THE PARTIAL SYNTHESIS OF 16-EPI-PLEIOCARPAMINE

Shin-ichiro Sakai* and Nobuo Shinma

Faculty of Pharmaceutical Sciences, Chiba University, Yayoi, Chiba, Japan

An indole alkaloid, 16-epi-pleiocarpamine was partially synthesized from geissoschizine methylether, using C/D ring opening and reclosing reactions with cyanogen bromide and HOAc-NH_4OAc respectively; determination of the absolute configuration of pleiocarpamine was accomplished by this chemical correlation.

We have been interested in the chemical transformation of geissoschizine (1b) to pleiocarpamine (4a) through a biomimetic route which involves the formation of bonding between Na and C-16.[1)]

Very recently, we completed the partial synthesis of 19,20β-dihydro-16-epi-pleiocarpamine from hirsutine.[2)] In this communication we wish to report the partial synthesis of 16-epi-pleiocarpamine (4b) from geissoschizine methylether (1a).[3)] It should be stressed that this forms the first correlation of pleiocarpamine (4a) with the other natural indole alkaloids whose absolute configuration are known.

The demethylation of (1a) with dry HCl in acetone generated (1b, 33%) and apogeissoschizine[4)](20%). Reaction of ethyl chlorocarbonate with (1b) in the presence of Na_2CO_3 in $CHCl_3$ at 0° for 2hrs gave rise to carbonate (1c, $\lambda_{max}^{CHCl_3}$ 1760 cm^{-1}). This protected compound (1c) was submitted to the C/D ring cleavage reaction using BrCN in ca. 15% EtOH-$CHCl_3$ in the presence of Na_2CO_3 under N_2 atmosphere.[5)] An amorphous 3-(R)-ethoxy derivative (2a) was obtained as the main product { $\nu_{max}^{CHCl_3}$ 2200 (C≡N), 1765 (O-CO-O), 1710 cm^{-1} (CO_2CH_3) }, which was hydrolyzed to give (2b) { 44% from (1b); m/e 423 (M^+,

100%); CD, $\Delta\varepsilon$ +4.2 (294 nm, MeOH)] with aq-NaOH in MeOH at room temperature. Compound (2b) was oxidized in 79% yield to a mixture of diastereoisomers of C-16-deformyl-chlorinated compounds with freshly distilled t-BuOCl (1.05 molar equivalent) in CCl_4 at -78°. This compound (2c) showed the expected spectral data [λ_{max}^{MeOH} 225, 285, 293 nm, (indolic, showing no shift on addition of aq-NaOH) m/e 429 (M^+, 72%), 431 (M^++2, 30%), 394 (M^+-Cl, 100%)]. The ring closing between Na and C-16 of (2c) was accomplished by treatment with NaH in Me_2SO under N_2 atmosphere at 80°. The reaction mixture was treated with CH_2N_2 to convert the partially hydrolyzed carboxylic acid to methylester. After the purification of the methylated mixture through silica gel column chromatograph, (3) was obtained as an amorphous powder [41%, λ_{max}^{MeOH} 229, 279, 286(shoulder), 300 nm(sh.); $\nu_{max}^{CHCl_3}$ no NH, 2200(C≡N), 1735 cm^{-1}(C=O)]. The mass spectrum of (3) exhibited the M^+ at m/e 393 and a characteristic quinolinium ion m/e 180 (fragment a). Furthermore the nmr spectrum of (3) showed the very characteristic signal of C-21-Ha (δ 0.10, 1H, doublet), which is highly shielded by the indole ring. Configuration of C-16-H was assumed from the stability of (3) to base. The final ring closure of (3) was achieved by heating with aq-HOAc and NH_4OAc to give the 16-epi-pleiocarpamine (4b) [22%, λ_{max}^{MeOH} (log ε) 228(4.22), 288(3.75) nm; $\nu_{max}^{CHCl_3}$ no NH, 1740 cm^{-1}(C=O), m/e 322 (M^+, 100%), 263(M^+-CO_2CH_3, 74%), 180(fragment a, 51%); CD $\Delta\varepsilon_{max}^{MeOH}$(nm), +4.16 (301), +1.96(262), -9.47(236), [α]$_D$: +234°(MeOH)]. NMR and ir spectra of the partially synthesized specimen were completely superimposable with those of the authentic 16-epi-pleiocarpamine[6] derived from base catalyzed isomerization of pleiocarpamine (4a).[7]

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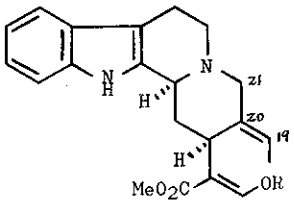
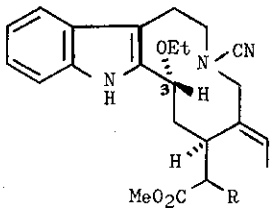


(Ia) R = CH_3

(Ib) R = H

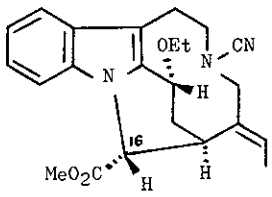
(Ic) R = $CO_2C_2H_5$



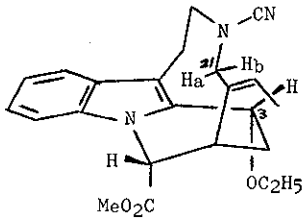
(2a) R = =CH-$OCO_2C_2H_5$

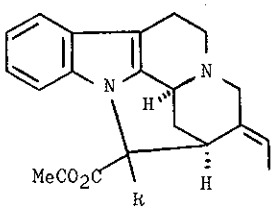
(2b) R = =CH-OH

(2c) R = ~Cl



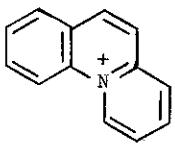
(3)





(4a) R = α - H

(4b) R = β - H



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