Autoxidation of Indolo[3,2,1-*de*][1,5]naphthyridines

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(Received May 9, 1987)

Synopsis. The yellow keto lactam and the blue dimeric pigment were formed by the autoxidation of indolo[3,2,1-*de*]-[1,5]naphthyridines.

Autoxidation of indole compounds gave various products via indoleninyl hydroperoxides.[1] The well known conversion of indoxyl into indigo and the synthesis of trichotomine dimethyl ester (**3**)[2,3] prompted us to study the autoxidation of indolo[3,2,1-*de*][1,5]-naphthyridines **2c** and **7**.

L-Tryptophan was condensed with 2-oxoglutaric acid to give **1a** and **2a**,[4] which were converted into **1b**[5] and **2b** with methanolic hydrogen chloride. The proton at C-3a in **2b** was suggested to have the same β-configuration as the corresponding proton in **1b** had, since the CD spectrum of **2b** ($[\theta]_{221}$−28800) was similar to that of **1b** ($[\theta]_{232}$−22600).[6]

When **1b** (mp 202—203 °C) was heated at 205—208 °C for 30 min, it changed into blue oil. Separation of the colored product afforded the blue pigment **3** (1%), which was identical with **3** synthesized by the procedure of Iwadare et al. (TLC, IR, and ^{1}H NMR).[2]

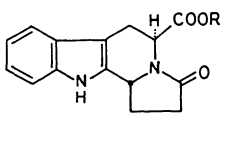
Similarly, **2b** was heated above its melting point, but no blue spot was detected on the TLC. In order to protect the NH group, **2b** was converted into the acetate **2c**. When **2c** was heated at 168—172 °C for 30 min, it changed into green oil, which showed the yellow and blue spots on the TLC. Separation of the colored products gave the yellow compound **4** and the blue pigment **5** in very low yields.

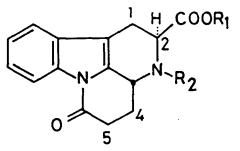
On the other hand, pyridinium dichromate oxidation of **2c** in *N*,*N*-dimethylformamide (20 °C, 18 h) afforded **4** (20%), which showed the same R_f value on the TLC as **4** obtained above. The structure of **4** was in agreement wih the spectral data: UV 402 nm (ε 11400); ^{1}H NMR ABX signals of C-1 and C-2 protons and a singlet of C-4 proton at δ=6.49; ^{13}C NMR signals of four carbonyl carbons at δ=152.1, 169.8, 170.6, and 177.6.

The dimeric structure **5** was suggested for the blue pigment, since the coloration of **1b** above its melting point resulted from the formation of **3**. In order to confirm the structure, **5** was synthesized as follows.

Shono et al. reported the α-methoxylation of carbamates by electrolysis.[7] Since **2c** showed the anodic peak at 1.57 V vs. SCE in the cyclic voltammetry, it was electrolyzed at 1.3 V vs. SCE in methanol to give **6**, which showed a singlet at δ=3.00 (3H, OCH_3) in the ^{1}H NMR spectrum. Treatment of **6** with formic acid in chloroform under argon afforded **7**. When a colorless solution of **7** in 1-butanol was stirred at room temperature for 47 h, it became blue. Separation of the products gave **4** (6%) and **5** (12%), the latter of which was identical with that obtained by the autoxidation of **2c** (TLC, IR). The structure of **5** was in line with the spectral data: UV 648 nm (ε 38700); ^{1}H NMR ABX signals of C-1 and C-2 protons and a singlet of C-4 proton at δ=8.57; MS *m*/*z* 644 (M^+).

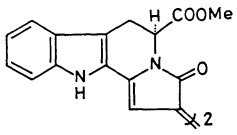
The autoxidation of **2c** at elevated temperature might proceed via **7**. Formation of **4** and **5** from **7** seemed to proceed via the plausible intermediate **8**, since the autoxidation of **7** is similar to that of indoxyl.[8]





1a R=H
1b R=Me

2a R_1=R_2=H
2b R_1=Me R_2=H
2c R_1=Me R_2=Ac



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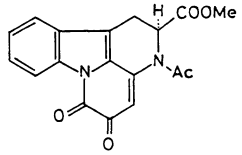

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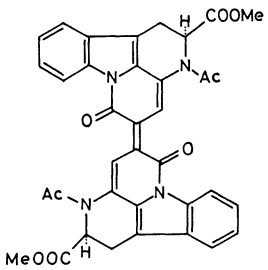

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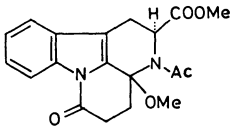

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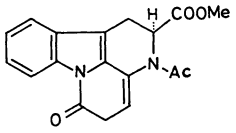

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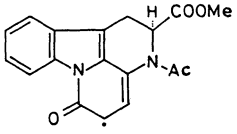

8

Experimental

All melting points were uncorrected. IR spectra were recorded on a Hitachi EPI-G_3 in $CHCl_3$. ^{1}H NMR spectra were obtained on a Varian EM-390 (90 MHz) in $CDCl_3$, and ^{13}C NMR on a JNM-PFT-60 (15 MHz) or a JNM-FX-99 (22.5 MHz) in $CDCl_3$. UV spectra were measured on a JASCO UVIDEC-510 in CH_3OH, and CD spectra on a JASCO J-500 in CH_3OH. Mass spectra were obtained on a Hitachi M-52 or M-80 operating with an ionization energy (70 eV). The cyclic voltammetry of **2c** was recorded on a Yanaco P-1100 in

acetonitrile containing tetrabutylammonium perchlorate (0.10 mol dm^{-3}). Preparative and analytical TLC were carried out on silica-gel plates (Kieselgel 60 F_{254}, E. Merk).

Preparation of 2b. According to the literature,[4] a solution of L-tryptophan (25.0 g) and 2-oxoglutaric acid in 4 mol dm^{-3} hydrochloric acid (250 ml) was heated at 87—91 °C for 2 h. The precipitate was collected and dried. A suspension of the precipitate in 4 wt% hydrogen chloride-CH_3OH (500 ml) was refluxed for 6 h and cooled to room temperature to give the hydrochloride of **2b** (13.1 g), which was freed with aqueous $NaHCO_3$ and crystallized from CH_3OH to give **2b**: mp 154—156 °C; UV 240 (ε 20300), 264 (10400), 292 (4360), and 301 nm (4220); IR 1742 and 1710 cm^{-1}; ^1H NMR δ=1.5—3.2 (7H, m), 3.81 (3H, s), 3.7—4.1 (2H, m), 7.1—7.5 (3H, m), and 8.32 (1H, m); ^{13}C NMR δ=24.9, 28.9, 33.0, 50.2, 52.3, 56.6, 111.8, 116.1, 118.0, 124.0, 124.6, 129.4, 134.8, 135.7, 167.8, and 172.8; MS m/z 284 (M^+); CD $[\theta]_{300}$ −9600, $[\theta]_{276}$ 0, $[\theta]_{267}$ +5100, $[\theta]_{253}$ 0, $[\theta]_{221}$ −28800, and $[\theta]_{211}$ 0. Anal. ($C_{16}H_{16}N_2O_3$) C, H, N.

The mother liquor was concentrated. The residue was neutralized with aqueous $NaHCO_3$, followed by isolation with $CHCl_3$ to give **1b** (3.9 g).[5]

Preparation of 2c. A solution of **2b** (0.91 g) in acetic anhydride (8 ml) and pyridine (8 ml) was allowed to stand at 11—13 °C for 18 h, and concentrated. The residue was crystallized from CH_3OH to give **2c** (1.0 g): mp 168—169 °C; $[\alpha]_D$ +165° (*c* 0.185, CH_3OH); UV 240 (ε 20800), 264 (10700), 292 (4620), and 300 nm (4480); IR 1747, 1713, 1659, and 1644 cm^{-1}; ^1H MNR δ=2.25 (3H, s), and 3.53 (3H, s); ^{13}C NMR δ=22.7, 23.9, 27.1, 33.4, 49.2, 52.6, 56.2, 110.5, 116.2, 118.2, 124.1, 124.9, 128.5, 133.0, 135.2, 167.8, and 170.8; MS m/z 326 (M^+); CD $[\theta]_{301}$ −8300, $[\theta]_{281}$ 0, $[\theta]_{268}$ +17800, $[\theta]_{255}$ +10400, $[\theta]_{250}$ +15000, $[\theta]_{243}$ 0, $[\theta]_{221}$ −53500, and $[\theta]_{210}$ 0. Anal. ($C_{18}H_{18}N_2O_4$) C, H, N.

Autoxidation of 1b. Colorless crystals of **1b** (103 mg) were placed in a 100 ml Erlenmeyer flask and heated at 205—208 °C for 30 min, open to the atmosphere. Separation of the resulting blue oil with column chromatography afforded **3**[2] (1 mg) in addition to **1b** (77 mg).

Autoxidation of 2c. Colorless crystals of **2c** (104 mg) were placed in a 100 ml Erlenmeyer flask and heated at 168—172 °C for 30 min, open to the atmosphere. The resulting green oil showed the yellow spot of **4** (R_f 0.59), the blue spot of **5** (R_f 0.74), and the spot of **2c** (R_f 0.45) on TLC (ethyl acetate). Separation with column and thin-layer chromatography afforded **4** (<0.1 mg) and **5** (<0.3 mg), respectively, in addition to **2c** (83 mg).

Oxidation of 2c with Pyridinium Dichromate. To a solution of **2c** (98 mg) in DMF (4 ml) was added PDC (1.7 g). The mixture was stirred at 20 °C for 18 h, and poured into water. Isolation in a usual way, purification with column chromatography, and crystallization with $CHCl_3$-hexane afforded **4** (20 mg) in addition to the starting material **2c** (12 mg). **4**: mp 188—190 °C; UV 211 (ε 35400), 248 (12600), 275 (13400), 324 (10600), and 402 nm (11400); IR 1745, 1722, 1697, 1663, 1615, and 1606 cm^{-1}; ^1H NMR δ=2.49 (3H, s), 3.22 (1H, dd, J=18.0 and 6.0 Hz), 3.66 (1H, dd, J=18.0 and 1.8 Hz), 3.71 (3H, s), 5.79 (1H, dd, J=6.0 and 1.8 Hz), 6.49 (1H, s), 7.2—7.7 (3H, m), and 8.33 (1H, m); ^{13}C NMR δ=23.4 (t), 24.7 (q), 53.4 (q), 55.4 (d), 112.3 (d), 117.0 (d), 121.5 (d), 122.7 (s), 125.9 (d), 127.7 (s), 129.7 (d), 138.6 (s), 143.7 (s), 152.1 (s), 169.8 (s), 170.6 (s), and 177.6 (s). Found: C, 63.79; H, 4.23; N, 7.94%. Calcd for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28%.

Anodic Oxidation of 2c. A mixture of **2c** (74 mg), tetrabutylammonium tetrafluoroborate (330 mg), and CH_3OH (80 ml) was placed in a beaker-type undivided cell, and glassy carbon rods were used as an anode and a cathode, respectively. After electrolysis at constant potential of 1.3 V vs. SCE (electricity: ca. 3 F mol^{-1} (1 F=96480 C)), the electrolytic solution was concentrated. The residue was dissolved in benzene, washed with water, and dried over Na_2SO_4. Evaporation of the solvent and crystallization from CH_3OH gave **6** (45 mg): mp 130—134 °C; UV 238 (ε 21200), 263 (11500), 292 (6200), and 302 nm (6570); IR 1749, 1716, 1661, and 1643 cm^{-1}; ^1H NMR δ=2.50 (3H, s), 2.6—3.5 (4H, m), 3.00 (3H, s), 3.07 (1H, dd, J=16.8 and 5.7 Hz), 3.50 (1H, dd, J=16.8 and 2.1 Hz), 3.57 (3H, s), 5.85 (1H, m), 7.2—7.6 (3H, m), and 8.43 (1H, m); ^{13}C NMR δ=22.8 (t), 24.0 (q), 31.5 (t), 33.3 (t), 49.2 (q), 52.5 (q), 56.3 (d), 84.2 (s), 116.4 (s), 116.8 (d), 118.9 (d), 124.3 (d), 126.2 (d), 126.9 (s), 129.8 (s), 135.7 (s), 167.6 (s), 171.6 (s), and 173.0 (s). Found: m/z 356.1393. Calcd for $C_{19}H_{20}N_2O_5$: M, 356.1371.

Treatment of 6 with HCOOH. To a solution of **6** (40 mg) in $CHCl_3$ (10 ml) was added 99% HCOOH (0.2 ml) under argon. The solution was kept at 20 °C for 24 h, washed with aqueous $NaHCO_3$, and dried over Na_2SO_4. Evaporation of the solvent gave **7** in almost quantitative yield. **7**: IR 1743, 1703, 1659, and 1605 cm^{-1}; ^1H NMR δ=2.38 (3H, s), 3.06 (1H, dd, J=16.8 and 6.0 Hz), 3.51 (1H, d, J=16.8 Hz), 3.62 (3H+2H, s), 5.5—6.2 (2H, m), 7.2—7.6 (3H, m), and 8.37 (1H, m); ^{13}C NMR δ=23.3, 23.4, 35.4, 52.8, 53.8, 110.3, 112.4, 116.3, 119.0, 124.6, 126.0, 126.5, 128.8, 134.8, 165.2, 170.0, and 170.6. Found: m/z 324.1096. Calcd for $C_{18}H_{16}N_2O_4$: M, 324.1108.

Without further purification, **7** was subjected to the next autoxidation.

Autoxidation of 7. A solution of **7**, obtained above, in 1-butanol (20 ml) was stirred at 15—20 °C for 47 h. The resulting blue solution was concentrated. Separation with column and thin layer chromatography afforded **4** (2.2 mg) and the blue oil, which was precipitated with $CHCl_3$ and hexane to give **5** (4.6 mg): UV 228 (ε 59600), 264 (22300), 302 (15200), 348 (12900), 607 (40500), and 648 nm (38700); IR 1742, 1671, 1615, and 1601 cm^{-1}; ^1H NMR δ=2.17 (1H×2, dd, J=18.0 and 6.0 Hz), 2.94 (3H×2, s), 3.20 (1H×2, d, J=18.0 Hz), 3.52 (3H×2, s), 5.87 (1H×2, d, J=6.0 Hz), 7.2—7.5 (3H×2, m), 8.38 (1H×2, m), and 8.57 (1H×2, s). ^{13}C NMR δ=22.8, 24.6, 52.8, 53.7, 115.1, 116.3, 116.6, 120.2, 125.1, 127.1, 128.0, 128.3, 129.5, 130.8, 137.3, 159.9, 170.5, and 170.8; MS m/z 644 (M^+). Found: m/z 644.1887. Calcd for $C_{36}H_{28}N_4O_8$: M, 644.1905.

We would like to thank Professor Akira Tatematsu and Dr. Hiroshi Sakurai of Meijo University, and Dr. Yoshikazu Shizuri of Keio University for obtaining the mass spectra. We also express our thanks to Dr. Kanzo Sakata and Mr. Akihito Yagi of Shizuoka University for measuring the ^{13}C NMR spectra.

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