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Photosensitized Oxygenation of N_b-Methoxycarbonyltryptamines. A New Pathway to Kynurenine Derivatives

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Abstract: Photosensitized oxygenation of N_b-methoxycarbonyltryptamine (**1a**) has been found to give 3a-hydroperoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole(**4a**) which then undergoes rearrangement to formylkynurenamine (**6a**) and N_b-formylkynurenamine (**7**) accompanied by the reduction product **5a**, showing that participation of the ethylamino side chain in **3** predominates over the hydroperoxy group. This suggests a new reaction pathway for the oxygenation of tryptophan to kynurenine other than the well-known hypothetical dioxetane pathway. N_b-Methoxycarbonyl-N_b-methyltryptamine (**1b**) under the same conditions, however, was converted to formylkynurenine derivative **6b**, demonstrating that the hydroperoxy group participates to form the dioxetane **9** when the ethylamino side chain is prevented from participation. In the case of N_a-methyl-N_b-methoxycarbonyltryptamine (**1c**), moreover, there is clearly a temperature dependence with regard to participation of the two neighboring groups: at about −70 °C **4c** was exclusively formed while at 5–10 °C the predominant product was **6c**. In contrast to **4a, 4c**, rearranged neither to compound **6c** nor **7**. On the other hand, **4** underwent an acid-catalyzed rearrangement to give the 1,4-benzoxazine derivative **14**.

Although the photosensitized oxygenation of tryptophan[1] and related compounds[2] has been extensively studied, the dynamic chemistry of these photoproducts in organic solvents was not well known. Prior to our preliminary publication[3] of part of this work, the only detailed study of the photosensitized oxygenation of tryptophan in nonaqueous solvent had been that of Scoffone and co-workers,[4] who showed that proflavine-sensitized photooxygenation of tryptophan derivatives in an acidic solvent, such as formic or acetic acid, results in high yields of the corresponding kynurenine derivatives, but the mechanism remained to be identified. More recent work has demonstrated that singlet oxygen is indeed involved in the methylene blue sensitized photooxygenation of tryptophan,[5] although it is probable that non-singlet-oxygen reaction becomes more important in certain conditions.[6]

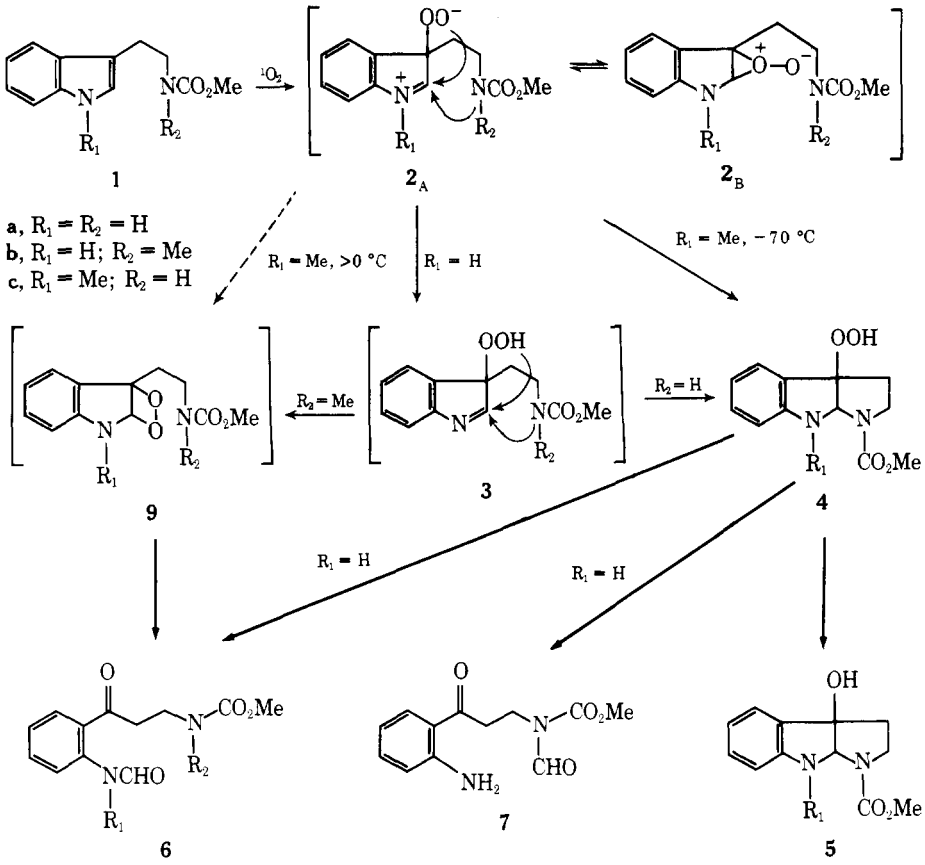
The reaction of singlet oxygen with enamines having an NH hydrogen has been shown to give the azomethine hydroperoxide, RN=CCOOH,[7] whereas tertiary enamines undergo, 1,2-cycloaddition to give dioxetanes which readily decompose to carbonyl fragments.[8] The photosensitized oxygenation of tryptophan to kynurenine, therefore, seems to proceed via the dioxetane pathway as has been suggested,[2a,8c-e,9] i.e., the primary 3-hydroperoxyindolenine **3** collapses to the formylkynurenine via the dioxetane intermediate **9**, for which there is no direct evidence so far.

Recently, we have succeeded in isolating tricyclic hydroperoxides, such as **4a** and **10b** which show the existence of the intermediate **3** in the photosensitized oxygenation of tryptamine derivatives.[3,10] As a continuation of our work, we investigated the rose bengal sensitized oxygenation of N_b-methoxycarbonyltryptamines in various organic solvents. We have now found a new class of reactions in the oxygenation of tryptamine derivatives to kynurenine derivatives involving a tricyclic hydroperoxide, instead of a dioxetane.

Results and Discussion

When N_b-methoxycarbonyltryptamine (**1a**) was irradiated in thoroughly O_2-saturated anhydrous benzene with a 200-W halogen lamp for 20 h in the presence of rose bengal under ice cooling (the reaction temperature was 5–10 °C) followed by

Scheme I



chromatography on alumina and silica gel columns, the 3a-hydroxypyrroloindole **5a** was obtained as the main product, in addition to 2,3-bond cleavage compounds **6a** which was not isolated from the analogous reaction of N_b-methyltryptamine[10] but has been widely known as the normal product of photosensitized oxygenation of tryptophan[1,4] and indoles.[2,11] In addition, two unknown dimeric compounds were obtained each in 4% yield. However, when **1a** was similarly oxygenated in more polar solvents such as MeOH, 5% pyridine–MeOH, 30% pyridine–MeOH, acetone, or *t*-BuOH, chromatographic separation on silica gel gave a new compound **7** as the major product which has not previously been known as an oxidation product of tryptophan, besides products **5a** and **6a.** The reaction mixture in all solvents except benzene showed a spot indicative of the presence of an intermediate besides those of **5a** and **6a** on TLC and gave a positive starch–KI test.[12] Control experiments showed that both sensitizer and light were essential for the formations of **5a, 6a,** and **7** and these products were also obtained in control experiments with a free-radical inhibitor added, 2,6-di-*tert*-butylphenol, suggesting the involvement of singlet oxygen in the major pathway for rose bengal sensitized oxygenations of **1a.**

Structural assignments to the oxygenation products were made on the basis of elemental analyses, spectral properties (see Experimental Section), and chemical reactions. Alkaline hydrolysis of **5a** in ethanol provided the parent compound **8a,** the structure of which was identified by spectral data, satisfactory elemental analysis, and $LiAlH_4$ reduction to the known compound **10a,** [10] accompanied by **1a,** N_b-methyltryptamine, and minor amounts of **11** which was readily dehydrated by acid to **1a.** The mechanism of the reductive ring cleavage of **5a** is essentially the same as that found in the $LiAlH_4$ reduction of quinamine to cinchonamine[13] and oxazinoindole to N_b-hydroxy-N_b-methyltryptamine.[10]

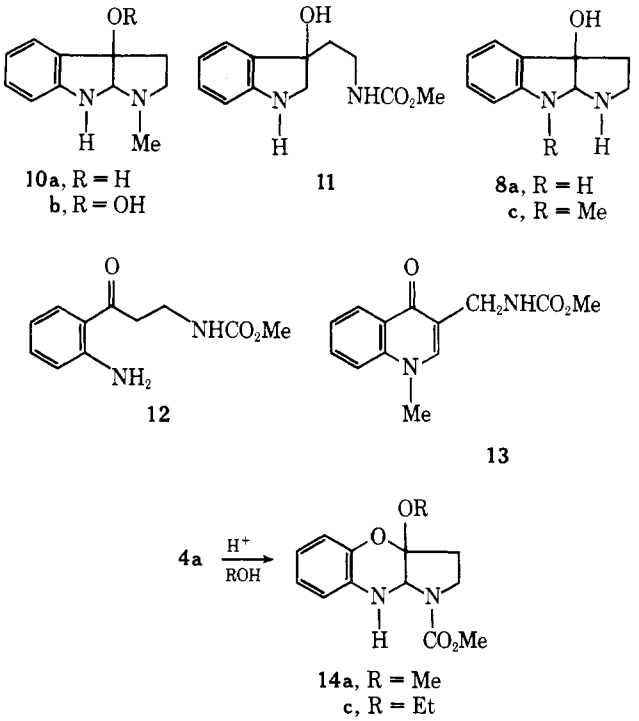
The keto amide **6a** was identified by direct comparison with an authentic sample prepared by ozonization of **1a** in methanol. The partial hydrolysis of the formyl groups of **6a** and **7** proceeded quantitatively by refluxing in methanol with alumina and in both cases led to N_b-methoxycarbonylkynurenamine (**12**). As a result of the unexpected production of **7** in the oxygenation of **1a,** the reaction was investigated in 5% pyridine–ethanol, in place of 5% pyridine–methanol, in order to determine whether the N_b-formyl group of **7** originates from the methanol used as the solvent to increase the solubility of the sensitizer. However, there was no significant change in the nature and ratio of products. This rules out the formation of the formyl group of **7** from methanol. Furthermore, no migration of the formyl group from N_a nitrogen to N_b nitrogen was observed when **6a** was irradiated under the reaction conditions.

With a view to trapping the intermediate **4a,** the reaction of **1a** in 5% pyridine–methanol was performed at low temperature (1–0 °C) for 90 min followed by evaporation of the solvent in vacuo at room temperature. The reaction mixture showed almost one spot corresponding to **4a** and no other significant spot was detected on TLC. Filtration of the residue through alumina to remove rose bengal and further purification by preparative TLC (alumina) provided the 3a-hydroperoxide **4a** in 41% yield; accompanied by minor amounts of **5a** (7%), **6a** (4%), and **7** (1.7%) probably formed during isolation. Accordingly, when at the end of the reaction dimethyl sulfide was added to the reaction mixture, **5a** became the sole product (71% yield) with neither **6a** nor **7** being obtained.

When a solution of **4a** in methylene chloride was treated with silica gel, a mixture of **5a, 6a,** and **7** resulted, while **4a** alone is stable in benzene, methylene chloride, or methanol at room temperature for 5 h. After 48 h in methylene chloride at room temperature, however, **4a** was converted to **5a, 6a,** and **7,** which were also obtained on refluxing in benzene for 18 h.

In summary, the foregoing evidence demonstrates that the oxygenation products **5a, 6a,** and **7** were formed from the

Scheme II



common intermediate **4a** during isolation and a part of **5a** and **6a** were formed under the reaction condition (<5 °C). Therefore, the N_b-formyl group must originate from the **8a** carbon, and these results eliminate the possible formation of **6a** via the dioxetane pathway. Recent experimental evidence[2b,14] and theoretical investigations[15] suggest that the reaction of singlet oxygen with enamines proceeds stepwise via a zwitterionic intermediates such as $\mathbf{2}_A$, rather than by a concerted process. Therefore, the first step presumably involves the formation of 3-hydroperoxyindolenine **3** via **2** (ene reaction), followed by cyclization exclusively to **4a.** Mechanistic details of these transformations of **4a** are not yet clear,[16] but these results are outlined in Scheme I.

The N_b-methyl derivative, **1b,** however, has been found, under comparable experimental conditions (0 °C), to give the product of 2,3-bond cleavage **6b** in 44% yield as the sole product, indicating that the direct formation of the keto amide **6** from **3** occurs in the absence of the ethylamino side chain participation probably via the dioxetane **9.**

By contrast, interesting differences were observed when the analogous oxygenation of **1c** was performed at different temperatures. When the reaction of **1c** was carried out at 5–10 °C, the 2,3-bond cleavage compound **6c** was obtained as the major product, accompanied by minor amounts of **5c** (14%) which readily hydrolyzed to **8c.** Low temperature (−70 °C) oxygenation of **1c,** however, proceeded exclusively to give **4c** which without isolation was reduced by dimethyl sulfide to give **5c** in 91% yield, based on consumed **1c** (45%). An aliquot removed at the end of this reaction after 5 days at room temperature was reduced with dimethyl sulfide to give **5c** in 75% yield, based on consumed **1c** (49%), with no other products arising from rearrangement of **4c.** By working at 0 °C, the hydroperoxide **4c** (11%) and two major products **6c** (44%) and **5c** (21%) were isolated after chromatographic separation. The structure of **6c** was confirmed by direct comparison with an authentic sample prepared by ozonization of **1c.** This compound shows an unusual UV spectrum (227, 250 sh, 285 nm) probably due to the steric hindrance of the N_a-methyl group, instead of the expected UV spectrum (232, 261, 323 nm) characteristic of formylkynurenine derivatives, such as **6a** or **6b.** Chemical evidence for the structure of **6c** was further obtained by its smooth conversion by base to 4-quinolone **13.**[17] In contrast to **4a,** the hydroperoxide **4c** rearranged neither to **6c** nor **7** in the presence of silica gel in methylene chloride but was preferentially converted to **5c.** It seems likely, therefore, that at least a major portion of **6c** obtained from the reaction conducted at 5–10 °C was not formed from **4c,** but formed via **9.** It is still not clear, however, why the introduction of an N_a-methyl group or the lower reaction temperature can produce such dramatic changes in the type of rearrangements which take place and in product distributions,[18] but similar temperature dependence has been observed in the singlet oxygen reaction of N_a-methyltryptophol.[2b]

Another characteristic reaction of **4a** is its facile acid-catalyzed rearrangement in methanol or ethanol at room temperature to give the 1,4-benzoxazine derivative **14** in high yield. Unequivocal proof of the structure of **14** was obtained by satisfactory elemental analysis and spectral properties, and by acid hydrolysis to *o*-aminophenol in 67% yield. Owing to the lack of a basic nitrogen in contrast to **10b,**[10] the first step of this rearrangement presumably involves the initial protonation on the hydroperoxy group in **4a** followed by subsequent phenyl migration analogous to the Baeyer- Villiger rearrangement.[19] Of some interest is that this rearrangement takes place under mild conditions by comparison with that of other hydroperoxides which usually need strong acid and higher temperature. More recently, Saito and Matsuura's analogous rearrangement has provided a general method for the transformation of indoles to 2,3-dihydro-1,4-benzoxazines.[2b]

The photosensitized oxygenation of tryptophan to kynurenine has been considered to proceed via formylkynurenine derived from a dioxetane intermediate such as **9.** The evidence presented herein provides an alternate pathway for formation of kynurenine and has significant implications for the biological oxidation of tryptophan.[20]

Experimental Section

Instrumental techniques, etc., were as described in the preceding paper.[8] Unless otherwise noted, electronic spectra (λ in nm) refer to solutions in 95% EtOH, and IR spectra (ν in cm^{-1}) to KBr disks.

Photosensitized Oxygenation of N_b-Methoxycarbonyltryptamine (1a). A. A solution of **1a** (1 g, 4.6 mmol) and rose bengal (450 mg, 0.46 mmol) in 50% pyridine–methanol (250 mL) was irradiated in an ice bath (about 5–10 °C, inner temperature) by a 200-W halogen lamp for 3 h, while a stream of oxygen was bubbled through the reaction vessel. The solvent was evaporated in vacuo to leave a dark-brown oil which was dissolved in methylene chloride (80 mL) and filtered through an alumina column (20 g) to remove the sensitizer. Elution with 2% methanol–methylene chloride gave an oil (1.1 g) which was chromatographed on silica gel (30 g). First elution with methylene chloride gave **7** (137 mg). Second elution with methylene chloride gave a mixture of **1a** and **7** (11 mg). Third elution with 2% methanol–methylene chloride provided **6a** (76 mg) as pale yellow crystals. Fourth elution with the same solvent gave a mixture of **5a** and **6a** (113 mg). Further elution with the same solvent gave **4a** (136 mg). The second and fourth fractions were rechromatographed on preparative TLC (silica gel–methylene chloride–acetone, 6:1), giving total yield of **5a,** 190 mg, 18%; **6a,** 101 mg, 9%; **7,** 196 mg, 17%; and recovered **1a,** 42 mg, 4%. Recrystallization of **5a** from hexane–benzene gave colorless prisms: mp 126–127 °C; UV max 242 nm (ε 8750), 298 (2390); IR 3345 (NH, OH), 1694, 1674 (NCO_2CH_3), 1620 cm^{-1} (PhNCN); NMR 2.20–2.50 (m, CH_2), 2.80–3.90 (m, CH_2N), 3.62 and 3.70 (s, NCO_2CH_3, this splitting of the signals of the two methyl protons can be ascribed to hindered rotation about the amide group. At 53 °C, the methyl proton appears as a sharp singlet at 3.64), 5.10 (s, NCHN), 6.50–6.90, 7.00–7.40 (m, aromatic H); (C_5D_5N) 2.30–2.80 (m, CH_2), 3.00–3.50, 3.50–4.10 (m, CH_2N), 3.58 (s, CO_2CH_3), 5.58 (d, J = 10 Hz, NCHN), 6.60–7.00, 7.00–7.40, 7.40–7.60 ppm (m, aromatic H); mass spectrum *m/e* (rel intensity) 234 (100) M^+, 216 (8) $M - H_2O$, 175 (13) $M - CO_2CH_3$, 147 (28), 146 (48), 132 (35).

Anal. Calcd for $C_{12}H_{14}O_3N_2$: C, 61.52; H, 6.02; N, 11.96. Found: C, 61.70; H, 6.02; N, 11.94.

6a: mp 97.5–99 °C (from hexane–benzene); UV max 231.5 nm (ε

26 040), 235 (25 180), 261 (11 950), 268 (9750), 323 (4490); IR 3290 (NH), 1740 (CO_2CH_3), 1685 (NHCHO), 1664 (PhCO), 1540 cm^{-1} (NHCO); NMR 3.27 (t, CH_2CO), 3.55 (t, CH_2N), 3.65 (s, CO_2CH_3), 5.38 (broad s, $NHCO_2CH_3$, exchangeable), 7.15 (1 H, t, J = 8 Hz, aromatic H), 7.55 (1 H, t, J = 8 Hz, aromatic H), 7.90 (1 H, d, J = 8 Hz, aromatic H), 8.48 (s, CHO), 8.70 (1 H, d, aromatic H), 11.55 ppm (broad s, NHCHO); mass spectrum *m/e* (rel intensity) 250 (13) M^+, 232 (11) M − H_2O, 175 (33), 163 (72), 146 (72), 120 (100), 92 (49).

Anal. Calcd for $C_{12}H_{14}O_4N_2$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.57; H, 5.63; N, 11.21.

7: UV max 229, 257, 364 nm; IR 3460, 3340 (NH_2), 1740 (CO_2CH_3), 1685 (CONH), 1642 cm^{-1} (PhCO); NMR 3.18 (t, CH_2CO), 3.85 (s, CO_2CH_3), 4.04 (t, CH_2N), 6.10 (broad s, NH_2, exchangeable), 6.60 (2 H, m, aromatic H), 7.21 (1, H, m, aromatic H), 7.62 (1 H, d, J = 8 Hz, aromatic H), 9.18 ppm (s, NCHO); mass spectrum *m/e* (rel intensity) 250 (60) M^+, 232 (10) M − H_2O, 147 (35), 146 (37), 120 (100), 92 (10). Picrate, mp 99.5–100.5 °C (from EtOH). Anal. Calcd for $C_{18}H_{17}O_{11}N_5$: C, 45.12; H, 3.57; N, 14.61. Found: C, 45.05; H, 3.54; N, 14.61.

B. A solution of **1a** (1 g, 4.6 mmol) in 5% pyridine–methanol (250 mL) was oxygenated at 0 °C by the method described above for 3 h. After 3 h irradiation, dimethyl sulfide (10 mL) was added and the reaction mixture was stirred for 2 h at room temperature until a starch–KI test became negative. Workup by the method described above gave **5a,** 766 mg, 71%. Trace amounts of **6a** and **1a** were detected on TLC.

C. To a solution of **1a** (1 g, 4.6 mmol) in anhydrous benzene (220 mL) was added rose bengal (50 mg) dissolved in methanol (10 mL) and the reaction was carried out as described above for 20 h at about 5–10 °C. During this period rose bengal (50 mg) in methanol (10 mL) was added every 5 h. Workup as described above gave **5a,** 209 mg, 19%; **6a,** 93 mg, 8%; dimer A, 43 mg, 4%; and dimer B, 39 mg, 4%. Dimer A: mp 223–224 °C (from benzene–hexane), colorless powder; UV max 246 nm (ϵ 25 550), 294 (4640); IR 3300, 1710, 1680 cm^{-1}; mass spectrum *m/e* (rel intensity) 466 (100) M^+, 243 (53), 233 (42), 147 (10), 146 (31).

Anal. Calcd for $C_{24}H_{26}N_4O_6 \cdot H_2O$: C, 59.49; H, 5.83; N, 11.56. Found: C, 59.63; H, 5.78; N, 11.62.

Dimer B: mp 180 °C (hexane–benzene), colorless powder; UV max 247, 295 nm; IR 3440, 1710, 1680 cm^{-1}; mass spectrum *m/e* (rel intensity) 466 (100), 234 (100), 233 (59), 147 (11), 146 (39).

Formation of β-Methoxycarbonylamino-2-aminopropiophenone (12). A. From 6a, A mixture of **6a** (360 mg, 1.4 mmol) and alumina (1 g, E. Merck Co., activity II–III) in methanol (30 mL) was refluxed for 8 h and then evaporated. Alumina column chromatography of the residue (methylene chloride as eluent) yielded **12,** 290 mg, 91%, mp 98–99 °C (from hexane–benzene), colorless prisms; UV max 229 nm (ϵ 25 800), 257 (6300), 364 (5400); IR 3425, 3320 (NH, NH_2), 1710 (CO_2CH_3), 1645, 1620, 1520 cm^{-1} (NHCO): NMR 3.17 (t, CH_2CO), 3.55 (t, CH_2N), 3.64 (s, CO_2CH_3), 5.34 (1 H, broad s, NH, exchangeable), 6.28 (2H, broad s, NH_2, exchangeable), 6.60 (2 H, m, aromatic H), 7.26 (1 H, t, J = 8 Hz, aromatic H), 7.66 ppm (1 H, d, J = 8 Hz, aromatic H); mass spectrum *m/e* (rel intensity) 222 (53) M^+, 214 (7), 147 (55), 146 (72), 120 (100), 92 (28).

Anal. Calcd for $C_{11}H_{14}O_3N_2$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.53; H, 6.33; N, 12.47.

B. From 7. N_b-Formylate **7** (24 mg, 0.1 mmol) was treated with alumina (100 mg) as in procedure A. Workup as before gave **12,** 9 mg, 42%, mp 96–98 °C, identical (TLC, IR, UV, and NMR spectroscopy) with the specimen prepared by procedure A.

Alkaline Hydrolysis of 5a. A solution of **5a** (1 g, 4.3 mmol), a 35% ethanolic solution of sodium ethoxide (20 mL), and water (2 mL) was refluxed for 5 h, evaporated, and then extracted with methylene chloride. Evaporation of the water-washed, dried (Na_2SO_4), methylene chloride extract yielded **8a** as pale yellow crystals, 740 mg, 98%, mp 173.5–175 °C (from methanol–ether or methylene chloride); UV max 243.5 nm (ϵ 8280), 301.5 (2440); UV max (95% EtOH–HCl) 236 nm (ϵ 7840), 294 (2350); IR 3380, 3260 (NH, OH), 1619 cm^{-1} (PhNCN); NMR (C_5D_5N) 2.20–2.80 (m, CH_2), 2.80–3.40 (m, CH_2N), 5.30 (broad s, NH, OH), 5.32 (s, NCHN), 6.60–7.00, 7.00–7.30, 7.50–7.70 ppm (m, aromatic H); mass spectrum *m/e* (rel intensity) 176 (100) M^+, 158 (10) M − H_2O, 149 (30), 148 (37), 147 (47), 146 (47), 133 (30), 132 (53), 130 (40).

Anal. Calcd for $C_{10}H_{12}ON_2$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.03; H, 6.86; N, 15.82.

$LiAlH_4$ Reduction of 5a. To a solution of $LiAlH_4$ (230 mg, 6 mmol) in anhydrous THF (50 mL) was added a solution of **5a** (620 mg, 2.6 mmol) in anhydrous THF (100 mL) over a period of 45 min. The mixture was further refluxed for 1.5 h, decomposed with 10% NaOH, and filtered. The filtrate was diluted with methylene chloride (300 mL) and washed with water, dried (Na_2SO_4), and evaporated to give an oil (450 mg) which was separated by preparative TLC (silica gel–methylene chloride–methanol–triethylamine, 40:3:2) into three bands (R_f 0.4, 0.5, 0.9). These were extracted separately with 20% methanol–methylene chloride to give N_b-methyltryptamine, 40 mg, 9%; **10a,** 42 mg, 8%, mp 142–148 °C (from methylene chloride), an oil, 173 mg, which was further separated by preparative TLC (silica gel–methylene chloride–acetone, 3:1) into two bands. The upper band gave **1a,** 23 mg, 4%, whereas the lower band gave an oil **11,** 40 mg, 6% upon extraction with 25% acetone–methylene chloride: UV max 251, 292 nm; mass spectrum *m/e* 218 M − H_2O, other fragments are similar to those of **1a; 11** was converted to **1a** upon addition of dilute HCl in ethanol, confirmed by TLC and UV spectrum.

Isolation of 1-Methoxycarbonyl-3a-hydroperoxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (4a). A solution of **1a** (300 mg, 1.4 mmol) and rose bengal (150 mg, 0.15 mmol) in 5% pyridine–methanol (150 mL) was cooled in an ice–salt bath and irradiated for 1.5 h as above; TLC (alumina–*i*-Pr_2O) of the reaction mixture showed a new spot (R_f 0.5) together with that of **5a** (trace). The solvent was evaporated in vacuo at room temperature. The residue (480 mg) dissolved in methylene chloride (20 mL) was filtered through alumina (12 g) to remove the sensitizer. Elutions with methylene chloride and 2% methanol–methylene chloride were evaporated to give an oily residue which was purified by preparative TLC alumina–*i*-Pr_2O). The main band corresponding to R_f 0.4 was collected and extracted with 20% methanol–methylene chloride to yield **4a** as a calamel, which TLC indicated to be a single component, 140 mg, 41%, along with **5a,** 23 mg, 7%; **6a,** 14 mg, 4%; and **7,** 6 mg, 1.7%. **4a:** starch–KI test positive; UV max 244, 305 nm; IR 3400 (NH, OH), 1690 cm^{-1} (C=O); NMR 2.10–2.80 (m, CH_2), 3.00–3.40, 3.40–4.00 (m, CH_2N), 3.68 (s, CO_2CH_3), 4.80 (broad s, OOH or NH, exchangeable), 5.10 (broad s, OOH, or NH, exchangeable), 5.62 (s, NCHN), 6.40–6.90, 7.00–7.40 ppm (m, aromatic H); mass spectrum *m/e* (rel intensity) 250 (35) M^+, 234 (58) M − O, 233 (17) M − OH, 232 (100) M − H_2O, 146 (55), 130 (25), 120 (45).

NaBH Reduction of 4a to 5a. To a stirred solution of **4a** (110 mg, 0.44 mmol) in methanol (15 mL) was added $NaBH_4$ (130 mg, 3.4 mmol). The mixture was stirred for 30 min, diluted with water (20 mL), evaporated, and extracted with methylene chloride. Evaporation of the water-washed, dried (Na_2SO_4), methylene chloride extract gave **5a,** 97 mg, 94%, mp 123–125 °C (from benzene–hexane), identical (TLC, UV, IR) with the sample obtained by direct photosensitized oxygenation of **1a** as described above.

Transformation of 4a to 5a, 6a, and 7. A. Silica Gel–CH_2Cl_2. The hydroperoxide **4a** (70 mg) was dissolved in a small amount of methylene chloride and put on a silica gel column (3 g) prepared in methylene chloride. The mixture was left for 14 h and eluted with methylene chloride to afford **7,** 31 mg, 44%; **6a,** 12 mg, 17%; and **5a,** 12 mg, 18%.

B. Reflux in Benzene. A solution of **4a** (120 mg, 0.48 mmol) in dry benzene (10 mL) was refluxed for 14 h until a starch–KI test became negative, and then evaporated to leave an oil (116 mg) which was chromatographed on silica gel (5 g) prepared in methylene chloride. Elution with methylene chloride gave **7,** 29 mg, 24%; **6a,** 15 mg, 13%; **5a,** 11 mg, 10%.

Acid-Catalyzed Rearrangement of 4a to 14. A. Formation of 14a, A solution of **4a** (90 mg, 0.36 mmol) in methanol (50 mL) was acidified with 10% HCl to pH 2–3. Stirring was continued for an additional 10 min, and then the mixture was poured into saturated brine and extracted with methylene chloride. Evaporation of the water-washed, dried (Na_2SO_4) methylene chloride extract yielded **11a** as pale yellow crystals, 84 mg, 88%, which showed one spot on TLC. Recrystallizations from methanol gave colorless prisms: mp 202–203 °C; UV max 242 nm (ϵ 9080), 292 (3900); IR 3410 (NH), 1705 (CO), 1622 cm^{-1}; NMR 1.80–2.20, 2.82–2.60 (m, CH_2), 3.30–3.90 (m, CH_2N), 3.42 (s, OCH_3), 3.68 (s, CO_2CH_3), 5.00 (d, J = 4 Hz, NCHN), 5.21 (broad s, NH, exchangeable), 6.50–7.00 ppm (aromatic H); mass spectrum *m/e* (rel intensity) 264 (100) M^+, 249 (39), 232 (58), 157 (75), 149 (40), 142 (49).

Anal. Calcd for $C_{13}H_{10}O_4N_2$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.17; H, 6.05; N, 10.44.

A solution of **14a** (104 mg) in methanol (8 mL) containing 2 N H_2SO_4 (4 mL) was refluxed for 2 h under a stream of nitrogen. The reaction was basified with 10% NaOH to pH 8, evaporated, and extracted with methylene chloride. Evaporation of the water-washed, dried (Na_2SO_4) methylene chloride extract yielded crude *o*-aminophenol, mp 162–169 °C (from benzene), identical (IR, UV, mass spectrum, mixture melting point) with an authentic specimen.

B. Formation of 14b. A solution of **4a** (108 mg, 0.4 mmol) in ethanol (50 mL) was treated as above. The similar workup produced **14b,** 98 mg, 88%, colorless prisms, mp 163–164 °C (from ethanol–ether): UV max 242, 292 nm; IR 3390 (NH), 1690 (CO_2CH_3), 1610 cm^{-1}; NMR 1.13 (t, CH_3), 1.85–2.55 (m, CH_2), 3.30–4.00 (m, OCH_2, NCH_2), 3.68 (s, CO_2CH_3), 5.00 (d, J = 4 Hz, NCHN), 5.20 (broad s, NH, exchangeable), 6.50–7.00 ppm (m, aromatic H); mass spectrum *m/e* (rel intensity) 278 (65) M^+, 250 (15), 249 (38), 232 (11), 171 (58), 170 (51), 142 (100).

Photosensitized Oxygenation of N_b-Methoxycarbonyl-N_b-methyltryptamine (1b). A solution of **1b** (1 g, 4.3 mmol) and rose bengal (450 mg, 0.46 mmol) in 5% pyridine–methanol (250 mL) was irradiated by the same method as described in case of **1a** (A); TLC showed only two spots corresponding to **6b** and **1b** after 3 h. Workup in the usual way provided **6b,** 493 mg, 43%. Recrystallization from benzene–hexane gave colorless prisms, mp 103–104 °C: UV max 231 nm (ϵ 25 500), 236 (25 000), 261 (11 700), 268 (9900), 323 (4430); IR 3215 (NH), 1710 sh, 1690, 1660 cm^{-1} (CO); NMR 2.94 (s, NCH_3), 3.10–3.45 (m, CH_2CO), 3.45–3.80 (m, CH_2N), 3.66 (s, NCO_2CH_3), 7.14 (1 H, t, J = 8 Hz, aromatic H), 7.54 (1 H, t, J = 8 Hz, aromatic H), 7.91 (1 H, d, J = 8 Hz, aromatic H), 8.44 (s, NCHO), 8.68 (1 H, d, J = 8 Hz, aromatic H), 11.44 ppm (broad s, NH, exchangeable); mass spectrum *m/e* (rel intensity) 264 (17) M^+, 246 (33) M − H_2O, 175 (39), 174 (39), 162 (39), 148 (53), 146 (48), 120 (30), 102 (100), $CH_2{=}N^+(CH_3)CO_2CH_3$.

Anal. Calcd for $C_{13}H_{16}O_4N_2$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.15; H, 6.13; N, 10.79.

Photosensitized Oxygenation of N_b-Methoxycarbonyl-N_a-methyltryptamine (1c). A. A solution of **1c** (1 g, 4.3 mmol) and rose bengal (450 mg) in 5% pyridine–methanol (250 mL) was irradiated in the above manner with an ice-bath cooling; TLC (silica gel–methylene chloride–acetone, 8:1) showed four spots corresponding to **1c** (R_f 0.8), **4c** (0.7), **5c** (0.5), **6c** (0.4). The solvent was evaporated in vacuo at room temperature to leave a residual oil (1.6 g) which was dissolved in methylene chloride and filtered through alumina (15 g). Elution with 2% methanol–methylene chloride provided an oil (1.2 g) which was chromatographed over silica gel (30 g). Elution with methylene chloride gave **1c,** 28 mg, 3%; and **5c,** 105 mg. Elution with 2% methanol–methylene chloride gave a mixture of **5c** and **6c** (155 mg) which was separated by preparative TLC (silica gel–methylene chloride–acetone, 4:1) to give **5c,** 44 mg; **6c,** 83 mg. Further elution with the same solvent yielded **6c,** 411 mg. Total yield: **5c** as a chromatographically homogeneous oil, 149 mg, 14%; and **6c,** 494 mg, chromatographically homogeneous oil, 43%. **5c:** UV max 251,300 nm; IR 3400 (OH), 1700 sh, 1680 (CO), 1605 cm^{-1}; NMR 2.00–2.50 (m, CH_2), 2.50–3.50, 3.50–4.10 (m, CH_2N), 2.92 (s, NCH_3), 3.70 (s, CO_2CH_3), 5.17 (s, NCHN), 6.40 (1 H, d, J = 8 Hz, aromatic H), 6.68 (1 H, t, J = 8 Hz, aromatic H), 7.15 (1, H, t, J = 8 Hz, aromatic H), 7.18 (1 H, d, J = 8 Hz, aromatic H) mass spectrum *m/e* (rel intensity) 248 (100) M^+, 230 (5) M − H_2O, 160 (27), 146 (80). **6c:** UV max 227, 250 sh, 285 nm; IR ($CDCl_3$) 3450 (NH), 1710 1705 sh, 1678 cm^{-1} (CO); NMR 3.10 (m, CH_2) 3.20 and 3.38 (s, NCH_3), 3.50 (m, CH_2N), 3.64 (s, CO_2CH_3), 5.44 (broad s, NH, exchangeable), 7.10–7.80 (m, aromatic H), 8.05, 8.07 ppm (s, NCHO); mass spectrum *m/e* (rel intensity) 264 (6) M^+, 246 (16) M − H_2O, 236 (10) M − CO, 171 (44), 162 (52), 134 (100), 120 (6).

B. A solution of **1c** (430 mg, 1.9 mmol) in 5% pyridine–methanol (400 mL) was irradiated as above at −70 °C for 7 h. To a part of the reaction mixture (300 mL) was added dimethyl sulfide (2.5 mL). The mixture was stirred for 2 h. The usual workup produced **5c,** 141 mg, 41% (91% yield based on the recovered **1c**), and **1c,** 177 mg, 55%, was recovered. The rest of the above reaction mixture (100 mL) was left for 5 days at room temperature; no appreciable change was observed after 5 days, showing only two spots corresponding to **4c** and **5c** along with that of **1c.** The mixture was then treated with dimethyl sulfide (1 mL) as above, giving **5c,** 42 mg, 37% (75% yield based on the recovered **1c**), and recovered **1c** 55 mg, 51%.

Hydrolysis of **5c** (100 mg, 0.4 mmol) in a similar way provided **8c,** 31 mg, 40% mp 126–128 °C (from hexane–benzene): UV max 253, 308 nm; UV max (95% EtOH–HCl) 244, 300 nm; IR 3240 (OH, NH), 1605 cm^{-1}; NMR 2.00–2.40 (m, CH_2), 2.40–3.30 (m, CH_2N), 2.58 (s, NH or OH, exchangeable), 275 (s, NCH_3), 4.48 (s, NCHN), 6.34 (1 H, d, J = 8 Hz, aromatic H), 6.64 (1 H, t, J = 8 Hz, aromatic H),7.12 (1 H, t, J = 8 Hz, aromatic H), 7.20 (1 H, d, J = 8 Hz, aromatic H); mass spectrum *m/e* (rel intensity) 190 (100) M^+, 172 (18) M − H_2O, 161 (25), 160 (37), 146 (74), 132 (32).

Isolation of 3a-Hydroperoxy-1-methoxycarbonyl-8-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (4c). A. A solution of **1c** (400 mg, 1.7 mmol) and rose bengal (200 mg) in 5% pyridine–methanol (400 mL)was irradiated with a 500-W halogen lamp for 8 h at −70 °C through an aqueous $CuCl_2$–$CaCl_2$ filter solution; TLC (silica gel–methylene chloride–acetone, 6:1) showed three spots corresponding to **1c** (R_f 0.9), **4c** (0.7), and **5c** (0.5). No spot corresponding to **6c** was detected. The reaction mixture was left for 12 h at room temperature (TLC, no appreciable change observed during this period) and then irradiated further for 6 h. The solvent was evaporated at about 20 °C in vacuo to give a residue which was dissolved in methylene chloride and filtered through alumina. Elution with 3% methanol–methylene chloride gave an oily residue (460 mg) which was separated by preparative TLC (silica gel–methylene chloride–acetone, 8:1). Extraction with 20% methanol–methylene chloride afforded **4c,** 34 mg, 7.5%; **5c,** 74 mg, 17%; and recovered **1c,** 239 mg, 60%. **4c:** starch–KI test positive; UV max 253, 310 nm; UV max (95% EtOH–HCl) 249, 295 nm; NMR 2.00–2.60 (m, CH_2), 2.90–4.10 (m, CH_2N), 3.00 (s, NCH_3), 3.75, 3.77 (s, CO_2CH_3), 5.25 (s, OOH), 5.64 (s, NCHN), 6.48 (1 H, d, J = 8 Hz, aromatic H), 6.74 (1 H, t, J = 8 Hz, aromatic H), 7.00–7.50 (m, aromatic H); mass spectrum *m/e* (rel intensity) 264 (28) M^+, 248 (97) M − O, 247 (7) M − OH, 246 (7) M − H_2O, 160 (54), 146 (100), 134 (38).

B. A solution of **1c** (320 mg, 1.4 mmol) was oxygenated in an ice–salt bath (inner temperature about 0 °C) as in the case of **1a.** Workup in a similar way as described in isolation of **4a** except using silica gel preparative TLC instead of alumina provided **4c,** 39 mg, 11%; **5c,** 71 mg, 21%; and **6c,** 161 mg, 44%.

Ozonization of 1. A. A solution of **1a** (2 g, 9.2 mmol) in absolute methanol (150 mL) was ozonized at −70 °C for 1 h. The mixture was reduced with dimethyl sulfide (1.5 mL) and left for 20 h at room temperature. The usual workup produced **6a,** 818 mg, 36%, colorless needles, mp 97.5–99 °C (from hexane–benzene), identical (TLC, UV, IR, mixture melting point) with the previously described sample.

B. A solution of **1c** (1 g, 4.3 mmol) in absolute methanol (100 mL) was ozonized as above to give **6c** as an oil, 840 mg, 74%, identical (TLC, UV, IR, NMR, mass spectrum) with the sample obtained by photosensitized oxygenation of **1c.**

Formation of 13. A solution of **6c** (434 mg, 1.6 mmol) in methanol (50 mL) was stirred and basified to pH 10 with 10% NaOH. Stirring was continued for 2 h, and then the solution was neutralized with 10% HCl and evaporated. The residue was extracted with methylene chloride. Evaporation of the water-washed, dried (Na_2SO_4), methylene chloride extract yielded **13,** 337 mg, 83%, mp 200–201.5 °C (from methanol): UV max 244 nm (ϵ 25 600), 283 sh (2650), 291 (3850), 327 (13 500), 340 (14 400); IR 3240 (NH), 1720 (NCO_2CH_3), 1640 (CO), 1550, 1540 cm^{-1} (NHCO); NMR (CF_3CO_2H) 3.92 (s, CO_2CH_3), 4.44 (s, NCH_3), 466 (s, CH_2), 6.70 (broad s, NH, exchangeable), 7.80–8.40, 8.50–8.90 ppm (m, aromatic H); mass spectrum *m/e* (rel intensity) 246 (55), 188 (14), 187 (100) M − CO_2CH_3.

Anal. Calcd for $C_{13}H_{14}O_3N_2$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.24; H, 5.76; N, 11.22.

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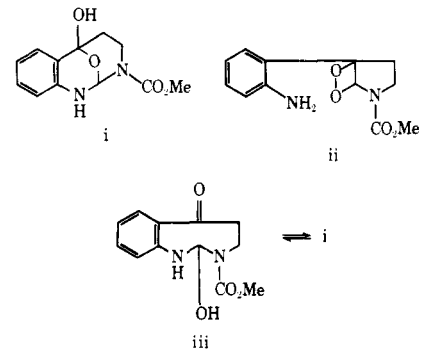

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Reaction Pathways in the Formation of the 1,3,5-Trinitrobenzene–Anilide σ Complex from Aniline and the 1,3,5-Trinitrobenzene–Methoxide σ Complex

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Abstract: The reversible reaction between the 1,3,5-trinitrobenzene-methoxide σ complex (TNB·OMe^-K^+) and aniline in dimethyl sulfoxide-methanol solutions, yielding the 1,3,5-trinitrobenzene-anilide σ complex (TNB·$NHPh^-K^+$), has been studied spectrophotometrically and found to obey a rate law which is of first order with respect to aniline, but of complex order with respect to TNB·OMe^-K^+. An additional feature of this system is that whereas TNB and aniline alone undergo no reaction in Me_2SO–methanol, in the presence of methoxide ion a rapid reaction occurs to give the TNB·OMe^- complex, which then undergoes a slow reversible conversion to the TNB·$NHPh^-$ complex. In both cases the kinetic data for the conversion of the methoxide complex (S) to the anilide complex (P) require a dissociative mechanism (Scheme IV) in which the interconversion of free TNB (I) and the protonated anilide complex (PH) constitutes the rate-determining step. Although the kinetic data do not rule against the intermediacy of the protonated methoxide complex (SH), the presence of this intermediate along the reaction pathway is considered unlikely. Further variations on the proposed dissociation mechanism (Scheme II), as well as displacement mechanisms (Scheme I) and a mechanism involving anilide ion (Scheme III), can be eliminated on kinetic grounds (cf. Table V and Figure 3). On the basis of the results of the present study, it is proposed that the lack of σ-complex formation between TNB and aniline in the absence of strong base is due to a thermodynamic, rather than kinetic, factor.

The σ complexes formed between polynitro aromatic compounds and bases[1-7] have been used as models of the reaction intermediates which are considered to be formed in activated nucleophilic aromatic substitution reactions.[8,9] Aliphatic primary and secondary amines have played a central role in such studies of S_NAr processes,[10-16] since they offer the possibility of base catalysis in the deprotonation of the initially formed zwitterionic intermediates (eq 1) and thereby provide kinetic evidence of the existence of such species.

Recent studies in this area have focused on the stable σ complexes formed between a number of nitroaromatic compounds and primary or secondary aliphatic amines, and on the catalytic processes involved in their formation and decomposition.[16-18] Such studies have led to a reconsideration of current