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# Photooxidation of 2,2'-Indolylindolines to 2,2'-Biindoles: Mild Formation of Ditryptophan Crosslinks

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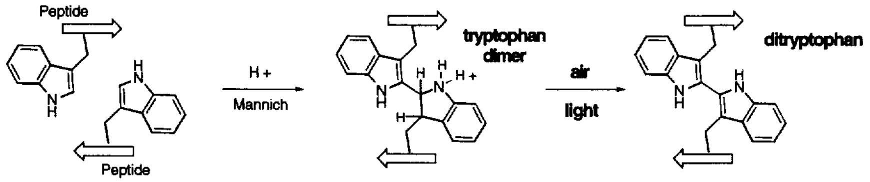
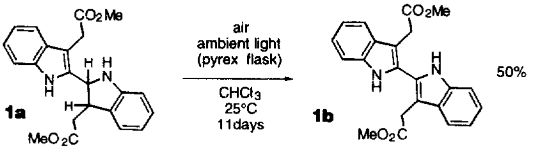
**Abstract**: 2,2'-Indolylindolines undergo facile photooxidation to form symmetrical fluorescent 2,2'-biindoles. The reaction proceeds slowly in air under ambient light, but direct irradiation facilitates the reaction. Peptide and *N*-glycosylated substrates are compatible with this mild photooxidation. Copyright © 1996 Elsevier Science Ltd

The formation of ditryptophan crosslinks between tryptophan sidechains is a new alternative to disulfides in the area of peptide chemistry.[1] The Mannich dimerization of tryptophan sidechains is easily achieved by stirring tryptophan-containing peptides in anhydrous acid.[2-4] In an effort to expand the compatibility of this transformation with proteins, and strengthen the analogy to cysteine disulfides, we have investigated the oxidation of 2,2'-indolylindolines to 2,2'-biindoles using air and light. The conditions for this photooxidation are mild and may also be relevant to the biosynthetic pathways leading to the formation of indolo[2,3-a]carbazole glycoside natural products.[5]



(1)

Preliminary screening of conditions for aromatization of tryptophan dimers to form ditryptophan crosslinks showed DDQ to be superior to other common conditions such as Pd-C/oxygen and nickel peroxide. However, during these investigations it was observed that solutions of tryptophan dimers were undergoing spontaneous oxidation to form the desired ditryptophans. In Shimonishi's original work on tryptophan dimers, chromatography was conducted using brown glass columns.[4] While no rationale was given for this experimental precaution, it is seems likely that this was to prevent the oxidation which serves as the theme of this paper. Because of our interest in ditryptophan chromophores, we undertook an investigation of this photooxidation to determine the parameters which are important for this reaction.



(2)

Our initial investigations were carried out utilizing **1a** as a model compound (Table 1).[6] The photooxidation is sluggish under ambient light, affording only 50% conversion after 11 days (entry 1). However, irradiation with a 150W bulb effects complete conversion (62% isolated yield) after only 20 h. Under these conditions, the temperature of the reaction was between 35 and 40°C. If light or air are excluded, no reaction is observed. The isolated yield increased from 62% to 70% by going to dilute conditions (2.6 mM), however further dilution (<0.26 mM) did not lead to an improvement in yield. Peroxides are detected in increasing amounts as the reaction progresses, although the nature and stoichiometry of these peroxides is unclear.

**Table 1**. Photooxidation of **1a** in Chloroform (Eq. 2)

| Entry | Conditions | Conc. (mM) | Time (h) | Yield |
|---|---|---|---|---|
| 1 | air, ambient light (pyrex) | 100 | 264 | 50% |
| 2 | air, 150W bulb (pyrex) | 100 | 12 | 62% |
| 3 | air, dark | 100 | 264 | 0% |
| 4 | N2, 150W bulb (pyrex) | 100 | 144 | 0% |
| 5 | air, 150W bulb (pyrex) | 2.6 | 20 | 70% |
| 6 | air, 150W bulb (pyrex) | 0.26 | 24 | 24% |

Solvent is an important parameter in this reaction as shown in Table 2. Chlorinated solvents are most effective, but are not essential (entries 1-3 and 9). In contrast to other solvents, photooxidations in dichloromethane remain colorless throughout the course of the reaction. The low yield in carbon tetrachloride was due primarily to excessive side reactions. THF can serve as a minor cosolvent in the photooxidation, however when THF was used as the sole solvent, no oxidation was observed over 24 h (entries 4 and 6). Thus, peroxides derived from THF are not implicated as the oxidizing species. Even as a minor cosolvent, methanol seems to shut down the reaction (entries 5 and 7).

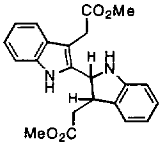
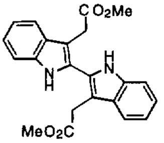
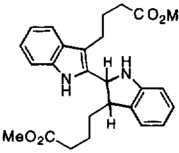
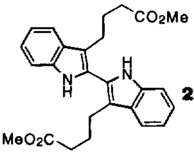
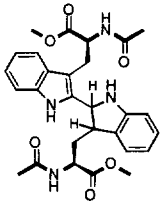
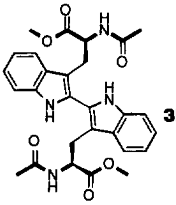
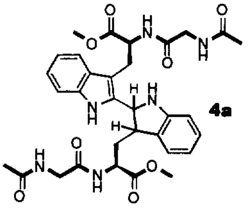
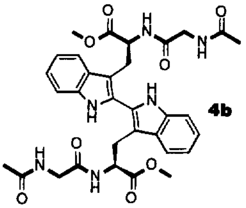
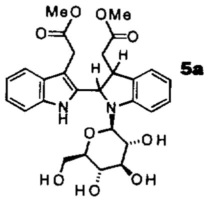
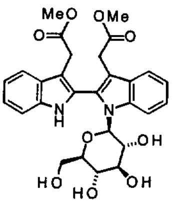
**Table 2**. Solvent Effects in the Oxidation of **1a** to **1b***

| Entry | Solvent | Time (h) | Yield |
|---|---|---|---|
| 1 | $CH_2Cl_2$ | 12 | 78% |
| 2 | $CHCl_3$ | 20 | 70% |
| 3 | $CCl_4$ | 10 | 30% |
| 4 | THF | 24 | 0% |
| 5 | $CH_3OH$ | 24 | 0% |
| 6 | THF/$CH_2Cl_2$ (1:9) | 24 | 90% |
| 7 | $CH_3OH$/$CH_2Cl_2$ (1:9) | 24 | 0% |
| 8 | $CH_3CN$ | 24 | 0% |
| 9 | $C_6H_6$ | 240 | 25% |
| 10 | ethyl acetate | 24 | 0% |
| 11 | acetone | 24 | 0% |

*2.6 mM **1a**, 150W light bulb, pyrex flask, 25-40°C

The indole moiety seems to be an important element for this reaction. Indoline itself does not undergo photooxidation using the best conditions (Table 2, entry 6).[7] Since the photosensitized oxidation of amines is a well known reaction, it is possible that the fluorescent biindolyl products are playing the role of sensitizer in the reaction mechanism, although this must await further study.[8-11] To further probe the substrate compatibility, a number of 2,2'-indolylindoline substrates were subjected to photooxidation (Table 3). The dimeric substrates were prepared by stirring the corresponding monomers in trifluoroacetic acid. The oxidation was carried out by stirring a 2.6 mM solution of the 2,2'-indolylindoline in 9:1 dichloromethane/THF in a pyrex flask open to air under direct irradiation from a 150W incandescent bulb. These photooxidation reactions appear clean by thin layer chromatography, thus, the balance of the starting material is being converted to oligomeric or highly polar materials. These conditions are extremely mild, and are compatible with both peptide and non-peptide systems. Interestingly, the reaction still works when the indoline nitrogen is *N*-glycosylated, although the reaction is sluggish and the yield is slightly lower.[12] The resultant bisindole *N*-glucoside **5b** is structurally related to the antitumor antibiotic rebeccamycin.

**Table 3.** Photooxidation of Indolylindolines[13]

| STARTING MATERIAL | PRODUCT | YIELD |
|---|---|---|
|  **1a** |  **1b** | $90\%^{a}$ |
|  **2a** |  **2b** | $48\%^{b}$ |
|  **3a** |  **3b** | $84\%^{a}$ |
|  **4a** |  **4b** | $58\%^{a}$ |
|  **5a** |  **5b** | $25\%^{a}$ |

[a] Isolated by silica gel chromatography, [b] Isolated by crystallization

In summary, 2,2'-indolylindolines undergo facile photooxidation to form symmetrical fluorescent 2,2'-biindoles. The reaction proceeds slowly in air under ambient light, but direct irradiation facilitates the reaction. The facility of this transformation is consistent with the notion that $\delta_1$, $\delta_1$'-ditryptophan formation is possible in proteins under bioologically relevant conditions.

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13. Characterization data for new compounds: (a) **2a**, IR (neat) 3040, 2950, 2860, 1720. 1610 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 8.14 (s, 2H), 7.56 (d, *J*=7.5 Hz, 2H), 7.25 (d, *J*=7.4 Hz, 2H), 7.17-7.08 (m, 8H), 6.83 (t, *J*=7.3 Hz, 2H) 6.69 (d, *J*=7.7 Hz, 2H), 4.83 (d, *J*=8.3 Hz, 2H), 4.24 (s, 2H), 3.63 (s, 6H), 3.56 (s, 6H), 3.31-3.39 (m, 2H), 2.85-2.73 (m, 4H), 2.37 (t, *J*=7.1 Hz, 4H), 2.31 (t, *J*=6.8 Hz, 4H), 2.22-1.96 (m, 8H); $^{13}$C NMR ($CDCl_3$) δ 174.0, 173.7, 149.9, 135.9, 135.5, 130.7, 128.8, 127.9, 124.0, 121.9, 119.1, 118.7, 111.9, 110.8, 109.3, 60.6, 51.4, 51.3, 49.3, 34.0, 33.6, 32.1, 25.9, 23.3, 21.9; MS (CI) 434(100), 347(17), 333(36), 218(19), 186(14), 130(17); HRMS Calcd 434.2205, Found 434.2222; Anal. Calcd for $C_{26}H_{30}N_2O_4$, C, 71.87; H, 6.96; N, 6.45. Found: C, 71.06; H, 7.03; N, 6.42. (b) **2b**, mp 181-182°C (EtOAc/ hexane); IR ($CHCl_3$) 3389, 2945, 1720 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 9.63 (s, 2H), 7.61 (d, *J*=8.1 Hz, 4H), 7.23 (t, *J*=7.5 Hz, 2H), 7.14 (t, *J*=7.3 Hz, 2H), 3.73 (s, 6H), 2.99 (dd, *J*=11.0, 8.3 Hz, 4H), 2.53 (t, *J*=5.5 Hz, 4H), 2.13 (m, 2H); $^{13}$C NMR ($CDCl_3$) δ 175.4, 135.6, 128.2, 126.9, 122.2, 119.3, 118.4, 113.2, 111.5, 51.8, 32.8, 35.7, 24.3; MS (CI) 432(100), 354(20), 257(8), 131(6); HRMS Calcd 432.2049, Found 432.2033; Anal. Calcd for $C_{26}N_{28}N_2O_4$, C, 72.19; H, 6.43; N, 4.48. Found C, 72.30; H, 6.50; N, 6.46. (c) **4b**, mp 238-239°C ($CH_3CN$/EtOAc); IR ($CHCl_3$) 3420, 3340, 2952, 1735, 1655 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 11.4 (s, 2H), 8.21 (d, *J*=7.5 Hz, 2H), 7.95 (t, *J*= 5.8 Hz, 2H), 7.59 (d, *J*= 7.7 Hz, 2H), 7.38 (d, *J*=8.1 Hz, 2H), 7.14 (t, *J*=7.2 Hz, 2H), 7.05 (t, *J*=7.3 Hz, 2H), 4.52 (dd, *J*=13.7, 8.2 Hz, 2H), 3.59 (dd, *J*=16.8, 5.9 Hz, 2H), 3.55 (dd, *J*=16.8, 5.8Hz, 2H), 3.20 (dd, *J*=14.3, 6.6Hz, 2H), 3.10 (dd, *J*=14.3, 6.6Hz, 2H), 3.33 (s, 6H), 1.80 (s, 6H); $^{13}$C NMR ($CDCl_3/CD_3OD$ 9:1) δ 171.9, 169.5, 168.9, 136.3, 128.3, 127.9, 127.7, 121.7, 118.9, 118.6, 111.4, 52.9, 51.66, 41.5, 27.4, 22.4; MS (FAB+) 633(89), 534(52), 457(18), 445(100), 329(14), 269(52), 257(56), 245(20); HRMS (FAB+) Calcd 632.2594, Found 633.2662; Anal. Calcd for $C_{32}H_{36}N_6O_8$, C, 60.75; H, 5.74; H, 13.29. Found: C, 60.74; H, 5.79; N, 12.97.

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