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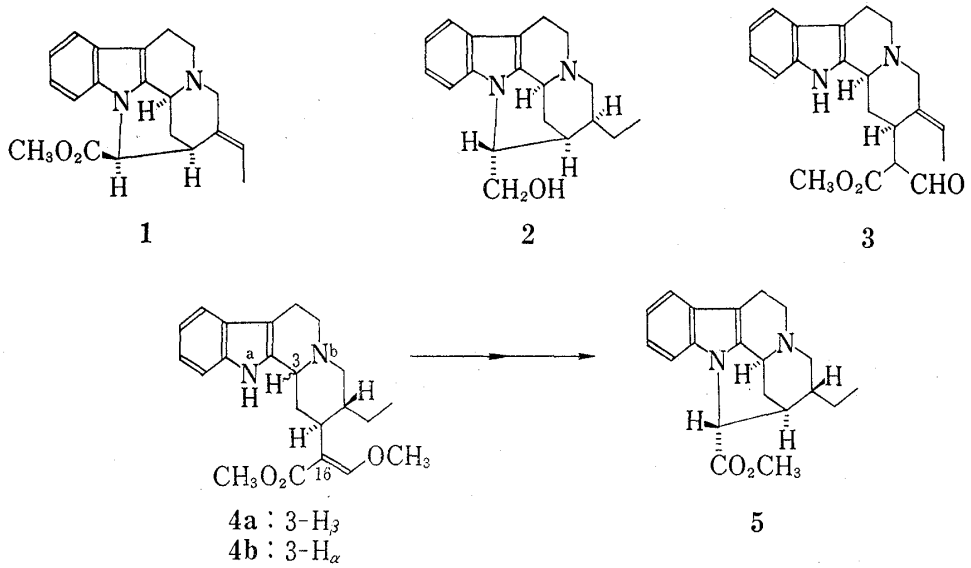
Transformation of Indole Alkaloids. The Chemical Transformation of Corynantheine Type Alkaloids to C-Mavacurine Type Alkaloids

Pleiocarpamine (**1**), an interesting indole alkaloid of apocynaceae plants, has C-mavacurine skeleton.[1] Recently, Boekelheide has reported a synthesis of closely related 19,20-dihydronormavacurine (**2**).[2] We have been interested in the chemical transformation of geissoschizine (**3**) to pleiocarpamine (**1**) through a biomimetic route which involves the formation of bonding between Na and C_{16}.[3,4] In this communication we wish to report that a partial synthesis of 20α-ethyl-19,20-dihydro-16-epipleiocarpamine (**5**) has been accomplished starting either from hirsutine (**4a**) or dihydrocorynantheine (**4b**).



1 **2** **3**

4a : 3-H_β
4b : 3-H_α

5

Chart 1

Very recently, we have described the facile C/D ring opening and regeneration reactions of **4a** and other indole alkaloids.[5] Desmethylhirsutine (**6a**) (mp 116—119°), which was derived from **4a** with acetone–HCl at 0° in 61% yield, was submitted to the C/D ring cleavage reaction using BrCN in 0.6% EtOH–$CHCl_3$. A mixture of 3-(*R*) and (*S*)-ethoxy isomers (**7a**) was obtained as an amorphous powder in 50% yield, which was characterized by the conversion

1) M. Hesse, W. V. Philipsborn, D. Schumann, G. Spiteller, M. Spiteller–Friedmann, W.I. Taylor, H. Schmid, and P. Karrer, *Helv. Chim. Acta.*, **47**, 878 (1964).
2) Dennis D.O'Rell, Fred G.H. Lee, and V. Boekelheide, *J. Am. Chem. Soc.*, **94**, 3205 (1972).
3) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **87**, 1580 (1965).
4) M. Pinar, M. Hanaoka, M. Hesse, and H. Schmid, *Helv. Chim. Acta.*, **54**, 15 (1971).
5) S. Sakai, A. Kubo, K. Katano, N. Shinma, and K. Sasago, *Yakugaku Zasshi*, **93**, 1165 (1973).

to a mixture of two known compounds, 3-(*R*)-ethoxy and 3-(*S*)-ethoxy-Nb-cyano-3,4-seco-hirsutine (**7b**), by methylation with CH_2N_2.

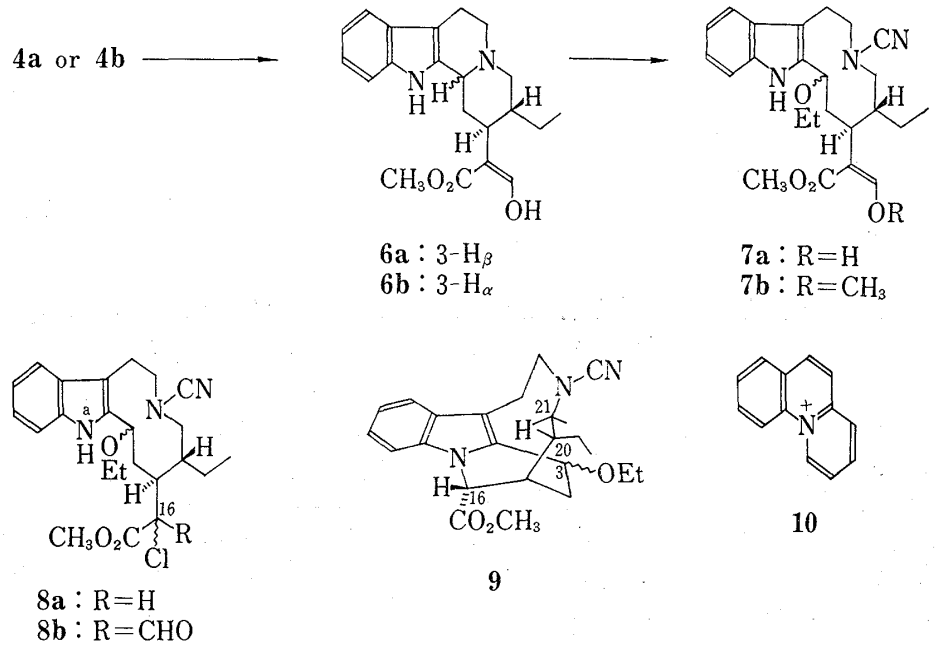
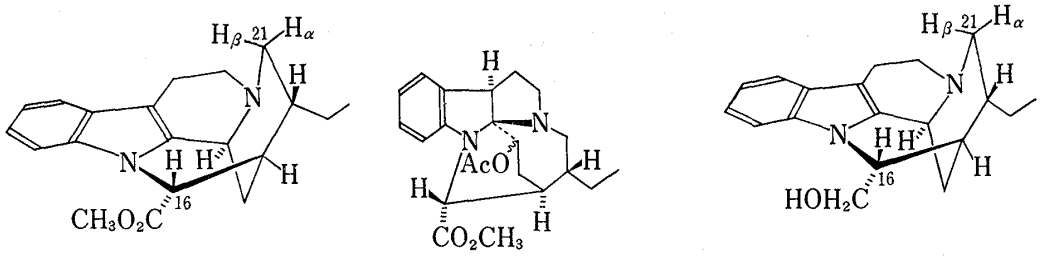


Chart 2

The epimeric mixture (**7a**) was oxidized in about 90% yield to the C_{16}-deformyl-chlorinated compound (**8a**) with freshly distilled 1.2 molar equivalent of *t*-BuOCl in CCl_4 solution at −78°. The ultraviolet (UV) spectrum of chlorinated compound (**8a**) showed the typical indolic chromophore (λ_{max}^{EtOH} 227, 285 and 293 nm) and no shift on addition of aq. NaOH, which indicated the absence of β-hydroxyacrylic ester moiety of the compound (**7a**). The mass spectrum of **8a** exhibited M^+ at *m/e* 431 (96%) and M^++2 at 433 (36%). The nuclear magnetic resonance (NMR) spectrum of **8a** showed a signal due to C_{16}–H at δ 4.23 ppm (d, 1H). A similar oxidation of **7a** at a higher temperature (0°) resulted in the formation of three compounds, which were separated by silica gel column chromatography. The first eluted compound (in 11% yield) showed *m/e* 461 (M^++2, 18%) and *m/e* 459 (M^+, 46%) in its mass spectrum and three singlet aldehyde signals at δ 9.08, 9.16 and 9.44 ppm (total 1H) in its NMR spectrum, which suggested that it contained at least three diastereomers (**8b**). The C_{16} chlorinated isomers (**8b**) were deformylated to give **8a** by heating with powdered glass under a reduced pressure. The second eluted compound (in 27% yield) was a compound (**8a**) described above. The third eluted compound (in 15% yield) showed the UV spectrum of a 2-acylindolic chromophore (λ_{max}^{EtOH} 228, 245 and 315 nm) and the presence of a β-hydroxyacrylic ester moiety was proved by adding aq. NaOH ($\lambda_{max}^{EtOH+NaOH}$ 283, 293 and 313 nm). The bond formation between Na and C_{16} of compound **8a** was accomplished by treatment with NaH and dimethyl sulfoxide (DMSO) under N_2 at 75°. The reaction product **9** was still a mixture of C_3 isomers, but its structure with a new strained ring was proved by the following characteristic spectral data. Thus the UV spectrum of **9** (λ_{max}^{EtOH} 229, 276 and 286 (sh.) nm) is similar to that of **1**. The mass spectrum of **9** exhibited the molecular ion peak at *m/e* 395 and a stable quinolinium ion **10** (*m/e* 180) which is characteristic of **1** and other mavacurine type compounds.[1] Furthermore the NMR spectrum of **9** showed a characteristic C_{21}–H_β (−0.90, 1H, m) which is highly shielded by the indole ring.

The final ring closure of **9** was achieved by heating with aq. HOAc and NH_4OAc to give the pure 20α-ethyl-19,20-dihydro-16-epi-pleiocarpamine (**5**), mp 169—171°, [$C_{20}H_{24}O_2N_2$ M^+; Calcd. *m/e* 324.1838, Found. *m/e* 324.1872, $M^+-CO_2CH_3$; *m/e* 265 and fragment **10**; *m/e* 180, λ_{max}^{EtOH} nm(log ε) 231.5 (4.37), 288 (3.81), 296 (3.73), NMR; δ, ppm 4.66 (s, 1H, C_{16}–H), 3.88



5 11 12

Chart 3

(s, 3H, $CO_2C\underline{H}_3$), 0.38 (dd, J=12 and 6 Hz, 1H, C_{21}–H_β), IR; $\nu_{max}^{CHCl_3}$ 1740 cm^{-1}] and an amorphous indoline derivative **11** [M^+; *m/e* 384, UV; λ_{max}^{EtOH} 253 and 307 nm, $\lambda_{max}^{EtOH-HCl}$ 243 and 294 nm, NMR; δ, ppm 4.24 (s, 1H, C_{16}–H), 3.72 (s, 3H, $CO_2C\underline{H}_3$), and 1.92 (s, 3H, $OCOC\underline{H}_3$)]. The α-configuration of methoxycarbonyl group on C_{16} of **5** was assumed from the comparison of the chemical shift values of C_{21}–H_β in the NMR spectra of **5** (*vide supra*) and the corresponding alcohol (**12**) [20α-ethyl-19,20-dihydronormavacurine: NMR; 0.41 ppm (dd, J=12.4 and 4 Hz, 1H, C_{21}–H_β]. Essentially no difference was observed between them, suggesting no deshielding effect of methoxycarbonyl group to C_{21}–H_β was present in **5** in contrast with the case of **1** which has 16-β-carbomethoxy group. The mass spectrum of this alcohol (**12**) showed the same fragmentation peaks [*m/e* 296 (M^+, 64%), 266 (23), 265 (100), 236 (13), 222 (10), 206 (18), 194 (14), 182 (22), 181 (12), and 180 (42)] as recorded for 20β-ethyl-19,20-dihydronormavacurine, even the relative intensities of the fragmentation peaks were very similar.

During this chemical transformation reaction, all the intermediates were mixtures of diastereomers, even though the desired compound (**5**), with the more stable α-carbomethoxy function at C_{16}, was obtained in pure form. In order to avoid this difficulty, we used dihydrocorynantheine (**4b**) as the starting material instead of hirsutine (**4a**). Treatment of desmethyldihydrocorynantheine (**6b**) with BrCN/20% EtOH–$CHCl_3$ then gave a sole 3-(*R*)-ethoxy derivative of **7a**, in 25% yield. When C_3-(*R*)-**7a** was treated with *t*-BuOCl in a previously described manner, C_{16}-deformyl-chlorinated compound C_3-(*R*)-**8a** was formed in 56% yield. Presumably a mixture of two diasteromers on C_{16} should be formed in this reaction. The reaction of C_3-(*R*)-**8a** with NaH in DMSO proceeded in 53% yield to give C_3-(*R*)-**9** after treatment of the reaction product with CH_2N_2. This compound was obtained as colorless prisms (mp 157—158°) from ether, and its spectral properties [λ_{max}^{MeOH} nm(log); 228.5 (4.49), 275 (3.85), 286 (3.77), and mass, IR and NMR spectra] and the values of elemental analysis are in very good agreement with the assigned structure **9**. Treatment of C_3-(*R*)-**9** with aq. HOAc and NH_4OAc, as in the case of the C_3 diastereomeric mixture **9** derived from hirsutine (**4a**), gave **5** and **11**. Though we expected only the desired **5** would be formed through a SN_2 reaction between C_3-(*R*)-OEt and Nb of C_3-(*R*)-**9**, the formation of the by-product (**11**) was unavoidable.

The convertion of geissoschizine (**3**) to pleiocarpamine (**1**) itself is under investigation.

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Errata for Chemical & Pharmaceutical Bulletin

Vol.	Page	Line	Error	Correction
22	1029	↑2	from hog pancreas	from bovine pancreas
	1167	footnote 1)	*Chem. Pharm. Bull.* (Tokyo), in **22**, 4 (1974).	*Chem. Pharm. Bull.* (Tokyo), **22**, 889 (1974).
	1186	footnote 4*c*)	Y. Tamana	T. Yamana
		footnote 4*f*)	Y. Tamana	T. Yamana
	1203	↓16	An ice-cooled stirred solution of a tertiary amine (1 mmole) in CH_2Cl_2 (2—3 ml).	To an ice-cooled stirred solution of a tertiary amine (1 mmole) in CH_2Cl_2 (2—3 ml) was added a solution of MSH (1 mmole) in CH_2Cl_2 (2—3 ml).
	1249	↑13	$-\log \frac{1+K_1t}{K_1t(1+K_Tt)}$	$\log -\frac{1+K_1t}{K_1t(1+K_Tt)}$
	1251	footnote 23)	*Chem. Rev.*, **57**, 1[(1957).	*Chem. Rev.*, **57**, 1 (1957).
	1252	footnote 25)	[*A.C.*, **34**, 4866 (1940)].	[*C.A.*, **34**, 4866 (1940)].
	1328	↑27	(98.1 g 0.5 mole)[1b]	(98.1 g 0.5 mole)[4c]
	2326	Fig. 4 ↑3	$p \leq 0.05$	$p \geq 0.05$