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# Synthesis of Peptide Alkaloid, Amphibine-I and Related Compounds

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Synthesis of amphibine-I ($I_{A-a}$) and its diastereoisomeric compounds ($I_{A-b}$), ($I_{B-a}$), and ($I_{B-b}$) was completed by condensation of four diastereoisomeric 1-(α-aminoethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines ($V_{A-a,b}$ and $V_{B-a,b}$) with benzyloxycarbonyl-L-valylglycine followed by removal of the protecting group.

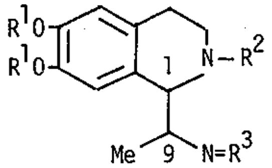
Amphibine-I ($I_{A-a}$) is one of the peptide alkaloids isolated from *Zizyphus amphibia* A. Cheval (Rhamnaceae) and its structure elucidation and synthesis were accomplished by Tschesche and his co-laborators1), 2), suggesting that the naturally occurring alkaloid is a mixture of the diastereoisomers having (S,R) and (R,S) configuration at C-1 and C-9, respectively.

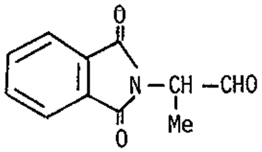
We report here the synthesis of amphibine-I and its diastereoisomers in optically active form using four diastereoisomeric 1-(α-aminoethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines ($V_{A-a,b}$ and $V_{B-a,b}$).

Condensation of the aldehyde (II) (racemic)[3] with dopamine hydrochloride in methanol under argon for 7 days gave a mixture of the diastereoisomeric tetrahydroisoquinolines ($III_A$ and $III_B$) revealed by thin layer chromatography in 37% yield. The mixture was, without further purification, subjected to the methylation with diazomethane followed by Eschweiler-Clarke condition to give a mixture of the non-phenolic isoquinolines. Separation of the mixture was carried out at this stage by preparative thin layer chromatography, furnishing a pair of diastereoisomers ($IV_A$) and ($IV_B$). The faster running one ($IV_A$), m.p. 126-127°, showed the following spectroscopic properties: IR ($CHCl_3$), 1760 and 1700cm$^{-1}$ (CO); NMR ($CDCl_3$), δ, 1.47 (3H, d, J=7Hz, CH-$C\underline{H}_3$), 2.52 (3H, s, N-$CH_3$), 3.11 and 3.82 (3H each, s, $OCH_3$), 6.24 and 6.61 (1H each, s, aromatic H), and 7.77 (4H, m, protons of the phthaloyl moiety). The slower running one ($IV_B$), m.p. 163-165°, showed the same carbonyl bands in its IR spectrum and NMR spectrum (δ) revealed 1.52 (3H, d, J=7Hz, CH-$C\underline{H}_3$), 2.27 (3H, s, N-$CH_3$), 3.90 and 3.92 (3H each, s, $OCH_3$), 6.67 and 6.81 (1H each, s, aromatic H), and 7.83 (4H, m, protons of the phthaloyl moiety). Removal of the phthaloyl moiety from ($IV_A$) and ($IV_B$) with hydrazine hydrate in the usual manner gave the corresponding amino-isoquinolines ($V_A$) and ($V_B$) in 85% yield, respectively.

The amino-isoquinolines ($V_A$) and ($V_B$) were resolved into four diastereoisomeric amino-isoquinolines ($V_{A-a}$, $V_{A-b}$, $V_{B-a}$ , and $V_{B-b}$) using di-(p-toluoyl)-l- and d-tartaric acids in acetonitrile and l- and d-tartaric acids in methanol, respectively. $[\alpha]_D$-Values of four diastereoisomeric amino-isoquinolines obtained by the above resolution were listed in Table II and CD curves of the corresponding benzoates ($VI_{A-a,b}$ and $VI_{B-a,b}$) were depicted in Fig. I. Based on the sign of the Cotton effect around 285nm, it was, at least, indicated that ($VI_{A-a}$) and ($VI_{B-a}$) have the S-configuration and ($VI_{A-b}$) and ($VI_{B-b}$) have the R-configuration at C-1 position$^{4)}$. The R-configuration at C-9 of ($V_{A-a}$) was proposed from the fact that NMR spectrum of amphibine-I synthesised from ($V_{A-a}$) was identical in the NMR spectrum with that of naturally occurring amphibine-I which had been confirmed to have the S- and R-configuration at C-1 and C-9, respectively, though it was reported that amphibine-I is contaminated with a small amount of the compound enantiomeric at both of the carbons. And configurations at C-9 position of the other diastereoisomers were culminated as indicated in the Chart.

Coupling reaction of each of the amino-isoquinolines ($V_{A-a,b}$ and $V_{B-a,b}$) and benzyloxycarbonyl-valylglycine$^{5)}$ with DCC in the presence of N-hydroxybenztriazole$^{6)}$ gave the diastereoisomeric isoquinolines ($VII_{A-a}$, $VII_{A-b}$, $VII_{B-a}$, and $VII_{B-b}$), which were hydrogenated with palladium as a catalyst in methanol to give the respective four diastereoisomers ($I_{A-a}$, $I_{A-b}$, $I_{B-a}$, and $I_{B-b}$). CD curves of these compounds were shown in Fig. II. Of



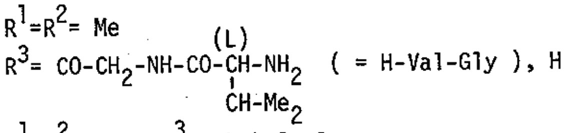


(II)

Suffix;

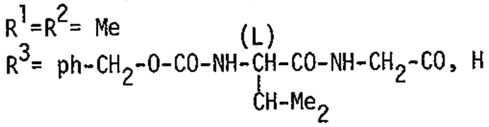
A: $C_1$= S, R, $C_9$= R, S
B: $C_1$= S, R, $C_9$= S, R
A-a: $C_1$= S, $C_9$= R
A-b: $C_1$= R, $C_9$= S
B-a: $C_1$= S, $C_9$= S
B-b: $C_1$= R, $C_9$= R

(I) $R^1$=$R^2$= Me



$R^3$= $CO\text{-}CH_2\text{-}NH\text{-}CO\text{-}\overset{(L)}{\underset{CH\text{-}Me_2}{CH}}\text{-}NH_2$ ( = H-Val-Gly ), H

(III) $R^1$=$R^2$= H, $R^3$= phthaloyl
(IV) $R^1$=$R^2$= Me, $R^3$= phthaloyl
(V) $R^1$=$R^2$= Me, $R^3$= $H_2$
(VI) $R^1$=$R^2$= Me, $R^3$= CO-ph, H
(VII) $R^1$=$R^2$= Me



$R^3$= $ph\text{-}CH_2\text{-}O\text{-}CO\text{-}NH\text{-}\overset{(L)}{\underset{CH\text{-}Me_2}{CH}}\text{-}CO\text{-}NH\text{-}CH_2\text{-}CO$, H

Table. I

| | ( $I_{A-a}$ ) | ( $I_{A-b}$ ) | ( $I_{B-a}$ ) | ( $I_{B-b}$ ) | Amphibine-I 1) (naturally occurring) |
|---|---|---|---|---|---|
| [ α ]$_D$ | - 20.6° | + 17° | - 40.5° | + 15° | - 50°<br>( benzene ) |

Table. II

|  | $[\alpha]_D$ free base | $[\alpha]_D$ salt |  | $[\alpha]_D$ benzoate |
|---|---|---|---|---|
| $V_{A-a}$ | + 21° | + 106° (methanol) | $VI_{A-a}$ | - 78° |
| $V_{A-b}$ | - 19.8° | - 100° (methanol) | $VI_{A-b}$ | + 70° |
| $V_{B-a}$ | + 10° | - 24° (water) | $VI_{B-a}$ | - 8.5° |
| $V_{B-b}$ | - 10° (pyridine) | + 24° (water) | $VI_{B-b}$ | + 9.0° (methanol) |

Fig. I

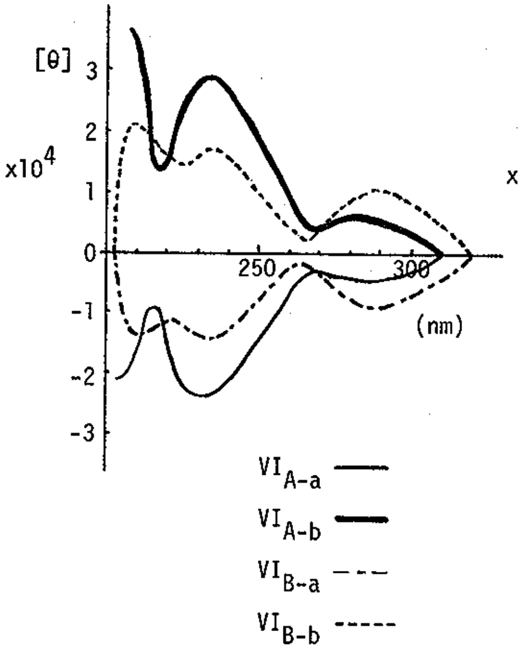
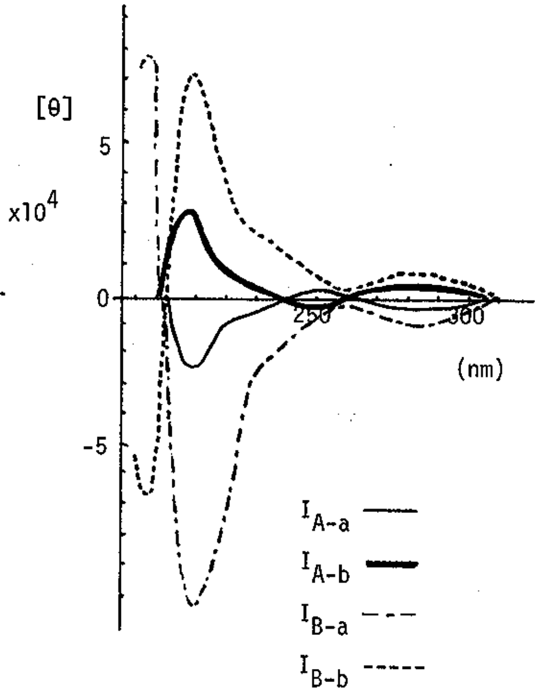


Fig. II



these compounds, ($I_{A-a}$) was identical with amphibine-I in spectroscopic comparison and TLC behaviour, though certain discrepancy of $[\alpha]_D$-values between our compound and that of literature is noted (see Table I).

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