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 <u>Clerodendron trichotomum</u> Thunb, and the structures elucidated on the basis of their spectral and chemical evidences.

A blue pigment trichotomine (<u>1</u>) was isolated from the fruits of <u>Clerodendron</u> <u>trichotomum</u> 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 <u>2</u> and <u>3</u>, and the monomethyl esters <u>4</u> and <u>5</u>, respectively.





The structure of <u>2</u> was deduced from the physical data: m.p. $189-190^{\circ}$; 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, <u>2</u> was synthesized in two manners.

Reaction of L-tryptophan methyl ester hydrochloride and dimethyl 2-oxoglutarate in MeOH afforded the dimethyl ester 2, $[\alpha]_D$ +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 CH_2N_2 to afford the trimethyl ester <u>6</u>: m.p. 142.0-142.5°; MS m/z 374 (M⁺). The compound <u>6</u> was converted into 2 with 8% HC1-MeOH.

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

The dimethyl ester $\underline{3}^{4}$ showed a mass spectrum similar to that of $\underline{2}$, 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 $\underline{2}$ with NaOMe did not result in epimerization, while $\underline{3}$ was converted into the enantiomer of $\underline{2}$ under the similar conditions. The epimerization product of $\underline{3}$ indicated the same IR, PMR, and CD spectra as those of

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

The structures of the monomethyl esters <u>4</u> and <u>5</u> 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 <u>4</u>⁶⁾, $[\alpha]_D$ +187° (c 0.214 MeOH), and <u>5</u>, $[\alpha]_D$ -110° (c 0.218 MeOH), whose identities with natural <u>4</u> and <u>5</u> were shown by TLC, IR, PMR, and CD spectra, respectively. The β-configuration of C-11b proton in <u>4</u> was estimated from the first positive maximum of the ORD curve of <u>4</u>.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 <u>9</u>, $[\alpha]_D +94^\circ$ (c 0.205 MeOH), which was obtained by LiAlH₄ reduction of <u>4</u>.^{8,9)} Treatment of <u>4</u> with NaOMe did not result in epimerization, while <u>5</u> was converted into the enantiomer of <u>4</u>, $[\alpha]_D$ -185° (c 0.200 MeOH), under the similar conditions, indicating the α -configuration of C-11b proton in <u>5</u>.

The aqueous MeOH solution of <u>10</u>, obtained by hydrolysis of <u>2</u> 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 <u>11</u> 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-5,11bdicarboxylic acids (<u>10</u> and the C-11b epimer of <u>10</u>) shows the involvement of α -ketoacid, 2-oxoglutaric acid, in the biosynthesis of trichotomine, and indicates an another example of G. Hahn's proposal.¹⁰)

References

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- 4) Spectral data of <u>3</u>: IR (CHCl₃) 3450, 1740, and 1705 cm⁻¹; MS m/z 342 (M⁺), 283, and 223; PMR (CDCl₃) 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 <u>4</u>: 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 <u>5</u>: 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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