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. Recently, Boekelheide has reported a synthesis of closely related 19,20-dihydropapavincovine (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}. In this communication we wish to report that a partial synthesis of 20-ethyl-19,20-dihydro-16-epipleiocarpamine (5) has been accomplished starting either from hirsutine (4a) or dihydrocorynantheine (4b).

![Chemical structures](image)

Chart 1

Very recently, we have described the facile C/D ring opening and regeneration reactions of 4a and other indole alkaloids. Desmethylichirsutine (6a) (mp 116—119°), which was derived from 4a with acetic anhydride-HCl at 0° in 61% yield, was submitted to the C/D ring cleavage reaction using BrCN in 0.6% EtOH-CHCl₃. 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

to a mixture of two known compounds, 3-(R)-ethoxy and 3-(S)-ethoxy-Nb-cyano-3,4-seco-
hirsutine (7b), by methylation with CH₃N₂.

\[ 4a \text{ or } 4b \rightarrow \]

\[
\begin{align*}
4a & : \text{R = H} \\
4b & : \text{R = CH₃}
\end{align*}
\]

\[
\begin{align*}
6a & : 3-\text{H}_3 \\
6b & : 3-\text{H}_ω
\end{align*}
\]

\[
\begin{align*}
7a & : \text{R = H} \\
7b & : \text{R = CH₃}
\end{align*}
\]

\[
\begin{align*}
8a & : \text{R = H} \\
8b & : \text{R = CHO}
\end{align*}
\]

**Chart 2**

The epimeric mixture (7a) was oxidized in about 90% yield to the C₁₆-deformyl-chlorinated
compound (8a) with freshly distilled 1.2 molar equivalent of t-BuOCl in CCl₄ solution at -78°C.
The ultraviolet (UV) spectrum of chlorinated compound (8a) showed the typical indolic chromophore ($λ_{max}$ 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 C₁₆–H at δ 4.23 ppm (d, 1H). A similar oxidation of 7a at a higher temperature (0°C) 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 C₁₆ chlorinated isomers (8b) were dechlorinated to give 8a by heating with powdered glass under a reduced pressure. The second eluted compound (27% yield) was a compound (8a) described above. The third eluted compound (in 15% yield) showed the UV spectrum of a 2-acylindolic chromophore ($λ_{max}$ 228, 245 and 315 nm) and the presence of a β-hydroxyacrylic ester moiety was proved by adding aq. NaOH ($λ_{max}$+NaOH 283, 293 and 313 nm). The bond formation between Na and C₁₆ of compound 8a was accomplished by treatment with NaH and dimethyl sulfoxide (DMSO) under N₂ at 75°C. The reaction product 9 was still a mixture of C₆ isomers, but its structure with a new strained ring was proved by the following characteristic spectral data. Thus the UV spectrum of 9 ($λ_{max}$ 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. Furthermore the NMR spectrum of 9 showed a characteristic C₁₆–Hₙ (−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 NH₄OAc to give the pure 20α-ethyl-19,20-dihydro-16-epi-pleiocarpamine (5), mp 169–171°C, [α]₂₀° +152°; Calcd. m/e 324.1838. Found. m/e 324.1872, M⁺−CO₃CH₄; m/e 265 and fragment 10; m/e 180, $λ_{max}$ nm (log ε) 231.5 (4.37), 288 (3.81), 296 (3.73), NMR; δ, ppm 4.66 (s, 1H, C₁₆–H), 3.88
(s, 3H, CO₂CH₃), 0.38 (dd, J=12 and 6 Hz, 1H, C₃₉-H₃), IR; vCH₂CH= 1740 cm⁻¹] and an amorphous indoline derivative 11 [M⁺; m/e 384, UV; λmax 253 and 307 nm, λmax-NHCl 243 and 294 nm, NMR; δ, ppm 4.24 (s, 1H, C₆-H), 3.72 (s, 3H, CO₂CH₃), and 1.92 (s, 3H, OCOCH₃)]. The α-configuration of methoxycarbonyl group on C₁₆ of 5 was assumed from the comparison of the chemical shift values of C₃₉-H₃ in the NMR spectra of 5 (vide supra) and the corresponding alcohol[12] [20α-ethyl-19,20-dihyronormavacurine: NMR; 0.41 ppm (dd, J=12.4 and 4 Hz, 1H, C₃₉-H₃)]. Essentially no difference was observed between them, suggesting no deshielding effect of methoxycarbonyl group to C₃₉-H₃ was present in 5 in contrast with the case of 1 which has 16-β-carboxemethoxy group. The mass spectrum of this alcohol (12) showed the same fragmentation peaks [m/e 296 (M⁺, 64%), 266 (29), 265 (100), 236 (13), 222 (10), 206 (18), 194 (14), 182 (22), 181 (12), and 180 (42)] as recorded for 20β-ethyl-19,20-dihyronormavacurine, 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-carboxemethoxy function at C₁₆, 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-CHCl₃ then gave a sole 3-(R)-ethoxy derivative of 7a, in 25% yield. When C₃₉(R)-7a was treated with t-BuOCl in a previously described manner, C₆-deformyl-chlorinated compound C₃₉(R)-8a was formed in 56% yield. Presumably a mixture of two diastereomers on C₁₆ should be formed in this reaction. The reaction of C₃₉(R)-8a with NaH in DMSO proceeded in 53% yield to give C₃₉(R)-9 after treatment of the reaction product with CH₂N₂. This compound was obtained as colorless prisms (mp 157—158°) from ether, and its spectral properties [λmax CH₂Cl₂ (log λ); 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 C₃₉(R)-9 with aq. HOAc and NH₄OAc, as in the case of the C₃₉ diastereomeric mixture 9 derived from hirsutine (4a), gave 5 and 11. Though we expected only the desired 5 would be formed through a SN₂ reaction between C₃₉(R)-OEt and Nb of C₃₉(R)-9, the formation of the by-product (11) was unavoidable.

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

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## Errata for Chemical & Pharmaceutical Bulletin

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