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SYNTHESIS OF TRICHOTOMINE, A BLUE PIGMENT OBTAINED FROM *CLERODENDRON TRICHOTOMUM* THUNB

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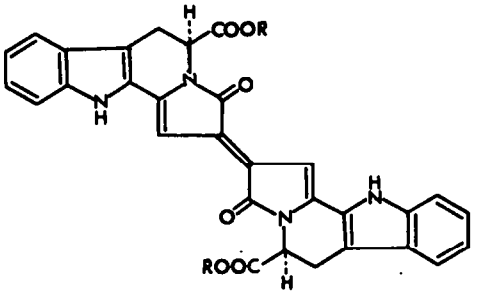
Abstract—The synthesis of trichotomine 1 possessing a new and novel chromophore has been achieved based on its biogenesis. Starting from L-tryptophan methyl ester and succinic anhydride, trichotomine 1 was synthesized by the following sequence: 7→8→9→6→2→1.

From the fruits of the plant *Clerodendron trichotomum* Thunb., a blue pigment trichotomine 1 was isolated in pure form, and the structure including the absolute configuration elucidated.[1] Trichotomine 1 contains a new and novel chromophore hitherto unknown in natural products. Synthesis of this pigment has been performed in our laboratory,[2] and the details of the synthetic studies are described in the present paper.



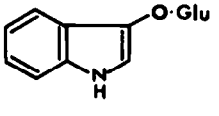
1: R=H
2: R=Me

This pigment is deduced to be produced in plants by oxidative dimerization of 3 - oxo - 2,3,5,6 - tetrahydro - 11 *H* - indolizino [8, 7-b] indole 5-carboxylic acid 5 or its equivalent, which, in turn, would be formed from L-tryptophan and a succinic acid equivalent (a C_4-unit). The formation of indigo 4 from indoxyl which exists in plants as a glucoside, indican 3 is a well-known example of this type of oxidative dimerization.[3]

Based on this biogenesis, the synthetic route of trichotomine 1 was devised, starting from L-tryptophan methyl ester[4] and succinic anhydride. Recently, Kapadia and Rao synthesised trichotomine 1 from tryptophan and α-ketoglutaric acid, the latter being used as a succinic acid equivalent, by consideration of the biogenesis similar to that described above.[5]

L-Tryptophan methyl ester was condensed with succinic anhydride in benzene under reflux to give an amide 7 in 76% yield, which was converted to the amide dimethyl ester 8 by ethereal diazomethane. The imide 9 was obtained in 90% yield by heating 8 at 200° for 1 h under reduced pressure. The Bischler-Napieralski cyclization of the imide 9 was effected under the atmosphere of nitrogen by employing phosphorus pentoxide[6] as dehydrating agent in benzene at 40° for 14 h and subsequently at refluxing temperature for 2 h, affording the tetracyclic lactam 6 in 28% yield together with the starting compound 9 (17% recovery) and trichotomine dimethyl ester 2 (5%). During the work-up procedure of the cyclization reaction products of 9, greenish-blue color gradually developed in the organic phase, indicating that the lactam 6 easily undergoes oxidative dimerization to form trichotomine dimethyl ester 2. While the lactam 6 in organic solutions is susceptible to oxidation by molecular oxygen, it is stable in crystalline form.

Effective oxidative dimerization of the lactam 6 could be achieved by passing air into the solution of the lactam 6 in *n*-butanol at 90° for 18 h, giving trichotomine dimethyl ester 2, m.p. 284–287° in 35% yield (based on reacted 6) together with the starting compound 6 (*ca.* 20% recovery). Synthetic 2 was shown to be identical by TLC comparison, by mixture melting point, and by UV,



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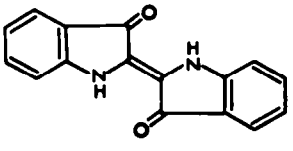

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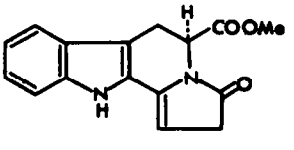
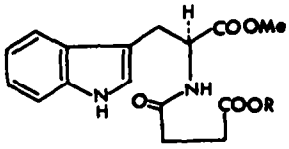
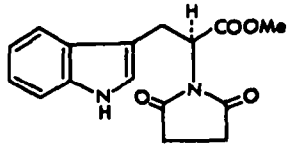


5: R=H
6: R=Me



7: R=H
8: R=Me



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IR, NMR (100 MHz), CD, and mass spectral comparison with natural trichotomine dimethyl ester 2. Hydrolysis of the synthetic 2 was carried out under the conditions[1c] established during the course of the structural studies of trichotomine, affording the deep blue amorphous compound, which was proved to be identical with natural trichotomine 1 by spectral (UV, IR, NMR and mass) and chromatographic comparison.

EXPERIMENTAL

M.ps were uncorrected. UV spectra were measured on a Perkin–Elmer Model 202 spectrophotometer. IR spectra were recorded with JASCO Model IRS and JASCO DS-402G instruments. NMR spectra were obtained using a Varian HA-100 instrument; chemical shifts (δ) are reported in ppm downfield from internal TMS. Low-resolution mass spectra were determined on a Hitachi RMU-6C spectrometer equipped with a direct inlet system. High-resolution mass spectrum was recorded on a JEOLCO GMS-01SG mass spectrometer. CD spectra were recorded on a JASCO ORD/UV-5 spectrophotometer. For TLC silica gel GF_{254} and PF_{254} (E. Merck, A.G., Germany) were used: thickness employed was 0.25 mm for analytical purpose, and 1.00 mm for preparative purpose. The organic solutions were washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, and evaporated by vacuum rotary evaporator.

Amide 7. A mixture of L-tryptophan methyl ester (470 mg) and succinic anhydride (216 mg) in dry benzene (60 ml) was refluxed for 5 h under N_2. After cooling, the mixture was extracted with saturated $NaHCO_3$ soln three times. The combined aqueous soln was made acidic (pH 2) with 5% HCl. The mixture was extracted with AcOEt three times. The combined AcOEt soln was dried and concentrated, affording colorless powder, recrystallization of which from benzene–AcOEt (1:1) gave 520 mg (76%) of 7, m.p. 95–97°: IR ($CHCl_3$) 1734, 1700 1672, 1518 cm^{-1}; NMR (CD_3COCD_3) 2.53 (4H, m), 3.22 (1H, dd, J = 5.4, 15.8 Hz), 3.24 (1H, dd, J = 7.6, 15.8 Hz), 3.63 (3H, s), 4.20 (2H, br.s, exchangeable with D_2O), 4.79 (1H, ddd, J = 5.4, 7.6, 7.8 Hz), 6.9–7.6 (4H, complex pattern), 10.00 (1H, br.s, exchangeable with D_2O); Mass 318 (M^+). (Found: C, 60.11; H, 5.52; N, 8.60. $C_{16}H_{18}N_2O_5$ requires: C, 60.37; H, 5.70; N, 8.80%).

Amide dimethyl ester 8. To a soln of the amide 7 (520 mg) in MeOH (20 ml) was added excess ethereal CH_2N_2 under ice-bath cooling. The soln was allowed to stand for 15 min and was evaporated to give colorless powder, recrystallization of which from AcOEt afforded 490 mg (90%) of pure crystalline 8, m.p. 151–152°: IR ($CHCl_3$) 1741, 1672, 1517 cm^{-1}; NMR (CD_3COCD_3) 2.53 (4H, m) 3.21 (1H, dd, J = 5.4, 15.8 Hz), 3.24 (1H, dd, J = 7.6, 15.8 Hz), 3.61 (3H, s), 3.64 (3H, s), 4.78 (1H, ddd, 5.4, 7.6, 7.8 Hz), 6.9–7.6 (4H, complex pattern), 9.50 (2H, br.s, exchangeable with D_2O); Mass 332 (M^+). (Found: C, 61.61; H, 5.73; N, 8.55. $C_{17}H_{20}N_2O_5$ requires: C, 61.43; H, 6.07; N, 8.43%).

Imide 9. The amide dimethyl ester 8 (1.32 g) in a round-bottomed flask was heated at 200° in an oil bath for 1 h under reduced pressure. After cooling the crude product was purified by preparative TLC with AcOEt–benzene (1:2) to give 9 (1.07 g, 90%) as amorphous powder: IR ($CHCl_3$) 3480, 1784, 1748, 1709 cm^{-1}; NMR ($CDCl_3$) 2.43 (4H, s), 3.61 (1H, dd, J = 7.5, 16.5 Hz), 3.62 (1H, dd, J = 9.5, 16.5 Hz), 3.80 (3H, s), 5.05 (1H, dd, J = 7.5, 9.5 Hz), 6.9–7.6 (4H, complex pattern), 8.18 (1H, br.s, exchangeable with D_2O); Mass 300 (M^+). (High-resolution mass spectrum, M^+ 300.1097; $C_{16}H_{16}N_2O_4$ requires 300.1110).

Tetracyclic lactam 6. To a soln of the imide 9 (1.01 g) in dry benzene (230 ml) was added P_2O_5 (18 g) in one portion. The mixture was stirred under N_2 at 40° for 14 h and then at refluxing temperature for 2 h. After cooling benzene layer was removed by decantation. The residue was dissolved in H_2O with cooling. The aqueous soln was carefully made basic (pH 8–9) by adding solid K_2CO_3. The aqueous mixture was extracted with AcOEt three times (3 × 300 ml). The AcOEt extracts were dried and concentrated to afford colorless powder (548 mg), which was dissolved in a small amount of AcOEt.

When the AcOEt soln was kept in a refrigerator overnight, crystals of 6 deposited: 161 mg. The residue obtained on evaporation of the mother liquor was separated by preparative TLC with AcOEt–benzene (1:2) to give crystals of 6 (109 mg), amorphous powder of the imide 9 (170 mg, 17% recovery) and deep blue crystals of 2 (18 mg).

The aqueous mixture (pH 8–9) was acidified with conc. HCl and the resulting acidic mixture (pH 1) was extracted with *n*-BuOH repeatedly. The combined *n*-BuOH soln was dried and concentrated to afford blue powder (218 mg), which was purified by preparative TLC with AcOEt–benzene (1:2) to give crystalline 2 (31 mg). The total amount of 6 obtained was 270 mg (28%) and that of 2 was 49 mg (5%). 6 m.p. 208–211°: UV (MeOH) λ_{max} nm (ε), 231 (25,200), 308 (21,200), 321 (19,400); IR (KBr) 1747, 1683, 1654 cm^{-1}; NMR ($CDCl_3$) 3.18 (2H, d, J = 3.2 Hz), 3.27 (1H, dd, J = 7.0, 16.0 Hz), 3.65 (1H, dd, J = 2.0, 16.0 Hz), 3.67 (3H, s), 5.17 (1H, dd, J = 2.0, 7.0 Hz), 5.23 (1H, t, J = 3.2 Hz), 7.0–7.7 (4H, complex pattern), 8.84 (1H, br.s, exchangeable with D_2O); Mass 282 (M^+); CD (MeOH) $[\theta]_{255} + 6{,}340$, $[\theta]_{320} + 2{,}060$, and $[\theta]_{311} - 1{,}510$. (Found: C, 68.16; H, 4.97; N, 9.67. $C_{16}H_{14}N_2O_3$ requires: C, 68.07; H, 5.00; N, 9.92%).

Trichotomine dimethyl ester 2. Air was bubbled with capillary tubing through a soln of the lactam 6 (50 mg) in *n*-BuOH (75 ml) kept at 90° for 18 h. The soln was deep blue at the end of the reaction. After cooling the soln was concentrated. Benzene was added to the residue and the mixture was evaporated to dryness. The residual mixture was separated by preparative TLC with AcOEt–benzene (1:2) to yield the starting compound 6 (10 mg) and crude blue crystals of 2. Recrystallization of the latter from MeOH afforded 14 mg (35% yield based on reacted 6) of pure crystalline 2, m.p. 284–287°, mixture m.p. with natural trichotomine dimethyl ester (m.p. 285–287°) 284–287°: UV ($CHCl_3$) λ_{max} nm (ε), 658 (70,000), 620 (61,000), 351 (34,000), 340 (30,000), 245 (32,000); IR ($CHCl_3$) 1745, 1672, 1606 cm^{-1}; NMR (CD_3COCD_3) 3.47 (2 × 1H, dd, J = 7.0, 17.5 Hz), 3.64 (2 × 3H, s), 3.78 (2 × 1H, dd, J = 2.0, 17.5 Hz), 5.25 (2 × 1H, dd, J = 2.0, 7.0 Hz), 7.0–7.7 (2 × 5H, complex pattern), 10.98 (2 × 1H, br.s, exchangeable with D_2O); CD ($CHCl_3$) $[\theta]_{329} - 31{,}900$ and $[\theta]_{372} + 23{,}600$. [Found: C, 68.51; H, 4.20; N, 9.55. $(C_{16}H_{12}N_2O_3)_2$ requires: C, 68.56; H, 4.32; N, 10.00%].

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