

## THE PARTIAL SYNTHESIS OF 16-EPI-PLEIOCARPAMINE

Shin-ichiro Sakai\* and Nobuo ShinmaFaculty 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<sub>4</sub>OAc respectively; determination of the absolute configuration of pleiocarpamine was accomplished by this chemical correlation.

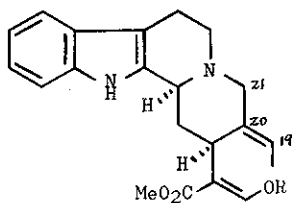
We have been interested in the chemical transformation of geissoschizine (1b) to pleiocarpamine (4a) through a biomimetic route which involves the formation of bonding between Na and C-16.<sup>1)</sup>

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

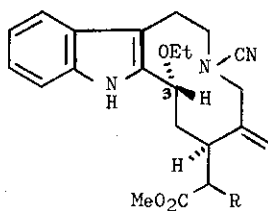
The demethylation of (1a) with dry HCl in acetone generated (1b, 33%) and apogeissoschizine<sup>4)</sup> (20%). Reaction of ethyl chlorocarbonate with (1b) in the presence of Na<sub>2</sub>CO<sub>3</sub> in CHCl<sub>3</sub> at 0° for 2hrs gave rise to carbonate (1c,  $\lambda_{\text{max}}^{\text{CHCl}_3}$  1760 cm<sup>-1</sup>). This protected compound (1c) was submitted to the C/D ring cleavage reaction using BrCN in ca. 15% EtOH-CHCl<sub>3</sub> in the presence of Na<sub>2</sub>CO<sub>3</sub> under N<sub>2</sub> atmosphere.<sup>5)</sup> An amorphous 3-(R)-ethoxy derivative (2a) was obtained as the main product  $\left[ \nu_{\text{max}}^{\text{CHCl}_3} 2200 (\text{CEN}), 1765 (\text{O-CO-O}), 1710 \text{ cm}^{-1} (\text{CO}_2\text{CH}_3) \right]$ , which was hydrolyzed to give (2b)  $\left[ 44\% \text{ from (1b)}; m/e 423 (\text{M}^+, \right.$

100%); CD,  $\Delta \epsilon +4.2$  (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  $-78^\circ$ . This compound (2c) showed the expected spectral data [  $\lambda_{\max}^{\text{MeOH}}$  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  $80^\circ$ . 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%,  $\lambda_{\max}^{\text{MeOH}}$  229, 279, 286(shoulder), 300 nm(sh.);  $\nu_{\max}^{\text{CHCl}_3}$  no NH, 2200(C $\equiv$ 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 ( $\delta$  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%,  $\lambda_{\max}^{\text{MeOH}}$  (log  $\epsilon$ ) 228(4.22), 288(3.75) nm;  $\nu_{\max}^{\text{CHCl}_3}$  no NH, 1740  $cm^{-1}$ (C=O), m/e 322 ( $M^+$ , 100%), 263( $M^+-CO_2CH_3$ , 74%), 180(fragment a, 51%); CD  $\Delta \epsilon_{\max}^{\text{MeOH}}$  (nm), +4.16 (301), +1.96(262), -9.47(236), [  $\alpha$  ]<sub>D</sub>: +234° (MeOH) ]. NMR and ir spectra of the partially synthesized specimen were completely superimposable with those of the authentic 16-epi-pleiocarpamine<sup>6)</sup> derived from base catalyzed isomerization of pleiocarpamine (4a).<sup>7)</sup>

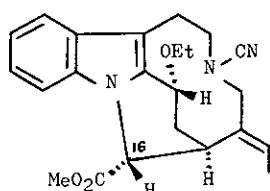
ACKNOWLEDGEMENT We thank The Naito Foundation for financial support.



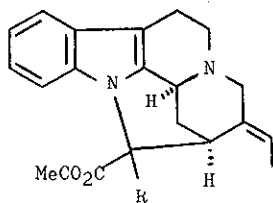
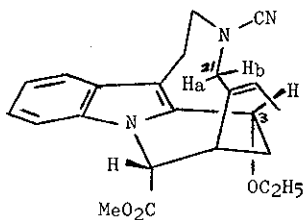
- (Ia) R = CH<sub>3</sub>  
 (Ib) R = H  
 (Ic) R = CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>



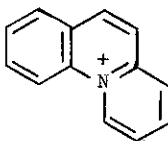
- (2a) R = =CH-OCO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>  
 (2b) R = =CH-OH  
 (2c) R = ~~~~~Cl



(3)



- (4a) R = α - H  
 (4b) R = β - H



a

REFERENCES

- 1 E.Wenkert and B.Wickberg, J.Am.Chem.Soc., 1965, 87, 1580.  
M.Pinar, M.Hanaoka, M.Hesse, and H.Schmid, Helv.Chim.Acta., 1971, 54, 15.
- 2 S.Sakai and N.Shinma, Chem. & Pharm. Bull., 1974, 22, 3013.
- 3 S.Sakai, E.Yamanaka, and L.J.Dolby, accompanying communication.
- 4 H.Rapoport, R.J.Windgassen JR., N.A.Hughes and T.P.Onak, J.Am.Chem.Soc., 1960, 82, 4404.
- 5 J.D.Albright, and L.Goldman, J.Am.Chem.Soc., 1969, 91, 4317.  
M.Lampe-Tirions, M.Kaisin, J.Pecher, Bull.Soc.Chim.Belges, 1971, 80, 27.  
S.Sakai, A.Kubo, K.Katano, N.Shinma, and K.Sasago, Yakugaku Zasshi, 1973, 93, 1165.
- 6 M.Hesse, W.v.Philipsborn, D.Schumann, G.Spiteller, M.Spiteller-Friedmann, W.I.Taylor, H.Schmid, and P.Karrer, Helv.Chim.Acta., 1964, 47, 878.
- 7 Pleiocarpamine (4a) was isolated from the roots of Amsonia elliptica by us.<sup>8)</sup>
- 8 S.Sakai, H.Ohtani, H.Ido, and J.Haginiwa, Yakugaku Zasshi, 1973, 93, 483.

Received, 21st February, 1976