spectrum of the reaction mixture obtained from L-tryptophan **8b** showed the ratio of **11b** and **12b** to be 4: 6. A mixture of **11** and **12** was subjected to fractional crystallizations from water or aqueous alcohol to give **11** and **12** directly or after rechromatography on an ion exchange column as above. (**11**, more polar isomer; **12**, less polar isomer; TLC, silica gel, *n*-PrOH–$H_2O$, 7: 3, detected by UV light, Ehrlich, and ninhydrin reagents). **11a**: mp 223—224° (dec.), more soluble isomer. **12a**: mp 251—252° (dec.), less soluble isomer. **11b**: mp 231.5—232° (dec.) (EtOH–$H_2O$) monohydrate, obtained by drying the product at 26° for 11 hr over $P_2O_5$ *in vacuo*; mp 231.5° (dec.), obtained when dried at 50° for 6 hr in a similar manner; $\lambda_{max}^{H_2O}$ nm ($\varepsilon$) 235.5 (6590), 294 (2140); $\nu_{max}^{KBr}$ $cm^{-1}$ 3450 br, 3270 s, 3140 br (NH, OH), 1615 ($CO_2^-$), 1470, 1380, 1318; $\delta$ ($D_2O$) see Table III; $\delta$ (5% $CF_3CO_2H$–$D_2O$) 2.92 (d, 2H, $J=7$ Hz, $CH_2$), 4.69 (t, 1H, $J=7$ Hz, $C_2$–H), 5.39 (s, 1H, NCHN), 6.86 (d, 1H, $J=8$ Hz, $C_7$– or $C_4$–H), 6.98 (t, 1H, $J=8$ Hz, $C_5$– or $C_6$–H), 7.30 (t, 1H, $J=8$ Hz, $C_6$– or $C_5$–H), 7.40 (d, 1H, $J=8$ Hz, $C_4$– or $C_7$–H); *m/e* 220 (100) $M^+$, 177 (32), 176 (10), 175 (32), 158 (27), 148 (20), 147 (71), 164 (67), 133 (29), 132 (98), 131 (36), 120 (30), 118 (21), 77 (38), 44 (26); CD ($c=4.94\times10^{-4}$, $H_2O$) [$\theta$] (nm) $+0.20\times10^3$ (215), $+1.44\times10^4$ (239), $+0.4\times10^3$ (262), $+3.4\times10^3$ (296). *Anal.* Calcd for $C_{11}H_{12}N_2O_3\cdot H_2O$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.34; H, 5.93; N, 11.49.

**12b**: mp 229.5—230° (dec.), dried at 50° for 3 hr over $P_2O_5$ *in vacuo*, more soluble isomer; $\lambda_{max}^{H_2O}$ nm ($\varepsilon$) 237 (6500), 294 (2000); $\nu_{max}^{KBr}$ $cm^{-1}$ 3530 s, 3300 s, 1620 br, 1480, 1405, 1370, 1340; $\delta$ ($D_2O$) see Table III; $\delta$ (5% $CF_3CO_2H$–$D_2O$) 2.73 (t, 1H, $J=12$ Hz, ABX, $C_3$–H), 3.00 (q, 1H, $J=12$ and 7 Hz, ABX, $C_3$–H), 4.28 (q, 1H, $J=12$ and 7 Hz, ABX, $C_2$–H), 5.51 (s, 1H, NCHN), 6.86 (d, 1H, $J=8$ Hz, $C_7$– or $C_4$–H), 7.01 (t, 1H, $J=8$ Hz, $C_5$– or $C_6$–H), 7.35 (t, 1H, $J=8$ Hz, $C_6$– or $C_5$–H), 7.46 (d, 1H, $J=8$ Hz, $C_4$– or $C_7$–H); *m/e* 220 (75) $M^+$, 202 (10) M–$H_2O$, 177 (27), 176 (27), 175 (24), 173 (14), 157 (24), 156 (10), 155 (9), 148 (19), 147 (71), 146 (70), 133 (27), 132 (100), 131 (26), 130 (56), 120 (25), 119 (18), 118 (26), 77 (49), 44 (34), 43 (37); CD ($c=4.78\times10^{-4}$, $H_2O$) [$\theta$] (nm) $-1.78\times10^4$ (238), $-0.4\times10^3$ (262), $-5.4\times10^3$ (295). *Anal.* Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.59; H, 5.49; N, 12.29.

**11c**: CD ($c=4.68\times10^{-4}$, $H_2O$) [$\theta$] (nm) $-1.42\times10^4$ (237), $-0.4\times10^3$ (262), $-3.0\times10^3$ (294). **12c**: CD ($c=4.73\times10^{-4}$, $H_2O$) [$\theta$] (nm) $+1.70\times10^4$ (237), $+0.4\times10^3$ (263), $+5.4\times10^3$ (295).

**Isolation of 2-Carboxy-3a-hydroperoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole 10b**——A solution of L-tryptophan **8b** (1.02 g, 5 mM) and Rose Bengal (15 mg, 0.015 mM) in water (285 ml) and ethanol (15 ml) was irradiated as described above. After 3.5 hr, the reaction mixture (active oxygen by iodometry, 99%) was

acidified with acetic acid (3 ml) and Rose Bengal was extracted with methylene chloride. The aqueous solution (active oxygen, 92%) was lyophilized to give **10b** as light-brown colored powder (active oxygen *ca.* 85%). This crude hydroperoxide (500 mg) was dissolved in water (50 ml) and applied to a Sephadex G-10 (300 g) column (9.2$\phi \times$15 cm) prepared in water. Elution with water followed by lyophilization gave **10b** as an almost colorless powder (300 mg; active oxygen, 82%); for spectral data see the text and Table III; TLC, *cis*-**10b** *Rf* 0.8 (brown), *trans*-**10b** *Rf* 0.7 (brown) (silica gel, *n*-PrOH–$H_2O$, 7: 3, sprayed with Ehrlich reagent) (*cf.* *Rf* values for the corresponding hydroxides in the some system, **11b**, *Rf* 0.6, red-purple, **12b**, *Rf* 0.7, red-purple). Reduction of **10b** with dimethyl sulfide in water provided a mixture of hydroxides, **11b** and **12b**, quantitatively.

**Transformation of 10 to Formylkynurenine 13 and Hydroxides 11 and 12**——1) Decomposition of **10b** in Water at Room Temperature: The hydroperoxide **10b** (189 mg; active oxygen by iodometry, 71% purity) in distilled water (50 ml) was stirred for 7 days at room temperature (20—25°) until the starch-KI test became negative. The reaction mixture was filtered to remove insoluble substances. The filtrate was washed with methylene chloride and concentrated to about 10 ml by lyophilization, then filtered again. The filtrate was chromatographed on Amberlite (CG-50, COOH form, column 3.3$\phi \times$27 cm). Elution with water gave the alcohols **11b** and **12b** (124 mg, 71%). Further elution with water provided formylkynurenine **13** (10.3 mg, 5.5%), identified by TLC, HPLC, and measurement of UV and NMR spectra.

2) Decomposition of **10b** in Boiling Water: a) The hydroperoxide **10b** (214 mg; active oxygen by iodometry, 78%) in distilled water (50 ml) was heated at 120—150° for 15 min until the starch-KI test became negative. The reaction mixture turned dark-brown and the insoluble materials were removed by filtration. The filtrate was concentrated to 10 ml by lyophilization and then filtered again. The filtrate was chromatographed on an Amberlite CG-50 (COOH form) column (3.8$\phi \times$30 cm). Elution with water afforded the alcohols **11b** and **12b** (110 mg, 56%). Further elution with water gave **13** (38 mg, 18%).

b) An aqueous solution (10 ml) of **10b** (224 mg; active oxygen by iodometry, 72%) was added to 190 ml of boiling water. The reaction mixture was kept for 10 min, then cooled, and filtered. The filtrate was treated as above to give the alcohols **11b** and **12b** (88 mg, 42%) and **13** (46 mg, 20%).

**Acid-catalyzed Rearrangement of 10**——A solution of **1a** (1.02 g, 5 mM) and Rose Bengal (15 mg, 0.015 mM) in water (285 ml) containing ethanol (15 ml) was irradiated with a 300W halogen lamp for 3.5 hr as described above, then 10% hydrochloric acid (20 ml) was added. The mixture was stirred under an $N_2$ atmosphere for 20 hr at room temperature and was adjusted to pH 8 by addition of 2 N NaOH and $NaHCO_3$ solutions. TLC analysis (silica gel, AcOH–*n*-PrOH, 1: 3) showed two spots corresponding to the alcohols (**11a** and **12a**, *Rf* 0.6) and *o*-aminophenol (*Rf* 0.7). The reaction mixture was extracted with methylene chloride. The combined extracts (450 ml) were washed with brine (30 ml) and dried. The solvent was removed to give *o*-aminophenol as a solid (210 mg, 40%), which after recrystallizations from ether–benzene gave a product with mp 165—170°. Mixed melting point with an authentic specimen showed no depression, and the IR and UV spectra, and *Rf* on TLC were identical. The aqueous solution was diluted to about 40 ml and chromatographed as described above to give a mixture of **11a** and **12a** (189 mg, 26%).

**Photooxygenation of 2-*tert*-Butyl-Nb-methoxycarbonyltryptamine 19**——A solution of 2-*tert*-butyl-Nb-methoxycarbonyltryptamine **19** (986 mg, 3.6 mM) and Rose Bengal (36 mg, 0.037 mM) in methanol (300 ml) was irradiated with a 500W halogen lamp equipped with a $CuCl_2$–$CaCl_2$ filter solution for 100 min at *ca.* −10° while oxygen was bubbled through and dimethyl sulfide was added. The reaction mixture was stirred for 45 min and the solvent evaporated off *in vacuo* at room temperature. The residue was passed through a column of alumina, and eluted with 5% methanol–methylene chloride. Removal of the solvent by evaporation at room temperature gave a yellow oil (1.04 g) which was crystallized from hexane–benzene to give **22** (646 mg, mp 163—166°). The mother liquor was evaporated to dryness and the residue taken up with methylene chloride. The methylene chloride extracts were washed with water to remove DMSO, dried, and concentrated *in vacuo* at room temperature. Crystallization of the residue from hexane–benzene provided **22** (160 mg, mp 160—165°); total 806 mg, 77%.

**22**: mp 157—159° (dec.), colorless needles; $\lambda_{max}^{MeOH}$ nm ($\varepsilon$) 216.5 sh (18500), 222 (20600), 228 sh (15200), 261 (4000), 282 sh (3000), 290 sh (2900); $\nu_{max}^{KBr}$ $cm^{-1}$ 3380, 3200 (NH), 1700 (CO), 1565 (NH), 1285, 1270, 770; $\delta$ 1.44 (s, 9H, *tert*-Bu), 2.00—2.50 (m, 2H, $CH_2$), 2.50—3.30 (m, 2H, $CH_2N$), 2.75 (s, 1H, OH or NH, exchangeable), 3.58 (s, 3H, $OCH_3$), 4.70 (broad s, 1H, NH or OH, exchangeable), 7.00—7.60 (m, 4H, aromatic H); *m/e* 290 (12) $M^+$, 233 (10) M–*tert*-Bu, 203 (19), 202 (100), 188 (11), 158 (22), 146 (44), 132 (12), 91 (21), 88 (12), 57 (30). *Anal.* Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.40; H, 7.66; N, 9.54.

**Isolation of 2-*tert*-Butyl-3-hydroperoxy-Nb-methoxycarbonyltryptamine 20**——2-*tert*-Butyl-Nb-methoxycarbonyltryptamine **19** (298 mg, 1.1 mM) in methanol (300 ml) was oxygenated in the presence of Rose Bengal (12 mg, 0.012 mM) as described above for 80 min, then the solvent was evaporated off *in vacuo* at room temperature. The residue was dissolved in a small amount of methylene chloride and subjected to preparative TLC (silica gel, methylene chloride–acetone, 20: 1). The main band corresponding to *Rf* 0.4 was collected and extracted with 5% methanol in methylene chloride. Removal of the solvent at room temperature afforded **20** as a colorless amorphous solid (290 mg, 87%). Recrystallization from hexane–methylene chloride gave a colorless powder, mp 120—122.5° (dec.); $\lambda_{max}^{MeOH}$ nm ($\varepsilon$) 217 sh (18100), 222 (20100), 228 sh (15000),

265 (3800), 290 sh (3000); $\nu_{max}^{KBr}$ $cm^{-1}$ 3420, 3360 (NH, OOH), 2700, 1730, 1700 (CO), 1530, 1520 (NH), 1260, 775, 760; $\delta$ 1.44 (s, 9H, *tert*-Bu), 2.10—2.50 (m, 2H, $CH_2$), 2.50—3.20 (m, 2H, $CH_2N$), 3.56 (s, 3H, $OCH_3$), 4.50 (broad s, 1H, NH or OOH, exchangeable), 7.00—7.60 (m, 4H, aromatic H), 8.90 (broad s, 1H, OOH or NH, exchangeable); *m/e* 306 (17) $M^+$, 290 (15) M–O, 289 (19) M–OH, 288 (18) $M-H_2O$, 231 (62), 214 (52), 204 (26), 203 (31), 202 (100), 187 (13), 186 (37), 174 (25), 160 (16), 159 (23), 158 (55), 147 (24), 146 (84), 130 (21), 88 (32), 78(25), 77 (30), 76 (15), 59 (13), 57 (69).

**Isolation of 8a-*tert*-Butyl-3a-hydroperoxy-1-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole 21**——A solution of **20** (98 mg) in methylene chloride was stirred for 24 hr at room temperature in the dark. The solvent was evaporated off and the residue was subjected to preparative TLC (alumina) with hexane–benzene (1: 2). The main band corresponding to **21** (*Rf* 0.8) was extracted with chilled 5% methanol–methylene chloride and the extracts were concentrated. Further purification by preparative TLC on alumina (iso-$Pr_2O$–hexane, 7: 9) gave **21** as a colorless oil; $\lambda_{max}^{EtOH}$ 241, 298 nm; $\nu_{max}^{CDCl_3}$ $cm^{-1}$ 3500, 3450 (NH, OOH), 1685 (CO), 1605 (PhNCN); $\delta$ 1.20 (s, 9H, *tert*-Bu), 2.40—2.80 (m, 2H, $CH_2$), 3.05—3.72 (m, 2H, $CH_2N$), 3.52 (s, 3H, $NCO_2CH_3$), 6.44 (s, 1H, NH or OOH, exchangeable), 6.60—6.90 (m, 2H, aromatic H), 7.05—7.40 (m, 2H, aromatic H), 7.96 (broad s, 1H, OOH or NH, exchangeable); *m/e* 306 (4) $M^+$, 290 (12), 289 (12), 288 (48), 249 (18), 246 (16), 234 (21), 233 (100), 232 (11), 231 (21), 216 (33), 201 (29), 186 (53), 175 (15), 159 (45), 158 (21), 147 (15), 146 (43).

**Isolation of 8a-*tert*-Butyl-3a-hydroxy-1-methoxycarbonyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole 23**——A solution of **22** (600 mg, 21 mM) in methylene chloride (50 ml) was refluxed for 11 hr and the solvent was removed *in vacuo*. The residue was chromatographed on alumina (35 g). Elution with hexane-benzene provided **23** (578 mg) as a colorless solid. Recrystallization from hexane–methylene chloride gave **23** (434 mg, 72%). From the mother liquor, **22** (101 mg, 17%) was recovered after preparative TLC. **23**: mp 136—138° (dec.), colorless prisms; $\lambda_{max}^{EtOH}$ nm ($\varepsilon$) 241 (9000), 296 (2500); $\nu_{max}^{KBr}$ $cm^{-1}$ 3460, 3380 (OH, NH), 1680 (CO), 1615, 745; $\delta$ 1.20 (s, 9H, *tert*-Bu), 1.90 (s, 1H, OH or NH, exchangeable), 2.36—2.60 (m, 2H, $CH_2$), 3.00—3.60 (m, 2H, $CH_2N$), 3.52 (s, 3H, $OCH_3$), 6.44 (broad s, 1H, NH or OH, exchangeable), 6.60—6.90 (m, 2H, aromatic H), 7.00—7.40 (m, 2H, aromatic H); *m/e* 290 (6) $M^+$, 234 (11), 233 (100) M—*tert*-Bu, 158 (9), 146 (19), 130 (7), 57 (12). *Anal.* Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.33; H, 7.78; N, 9.77.

**Rose Bengal-sensitized Photooxygenation of Nb-Methoxycarbonyltryptamine 25**——1) A solution of **25** (1.0 g, 4.6 mM) and Rose Bengal (500 mg, 0.51 mM) in methanol (250 ml) was irradiated with a 300W halogen lamp for 1.6 hr at 0° under oxygen until the spot corresponding to **25** disappeared on TLC (silica gel, methylene chloride–acetone, 6: 1), then dimethyl sulfide (12 ml) was added. The reaction mixture was stirred for 50 min and the solvent removed *in vacuo*. The residue was passed through a column of alumina and eluted with 3% methanol–methylene chloride. The residue after evaporation was chromatographed on silica gel (25 g). Elution with methylene chloride gave a mixture of **25**, **26**, and **27** (120 mg, fraction 1). Further elution with methylene chloride gave **26** (611 mg). Elution with 1% methanol–methylene chloride provided a mixture of **26** and more polar material (81 mg, fraction 2). Fractions 1 and 2 were rechromatographed in a similar manner. Total yields were as follows: **26** (670 mg, 62%), ketoamide **27** (41 mg, 4%), recovery of **25** (46 mg, 5%), and a trace of Nb-formylated compound corresponding to **7**. The structures of **26**, **27**, and the formylated compound were identified by comparison with those of authentic samples.[14]

2) A solution of **25** (1.0 g, 4.6 mM) and Rose Bengal (500 mg, 0.51 mM) in 5% $H_2O$–methanol (250 ml) was oxygenated as described above. Similar work-up afforded **26** (548 mg, 51%), the ketoamide **27** (27 mg, 2%), the Nb-formyl derivative (9 mg, 1%), and recovery of **25** (18 mg, 2%).

**Acknowledgement** Financial support from the Ministry of Education, Science and Culture (Grant-in-Aid for Special Project Research), the Foundation for the Promotion of Research on Medicinal Resources (Japan), and the Japan Society for Promotion of Science (International Cooperative Research Project) is gratefully acknowledged.

## References and Notes

1) *a*) O. Hayaishi, "Oxygenase," ed. by O. Hayaishi, Academic Press, New York, N.Y., 1962; *b*) O. Hayaishi, "Molecular Mechanism of Oxygen Activation," ed., by O. Hayaishi, Academic Press, New York, N.Y., 1974.
2) A. Ian Scott, *Bioorganic Chemistry*, **3**, 398 (1974).
3) Y. Kotake, T. Masayama, *Z. Physiol. Chem.*, **195**, 158 (1931).
4) P.L. Julian, E.W. Meyer, and H.C. Printy, "Heterocyclic Compounds," Vol. 3, ed. by R.C. Elderfield John Wiley and Sonsi, New York, N.Y., 1952, p. 1.
5) T. Sakan and O. Hayaishi, *J. Biol. Chem.*, **186**, 177 (1950); H. Mason and C.P. Berg, *ibid.*, **188**, 783 (1951).
6) O. Hayaishi, S. Rothberg, A.H. Mehler, and Y. Saito, *J. Biol. Chem.*, **229**, 889 (1957).
7) B. Witkop and J.B. Patrick, *J. Am. Chem. Soc.*, **73**, 2196 (1951).
8) A.Ek.H. Kissman, J.B. Patrick, and B. Witkop, *Experientia*, **8**, 36 (1952).
9) G.A. Hamilton, P. Feigelson, and F.O. Brady, "Molecular Mechanism of Oxygen Activation," ed., by O.

Hayaishi, Academic Press, New York, N.Y., 1974.
10) *a*) G.A. Hamilton, *Adv. Enzymol.*, **32**, 55 (1969); *b*) R.J. Sundberg, "Chemistry of Indoles," Academic Press, New York, 1970, p. 289.
11) B. Witkop, *Ann.*, **556**, 103 (1944).
12) *cf. a*) I. Saito, T. Matsuura, M. Nakagawa, and T. Hino, *Acc. Chem. Res.*, **10**, 346 (1977); *b*) I. Saito, M. Imuta, Y. Takahashi, S. Matsugo, T. Matsuura, *J. Am. Chem. Soc.*, **99**, 2005 (1977).
13) *a*) M. Nakagawa, H. Watanabe, S. Kodato, H. Okajima, T. Hino, J.L. Flippen, and B. Witkop, *Pro. Nat. Acad. Sci.*, USA, **74**, 4730 (1977); *b*) M. Nakagawa, S. Kato, S. Kataoka, and T. Hino, *J. Am. Chem. Soc.*, **101**, 3136 (1979).
14) Related papers: *a*) M. Nakagawa, T. Kaneko, K. Yoshikawa, and T. Hino, *J. Am. Chem. Soc.*, **96**, 624 (1974); *b*) M. Nakagawa, K. Yoshikawa, and T. Hino, *ibid.*, **97**, 6496 (1975); *c*) M. Nakagawa, H. Okajima, and T. Hino, *ibid.*, **98**, 635 (1976); *d*) M. Nakagawa, H. Okajima, and T. Hino, *ibid.*, **99**, 4424 (1977); *e*) M. Nakagawa, J. Chiba, and T. Hino, *Heterocycles*, **9**, 385 (1978).
15) The 2,3-bond-cleaved compound **6d** has been obtained by similar oxygenation in 90% yield. I. Saito, Y. Takahashi, M. Imuta, S. Matsugo, H. Kaguchi, and T. Matsuura, *Heterocycles*, **5**, 53 (1976).
16) The splitting of the signals of the methyl protons can be ascribed to hindered rotation about the carbamate group. At 80°, the methyl protons of the carbamate ester appear as a sharp singlet at $\delta$ 3.72. The split peaks of the ester group and **8a** proton also merged to sharp singlets at $\delta$ 3.24 and 5.22, respectively. Similar splitting of the signal was observed in compound **26**.[14d]
17) W.E. Savige, *Aust. J. Chem.*, **28**, 2275 (1975).
18) *cf.* I. Saito, S. Matsugo, and T. Matsuura, *J. Am. Chem. Soc.*, **101**, 4757 (1979).
19) A. Nishinaga, *Chem. Lett.*, **1975**, 273.