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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.

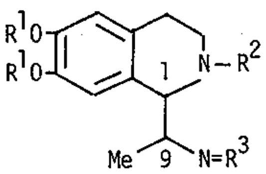
Amphibine-I (I_{A-a}) is one of the peptide alkaloids isolated from Zizyphus amphibia A. Cheval (Rhamnaceae) and its structure elucidation and synthesis were accomplished by Tschesche and his co-laborators$^{1), 2)}$, suggesting that the naturally occurring alkaloid is a mixture of the diastereoisomers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

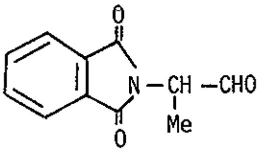
We report here the synthesis of amphibine-I and its diastereoisomers in optically active form using four diastereoisomeric 1-(α-aminoethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines ($V_{A-a,b}$ and $V_{B-a,b}$).

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



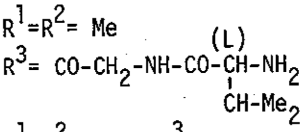


(II)

Suffix;

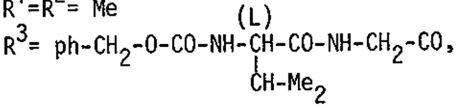
A: C_1= S, R, C_9= R, S
B: C_1= S, R, C_9= S, R
A-a: C_1= S, C_9= R
A-b: C_1= R, C_9= S
B-a: C_1= S, C_9= S
B-b: C_1= R, C_9= R

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



$R^3= \text{CO-CH}_2\text{-NH-CO-}\underset{\text{CH-Me}_2}{\overset{(L)}{\text{CH}}}\text{-NH}_2$ (= 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



$R^3= \text{ph-CH}_2\text{-O-CO-NH-}\underset{\text{CH-Me}_2}{\overset{(L)}{\text{CH}}}\text{-CO-NH-CH}_2\text{-CO}$, H

Table. I

	(I_{A-a})	(I_{A-b})	(I_{B-a})	(I_{B-b})	Amphibine-I 1) (naturally occurring)
$[\alpha]_D$	- 20.6°	+ 17°	- 40.5°	+ 15°	- 50° (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

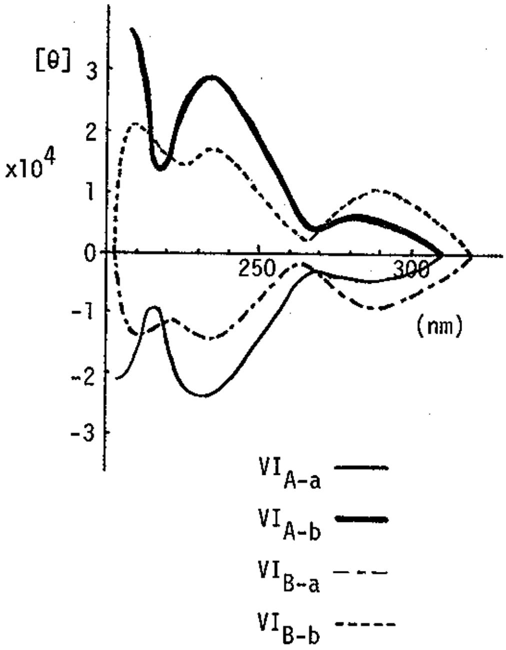
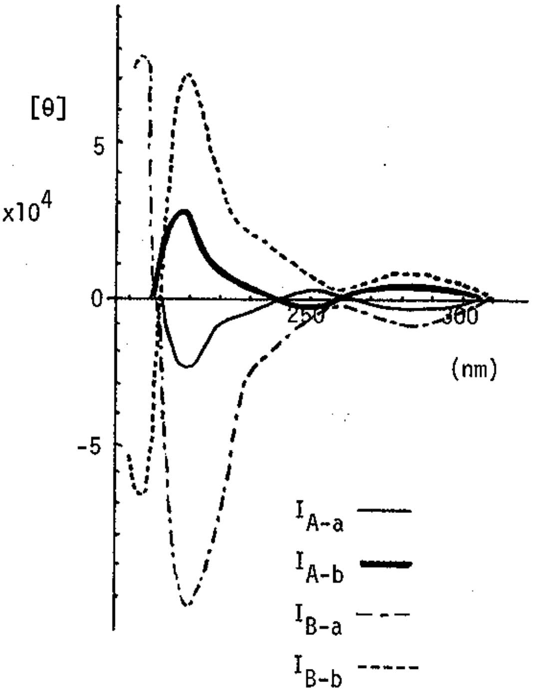


Fig. II



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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