Oxidative Formation of a Blue Pigment from a Dihydropyrrolo[2,1-*a*]-isoquinolin-3(2*H*)-one Derivative

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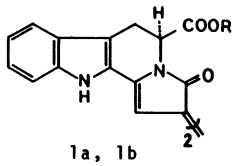
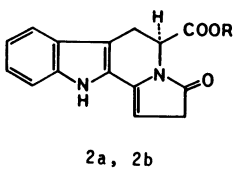
Synopsis. A dimeric blue pigment was formed by the autoxidation of a dihydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one derivative.

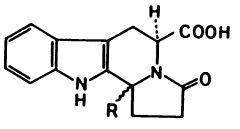
A blue pigment, trichotomine (**1a**, R=H), was isolated from *Clerodendron trichotomum* Thunb.[1] It was suggested that the biosynthesis of **1a** involved an oxidative dimerization of **2a** (R=H) formed from L-tryptophan and 2-oxoglutaric acid.[1,2] In the synthesis of **1a**, **1b** (R=Me) was obtained by the autoxidation of **2b** (R=Me).[3] We examined the extracts of the above plant, and isolated **3a** (R=α-H), **3b** (R=β-H), **3c** (R=α-COOH), and **3d** (R=β-COOH), which were other plausible precursors of **1a**.[4] Kapadia et al. reported the isolation of **4a** (R=H) and **4b** (R=Me); these formations were proposed to result from the condensation of 2-oxoglutaric acid with 3-demethylmescaline and mescaline, respectively.[2,5] The biosynthesis of **1a** caused us to anticipate the occurrence of natural dimeric pigments derived from such compounds as **4a,b**. In this paper, we wish to report on the oxidative dimerization of a dihydropyrrolo[2,1-*a*-]isoquinolin-3(2*H*)-one derivative **5** as a model compound.



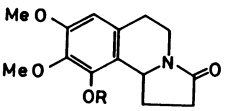
1a, 1b



2a, 2b



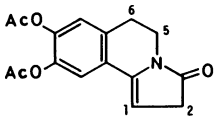
3a–3d



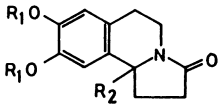
4a, 4b

The known compound, **6**[6], prepared from dopamine hydrochloride and 2-oxoglutaric acid, was acetylated with acetic anhydride and pyridine to an acetate **7**. Upon electrolysis in methanol containing $(n\text{-Bu})_4NCl$ as a supporting electrolyte, **7** underwent decarboxylative methoxylation[7] to a methoxy lactam **8**. The ^1H NMR spectrum of **8** showed a singlet (δ=3.16) of the methoxyl group on C-10b and an octet (δ=4.18) of the equatorial C_5-proton deshielded by the carbonyl group at C-3.[8] On electrolysis in methanol containing Et_4NOTs as an electrolyte, **7** yielded **8** and a methoxy α,β-unsaturated lactam **9** in a ratio of 5:2. The structure of **9** was in line with the ^1H NMR spectrum [a singlet at δ=3.17 (OCH_3), two doublets at δ=6.23 (C_2–H) and 7.13 (C_1–H), and a characteristic octet at δ=4.29 (equatorial C_5–H)]; **9** seemed to be formed via an intermediate **5**. Using a large excess of lead tetraacetate in the presence of methanol, **9** was also obtained from **7**; **9** may be similarly formed by an oxidative decarboxylation of **7** to **5**, followed by further oxidation. Upon heating at 85—90 °C for 7 h, **8** was converted to a β,γ-unsaturated lactam **5** after a loss of methanol [^1H NMR δ=3.25 (d, J=2.9 Hz, C_2–2H) and 5.57 (t, J=2.9 Hz, C_1–H)].

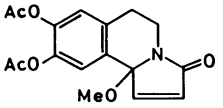
The oxidative dimerization of **5** was achieved by heating a solution of **5** in 1,1,2,2-tetrachloroethane under an oxygen atmosphere at 123—127 °C for 3 h to give a blue pigment **10**. The described structure of **10** is in agreement with the spectral data; UV 634 nm, SIMS m/z 599 $(M+H)^+$, ^1H NMR δ=3.04 (t, J=6.4 Hz, C_6–2H×2) and 3.83 (t, J=6.4 Hz, C_5–2H×2). Under similar conditions to those used for **5**, **9** also afforded **10**, which might be formed by an initial homolytic fission of the C_{10b}-oxygen bond in **9**, followed by coupling at C-2 of the resulting allylic radical **11** and dehydrogenation. The coloration of **5** and **9** upon heating at their melting points was due to the formation of **10**, respectively, as confirmed by the TLC R_f values.



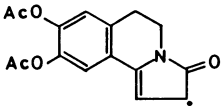
5



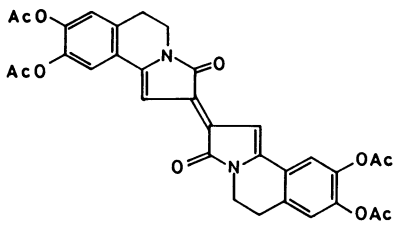
6 R_1=H R_2=COOH
7 R_1=Ac R_2=COOH
8 R_1=Ac R_2=OMe



9



11



10

The formation of **10** from **5** may also proceed via **11**; this is another type of well-known oxidative dimerization of indoxyl to indigo.[9]

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi EPI-G$_3$ using Nujol. ^{1}H NMR spectra were obtained on a JNM-GSX-400 (400 MHz) and ^{13}C NMR spectra on a JNM-PFT-60 (15 MHz) or a JNM-GSX-400 (100 MHz). UV spectra were measured on a JASCO-UVIDEC-510. Mass spectra were obtained on a Hitach M-52 or M-80 mass spectrometer at an ionization energy of 70 eV. Analytical TLC was carried out on silica-gel plates (Kieselgel 60 F_{254}, E. Merk).

Preparation of 7. According to the literature,[6] a solution of dopamine hydrochloride (5.70 g) and 2-oxoglutaric acid (5.84 g) in water (50 ml) was refluxed for 9 h, and cooled to room temperature to give **6** (4.03 g, 51%). A solution of **6** (2.26 g) in acetic anhydride (20 ml) and pyridine (20 ml) was allowed to stand at 20 °C for 23 h, and concentrated under reduced pressure. The residue was crystallized from $CHCl_3$–CH_3OH to afford **7** (2.77 g, 93%); mp (in a sealed tube) 239—241 °C; UV (CH_3OH) 205 (ε 28400), 269 (1150), and 275 nm (1150); IR 1760, 1720, and 1632 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=2.06 (1H, m), 2.26 (3H, s), 2.27 (3H, s), 2.30—2.50 (2H, m), 2.77—2.88 (3H, m), 3.22 (1H, m), 4.02 (1H, ddd, J=12.9, 5.5, and 4.0 Hz), 7.10 (1H, s), and 7.31 (1H, s); ^{13}C NMR (DMSO-d_6) δ=20.1, 26.8, 30.0, 32.1, 35.1, 66.1, 121.5, 123.2, 132.2, 134.6, 140.3, 141.1, 168.0, 172.1, and 173.2. Anal. ($C_{17}H_{17}NO_7$) C, H, N.

Anodic Oxidation of 7. 1) A mixture of **7** (150 mg, 0.43 mmol), (n-Bu)$_4$NCl (0.50 g), and CH_3OH (50 ml) was placed in a beaker-type undivided cell, and glassy carbon rods were used as an anode and a cathode, respectively.[10] After ca. 3.6 F mol^{-1} (1F=96480 C) of electicity (the voltage between the anode and cathode=2.1 V), the electrolytic solution was concentrated under reduced pressure to give a residue which was dissolved in benzene (80 ml). The solution was washed with water, and brine, and then dried over Na_2SO_4. Evaporation of the solvent and crystallization from CH_3OH gave **8** (67 mg, 47%); UV (CH_3OH) 205 (ε 26400), 268 (1220), and 274 nm (1230); IR 1780 and 1701 cm^{-1}; ^{1}H NMR (CD_3OD) δ=2.21 (1H, m), 2.26 (3H, s), 2.27 (3H, s), 2.42 (1H, m), 2.63—2.90 (4H, m), 3.16 (3H, s), 3.23 (1H, dddd, J=13.0, 10.0, 6.2, and 1.1 Hz), 4.18 (1H, ddd, J=13.0, 5.5, and 3.3 Hz), 7.08 (1H, s), and 7.27 (1H, s); ^{13}C NMR ($CDCl_3$) δ=20.6, 28.1, 30.7, 32.3, 35.2, 50.5, 90.7, 121.2, 123.5, 132.8, 135.8, 141.1, 141.8, 168.2, and 174.7; MS m/z 301 (M^+−32). Anal. ($C_{17}H_{19}NO_6$) C, H, N.

Compound **8** melted at 160—168 °C with decomposition and changed into **5**.

2) Using Et_4NOTs (0.48 g) as a supporting electrolyte, **7** (138 mg, 0.40 mmol) was electrolyzed under similar conditions to those described above (electricity: ca. 3 F mol^{-1}). The work-up mentioned above and crystallization from CH_3OH afforded a mixture of **8** and **9** (76 mg) in a ratio of 5:2, which was separated after column chromatography (SiO_2–$CHCl_3$). **9**; mp 138—140 °C; UV (CH_3OH) 212 (ε 18300) and 277 nm (sh, 2170); IR 1779 and 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.27 (3H, s), 2.29 (3H, s), 2.72 (1H, ddd, J=16.6, 4.2, and 1.5 Hz), 2.92 (1H, ddd, J=16.6, 11.9, and 6.1 Hz), 3.17 (3H, s), 3.23 (1H, ddd, J=13.0, 11.9, and 4.2 Hz), 4.29 (1H, ddd, J=13.0, 6.1, and 1.5 Hz), 6.23 (1H, d, J=5.9 Hz), 7.01 (1H, s), 7.13 (1H, d, J=5.9 Hz), and 7.33 (1H, s); ^{13}C NMR ($CDCl_3$) δ=20.6, 28.6, 34.5, 50.4, 90.8, 122.9, 123.9, 128.3, 132.5, 133.2, 140.7, 142.1, 147.9, 168.0, and 170.0. Found: m/z 331.1065. Calcd for $C_{17}H_{17}NO_6$: M, 331.1055.

Upon heating at the mp, **9** gave a colored oil, which showed a blue spot of **10** (R_f 0.55) and a spot of **9** (R_f 0.41) on TLC (CH_3OH:CH_2Cl_2=1:30).

Oxidation of 7 with Lead Tetraacetate (LTA). LTA (0.41 g, 0.93 mmol) was added to a solution of **7** (50 mg, 0.14 mmol) in benzene (20 ml), CH_3OH (0.5 ml), and pyridine (0.1 ml). The reaction mixture was stirred at 26 °C for 15 min, and washed successively with 0.5 wt% HCl, water, and brine, and then dried over Na_2SO_4. Evaporation of the solvent and crystallization from CH_3OH afforded **9** (18 mg, 38%), which was identical with that obtained as described above by spectroscopic (^{1}H NMR, IR) and TLC comparisons.

Preparation of 5. The crystals of **8** (58 mg, 0.17 mmol) were heated at 85—90 °C for 7 h under reduced pressure to give **5** almost quantitatively. Recrystallization from CH_3OH gave needles of **5**; mp 170—174 °C; UV (CH_3OH) 205 (ε 35700), 237 (21300), and 293 nm (5250); IR 1767, 1711, and 1626 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.30 (3H, s), 2.31 (3H, s), 2.95 (2H, t, J=6.2 Hz), 3.25 (2H, d, J=2.9 Hz), 3.75 (2H, t, J=6.2 Hz), 5.57 (1H, t, J=2.9 Hz), 7.08 (1H, s), and 7.40 (1H, s); ^{13}C NMR ($CDCl_3$) δ=20.6, 20.7, 28.5, 36.6, 38.2, 97.8, 119.1, 123.5, 125.7, 132.3, 138.5, 141.2, 142.2, 168.2, 168.3, and 176.3. Found: m/z 301.0913. Calcd for $C_{16}H_{15}NO_5$: M, 301.0948.

Upon heating at the mp, **5** gave a colored oil, which showed a blue spot of **10** (R_f 0.55) and a spot of **5** (R_f 0.35) on TLC (CH_3OH:CH_2Cl_2=1:30).

Dimerization of 5. A solution of **5** (30 mg, 0.10 mmol) in 1,1,2,2-tetrachloroethane (20 ml) was stirred at 123—127 °C for 3 h under oxygen atmosphere. The resulting blue solution was concentrated under reduced pressure. The residue was washed with CH_3OH and purified with column chromatography (SiO_2, 1 vol% CH_3OH–$CHCl_3$) to give **10** (5 mg, 17%) as amorphous powder; UV ($CHCl_3$) 316 (ε 28500), 590 (29900), and 634 nm (26500); IR 1767 and 1668 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.31 (3H×2, s), 2.34 (3H×2, s), 3.04 (2H×2, t, J=6.4 Hz), 3.83 (2H×2, t, J=6.4 Hz), 7.13 (1H×2, s), 7.19 (1H×2, s), and 7.60 (1H×2, s); MS (SIMS) m/z 599 $(M+H)^+$. Found: C, 63.87; H, 4.31; N, 4.60%. Calcd for $(C_{16}H_{13}NO_5)_2$: C, 64.21, H, 4.38, N, 4.68%.

Dimerization of 9. A solution of **9** (40 mg, 0.12 mmol) in 1,1,2,2-tetrachloroethane (20 ml) was stirred at 121—123 °C for 1 h. The resulting blue solution was worked up as described above to afford **10** (15 mg, 42%), which was identical to that obtained from **5** by spectroscopic (^{1}H NMR, IR) and TLC comparisons.

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