

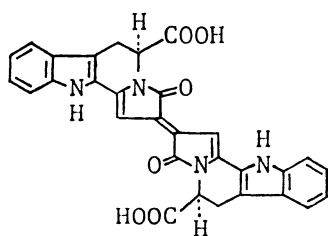
ISOLATION OF FOUR INDOLIZINO[8,7-b]INDOLE-5-CARBOXYLIC ACIDS
FROM CLERODENDRON TRICHOTOMUM THUNB

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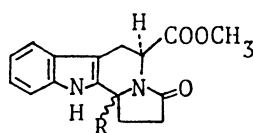
Four indolizino[8,7-b]indole-5-carboxylic acids were isolated as the methyl esters from Clerodendron trichotomum Thunb, and the structures elucidated on the basis of their spectral and chemical evidences.

A blue pigment trichotomine (1) was isolated from the fruits of Clerodendron trichotomum Thunb, and the structural elucidation and synthesis were reported by S. Iwadare et al..^{1,2)} Kapadia and Rao reported the biomimetic synthesis of trichotomine by one-pot reaction of L-tryptophan and 2-oxoglutaric acid.³⁾ We attempted to detect the anticipated precursors of trichotomine in the extracts of the fruits.

The extracts were chromatographed on TSK gel G-3000S and Sephadex LH-20 to yield four acidic compounds, which showed characteristic blue spots on TLC with Ehrlich's reagent. Treatment of the acidic compounds with CH_2N_2 and purification of the products by silica gel column chromatography afforded the dimethyl esters 2 and 3, and the monomethyl esters 4 and 5, respectively.



1

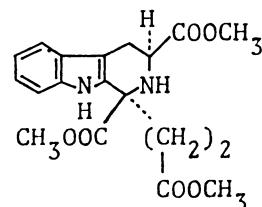


2 R = β -COOCH₃

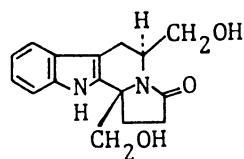
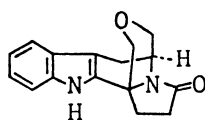
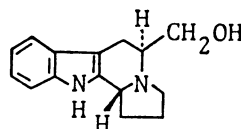
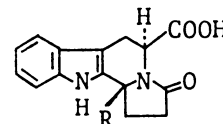
3 R = α -COOCH₃

4 R = β -H

5 R = α -H



6

78910 R = COOH11 R = H

The structure of 2 was deduced from the physical data: m.p. 189-190°; IR (CHCl₃) 3450, 1741, and 1696 cm⁻¹; MS m/z 342 (M⁺), 283, and 223; PMR (CDCl₃) 8.53 (1H, br s), 7.6-7.0 (4H, m), 5.48 (1H, dd, J=6.6 and 1.8 Hz), 3.81 (3H, s), 3.59 (3H, s), 3.31 (1H, dd, J=16.2 and 1.8 Hz), 3.06 (1H, dd, J=16.2 and 6.6 Hz), and 3.0-1.9 ppm (4H, m). In order to confirm the structure, 2 was synthesized in two manners.

Reaction of L-tryptophan methyl ester hydrochloride and dimethyl 2-oxoglutarate in MeOH afforded the dimethyl ester 2, [α]_D +110° (c 0.219 MeOH), whose identity with natural 2 was shown by m.p., TLC, IR, PMR, MS, ORD, and CD spectra. In a manner similar to that of Kapadia and Rao,³⁾ a mixture of L-tryptophan and 2-oxoglutaric acid in water was kept under nitrogen atmosphere at room temperature for a few weeks to give a yellow precipitate, which was treated with CH₂N₂ to afford the trimethyl ester 6: m.p. 142.0-142.5°; MS m/z 374 (M⁺). The compound 6 was converted into 2 with 8% HCl-MeOH.

The dimethyl ester 2 was reduced with NaBH₄ in MeOH-THF to give the diol 7: m.p. 226-227°; MS m/z 286 (M⁺), which was treated with TsCl in pyridine to afford the ether 8: m.p. >300°; MS m/z 268 (M⁺). Formation of the ether linkage in 8 indicated the 1,3-cis relationships of the two hydroxymethyl groups in 7 and the two methoxycarbonyl groups in 2. Therefore, the stereochemistries of 2, 6, and 7 were confirmed as shown in the figures including the absolute configurations, since 2 was prepared from L-tryptophan.

The dimethyl ester 3⁴⁾ showed a mass spectrum similar to that of 2, and characteristic PMR signals at 4.39 (C-5-H, dd, J=10.5 and 5.4 Hz), 3.87 (3H, s), and 3.83 ppm (3H, s). Treatment of 2 with NaOMe did not result in epimerization, while 3 was converted into the enantiomer of 2 under the similar conditions. The epimerization product of 3 indicated the same IR, PMR, and CD spectra as those of

the enantiomer of 2, $[\alpha]_D -107^\circ$ (c 0.205 MeOH), prepared from D-tryptophan methyl ester hydrochloride and dimethyl 2-oxoglutarate. Accordingly, the structure of 3 was determined as the C-11b epimer of 2.

The structures of the monomethyl esters 4 and 5 were assigned as shown in the figures from the spectral data,⁵⁾ and confirmed by the synthesis. Reaction of L-tryptophan methyl ester and 2-oxoglutaric acid in refluxing benzene gave 4⁶⁾, $[\alpha]_D +187^\circ$ (c 0.214 MeOH), and 5, $[\alpha]_D -110^\circ$ (c 0.218 MeOH), whose identities with natural 4 and 5 were shown by TLC, IR, PMR, and CD spectra, respectively. The β -configuration of C-11b proton in 4 was estimated from the first positive maximum of the ORD curve of 4.⁷⁾ It is also supported by the similarity in the positive $[\alpha]_D$ between the compound reported by S. Takano et al. and the mono-ol 9, $[\alpha]_D +94^\circ$ (c 0.205 MeOH), which was obtained by LiAlH_4 reduction of 4.^{8,9)} Treatment of 4 with NaOMe did not result in epimerization, while 5 was converted into the enantiomer of 4, $[\alpha]_D -185^\circ$ (c 0.200 MeOH), under the similar conditions, indicating the α -configuration of C-11b proton in 5.

The aqueous MeOH solution of 10, obtained by hydrolysis of 2 with KOH followed by neutralization with HCl, was allowed to stand at room temperature to become blue and showed a blue spot of trichotomine on TLC, whereas that of 11 did not indicate a blue color under the similar conditions.

Isolation of 2,3,5,6,11,11b-hexahydro-3-oxo-1H-indolizino[8,7-b]indole-5,11b-dicarboxylic acids (10 and the C-11b epimer of 10) shows the involvement of α -keto-acid, 2-oxoglutaric acid, in the biosynthesis of trichotomine, and indicates another example of G. Hahn's proposal.¹⁰⁾

References

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- 4) Spectral data of 3: IR (CHCl_3) 3450, 1740, and 1705 cm^{-1} ; MS m/z 342 (M^+), 283, and 223; PMR (CDCl_3) 8.25 (1H, br s), 7.6-7.0 (4H, m), 4.39 (1H, dd, $J=10.5$ and 5.4 Hz), 3.87 (3H, s), 3.83 (3H, s), 3.34 (1H, dd, $J=15.9$ and 10.5 Hz), 2.99 (1H, dd, $J=15.9$ and 5.4 Hz), and 3.0-2.1 ppm (4H, m).

- 5) Spectral data of 4: IR (CDCl₃) 3460, 1741, and 1685 cm⁻¹; MS m/z 284 (M⁺), 225, and 223; PMR (CDCl₃) 8.31 (1H, br s), 7.6-7.0 (4H, m), 5.34 (1H, dd, J=7.2 and 1.5 Hz), 5.16 (1H, m), 3.63 (3H, s), 3.44 (1H, dt, J=15.9 and 1.5 Hz), 3.10 (1H, ddd, J=15.9, 7.2, and 2.1 Hz), 2.9-1.7 ppm (4H, m). Spectral data of 5: IR (CHCl₃) 3460, 1745, and 1695 cm⁻¹; MS m/z 284 (M⁺), 225, and 223; PMR (CDCl₃) 8.02 (1H, br s), 7.6-7.0 (4H, m), 5.05 (1H, m), 4.12 (1H, dd, J=10.2 and 5.1 Hz), 3.82 (3H, s), 3.35 (1H, ddd, J=15.9, 10.2, and 2.1 Hz), 2.98 (1H, ddd, J=15.9, 5.1, and 1.8 Hz), and 2.7-2.0 ppm (4H, m).
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