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ISOLATION AND STRUCTURE OF TRICHOTOMINE

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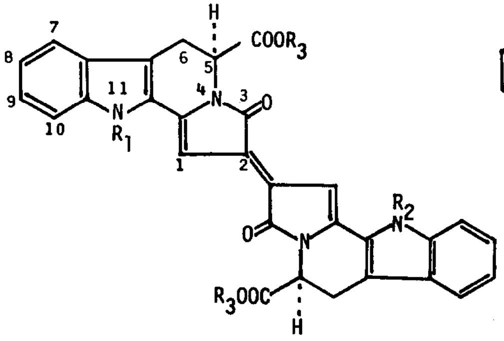
The isolation of blue pigments from the fruits of Clerodendron trichotomum Thunb was first undertaken by Giacomo Bionda et al.[1],[2] but they did not succeed in obtaining blue pigments in a pure form. We have isolated a blue pigment, named trichotomine (I) and established the structure of it as the oxidative dimeric compound of 3-oxo-2,3-5,6-tetrahydro-11H indolizino-[8,7-b] indole 5-carboxylic acid (I). This is the first example of a naturally occurring blue pigment having such a chromophore as mentioned above. In this paper, we wish to describe the isolation and structure of trichotomine (I).



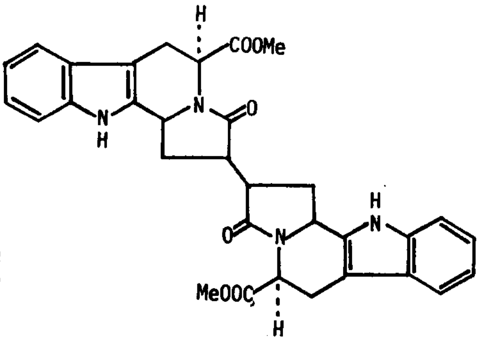
(I) $R_1 = R_2 = R_3 = H$

(II) $R_1 = R_2 = H$, $R_3 = Me$

(III) $R_1 = H$, $R_2 = Ac$, $R_3 = Me$

(IV) $R_1 = R_2 = Ac$, $R_3 = Me$

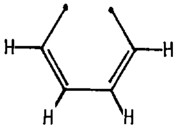
(VIII) $R_1 = R_2 = R_3 = Me$



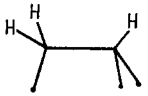
(V)

The acetone extracts of the fresh blue fruits of Clerodendron trichotomum Thunb (Japanese name "Kusagi") were chromatographed on Sephadex LH-20 and eluted with 10% aqueous MeOH to yield an amorphous blue powder of trichotomine in 0.0015% yield, which showed the following physical data: m.p. $>$ 300°; CD(MeOH) $[\theta]_{375}+21900$ and $[\theta]_{332}-32800$; [Found: C, 67.21; H, 3.63; N, 10.17%. $(C_{15}H_{10}N_2O_3)_2$ requires: C, 67.66; H, 3.79; N, 10.52%]; ν_{max}(KBr) 1712 (-COOH), 1650 and 1600cm^{-1}; λ_{max}(MeOH) 660, 618, 353, 337 and 242nm (ϵ, 6.9×10^4, 6.7×10^4, 3.3×10^4, 2.9×10^4 and 3.1×10^4, respectively); δ(CD_3COCD_3) 7.62(1H x 2, dd, J= 1.5, 7.8Hz, aromatic protons), 7.45(1H x 2, dd, J= 2.0, 7.6Hz, aromatic protons), ca. 7.3 (1H x 2, m, aromatic protons), 7.12 (1H x 2, dd, J= 2.0, 7.8Hz, aromatic protons), 7.22(1H x 2, s, vinyl protons), 5.20(1H x 2, dd, J= 2.0, 7.0Hz, $>C\underline{H}_X-CH_AH_B-$), 3.78(1H x 2, dd, J=2.0, 17.5Hz, $>CH_X-C\underline{H}_AH_B-$), 3.42(1H x 2, dd, J= 7.0, 17.5Hz, $>CH_XCH_A\underline{H}_B-$) and ca. 4.05(2H x 2, br.s, exchangeable).

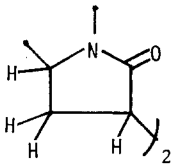
The IR spectrum of (I) indicates the presence of at least two carboxyl groups. Thus, treatment of trichotomine with CH_2N_2 in MeOH gave a methyl ester (II), m.p. 285-287°; [Found: C, 68.07; H, 4.06; N, 9.67%. $(C_{16}H_{12}N_2O_3)_2$ requires: C, 68.56; H, 4.32; N, 10.00%]; ν_{max}($CHCl_3$) 1745(-COOMe), 1672 and 1606(vs) cm^{-1}; λ_{max}($CHCl_3$) 658, 620, 351, 340 and 245nm (ϵ, 7.0×10^4, 6.1×10^4, 3.4×10^4, 3.0×10^4 and 3.2×10^4, respectively); δ(CD_3COCD_3) 10.97(1H x 2, s, exchangeable), 7.62(1H x 2, dd, J= 1.5, 7.8Hz, aromatic protons), 7.45(1H x 2, dd, J= 2.0, 7.6Hz, aromatic protons), ca. 7.3(1H x 2, m, aromatic protons), 7.12(1H x 2, dd, J= 2.0, 7.8Hz, aromatic protons), 7.25(1H x 2, s, vinyl protons), 5.24(1H x 2, dd, J= 2.0, 7.2Hz, $>C\underline{H}_X-CH_AH_B-$), 3.78(1H x 2, dd, J= 2.0, 17.5Hz, $>CH_X-C\underline{H}_AH_B-$), 3.47(1H x 2, dd, J= 7.2, 17.5Hz, $>CH_X-CH_A\underline{H}_B-$) and 3.64(3H x 2, s, -COOMe). The dimeric structure was based on its molecular weight determination (569 ± 10), which was carried out by osmometry using acetone as a solvent. In the light of molecular weight (569 ± 10), the NMR spectrum of (II) showed that only one half of the total proton signals were detectable. Therefore, trichotomine methyl ester must have a symmetric structure. The presence of the following groups (A) and (B) was estimated by the NMDR of (II)$^{3)}$. The presence of two OH or two NH



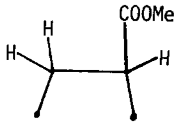
(A)



(B)



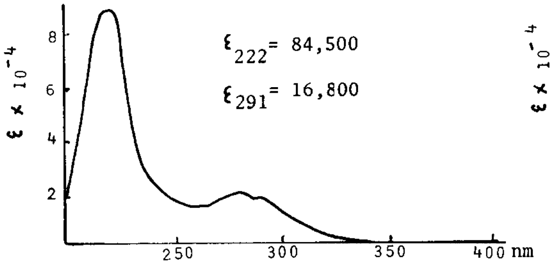
(C)



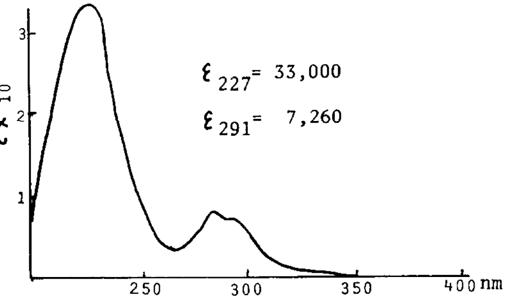
(D)

groups can also be confirmed by acetylation. When treated with Ac_2O/Py at 20° overnight, (II) afforded a mixture of mono- and di-acetylated compounds. [(III): m.p. 239-241°; ν_{max}(KBr) 1735, 1715, 1668 and 1580cm^{-1}; δ($CDCl_3$) 2.70(3H, s, $-NHCOCH_3$ or $-OCOCH_3$) and 9.40 (1H, s, exchangeable). (IV): m.p. 246-248°; ν_{max}(KBr) 1744, 1674 and 1584cm^{-1}; δ($CDCl_3$) 2.70(3H x 2, s, $-NCOCH_3$ or $-OCOCH_3$)].

Catalytic hydrogenation of trichotomine methyl ester over PtO_2 in AcOEt-MeOH afforded a hexahydro-compound(V), indicating the following physical data: $C_{32}H_{30}N_4O_6$; m/e 566(M^+), 507(M^+- COOMe) and 447(M^+- 119); ν_{max}($CHCl_3$) 3420($>$NH), 2900, 1743 1689(five membered lactam) and 1603(w) cm^{-1}; λ_{max}(MeOH) 222, 280 and 291nm (ϵ, 8.45 x 10^4, 1.97 x 10^4 and 1.68 x 10^4, respectively); δ($CDCl_3$) 7.70(1H x 2, s, $>$NH), 7.0-7.15(4H x 2, m, aromatic protons), 4.92(1H x 2, dd, J= 7.6, 9.4Hz, $>C\underline{H}-CHH-CH<$), 3.33(1H x 2, dd, J= 7.0, 7.6Hz, $>CH-CHH-C\underline{H}<$), 2.31(1H x 2, m, $>CH-C\underline{H}H-CH<$), 1.42(1H x 2, m, $>CH-CH\underline{H}-CH<$), 4.32(1H x 2, dd, J= 5.0, 7.5Hz, $>C\underline{H}_X-CH_AH_B-$), 3.30(1H x 2, dd, J= 7.5, 16.0Hz, $>CH_X-C\underline{H}_AH_B-$), 3.01(1H x 2, dd, J= 5.0, 16.0Hz, $>CH_X-CH_A\underline{H}_B-$) and 3.74(3H x 2, s, -COOMe). Particularly, the UV spectrum of a hexahydro-compound (V) is almost superimposable to that of ibogamine (see the figure), indicating that (V) has an α,β-disubstituted indole nucleus in consideration of the NMR spectral data [δ($CDCl_3$) 7.0-7.15 (4H x 2, m, aromatic protons)].

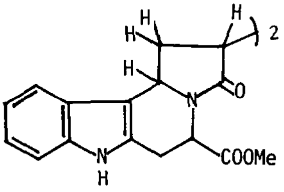


the UV spectrum of (V) (MeOH)

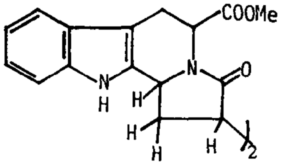


the UV spectrum of ibogamine (MeOH)

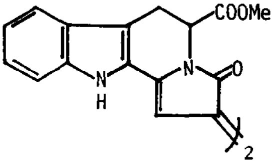
Furthermore, the IR spectrum of (V) [ν_{max}($CHCl_3$) 1689cm^{-1}] shows the presence of a five membered lactam. Accordingly, the IR absorption band at 1672cm^{-1} in trichotomine methyl ester (II) must be assigned to the conjugated five membered lactam grouping. Further informations of two partial structures [(C) and (D)] in (V) were obtained by the NMR spectral data, coupled with the NMDR measurements: irradiation at δ 4.92 caused each multiplet at δ2.31 and at δ1.42 to collapse to double doublet, whereas on irradiation at δ3.33 each one proton of this methylene group became double doublet. Although (II) absorbed three molecules of hydrogen leading to the formation of (V), the area intensity of total protons in the latter appeared to increase by three protons as compared with that of the original methyl ester (II). Therefore, the two indole moieties can be connected to each other in such a manner as shown in (C). In conclusion, hexahydrotrichotomine methyl ester (V) must have the partial structure (VI) or (VII). From a biogenetic point of view, the latter, which has a tryptophan framework, is more favourable than (VI). In fact, the above conclusion was supported by the NOE measurements of N,N'-dimethyl-trichotomine methyl ester (VIII)$^{4)}$, in which the area intensity of the vinyl protons at δ 7.20 was enhanced by 15% on irradiation at δ3.28 ($>$NMe) ($CDCl_3$-C_6D_6). Accordingly, the structure of trichotomine methyl ester (II) and trichotomine (I) must be represented by (IX) and (X), respectively.



(VI)



(VII)



(IX) R= Me

((X) R= H

The stereostructure of trichotomine, including the absolute configuration,was finally determined as (I) by X-ray analysis of the p-Br-benzoate derivative. (see the following paper).

REFERENCES AND FOOTNOTES

1) Giacomo Bionda, Ann. Chim. Applicata., 36, 210-211 (1946).

2) Victor Plouvier, Compt. rend., 231, 1546-1548 (1950).

3) Irradiation at δ7.62 caused double doublet at δ7.12 to collapse to doublet. Irradiation at δ 7.12 caused each double doublet at δ 7.62 and at δ 7.45 to collapse to doublet. In the case of irradiation at δ7.3, each double doublet at δ 7.62 and at δ 7.45 became doublet.

4) When treated with CH_3I/NaH in DMF at 20° for 20 min., (II) afforded N,N'-dimethyl-trichotomine methyl ester in good yield.