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STEREOSELECTIVE INTRAMOLECULAR ALDOL CONDENSATION OF SECOKETONES OBTAINED FROM GRAYANOTOXIN-II

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Grayanotoxin-II (1) and its dihydroderivatives can be oxidized with lead-tetraacetate to corresponding secoketones which easily isomerize by alkaline treatment into respective tetrahydroxyketones (2).

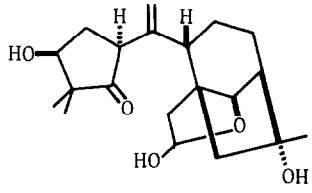
This paper deals with a circumstantial examination of the isomerization reaction towards both secoketone(I) and secoketone triacetate(II) obtained from Grayanotoxin-II and its triacetate respectively, and also with the stereochemistry of the products.

The secoketone(I) was treated with 3% methanolic sodium hydroxide for 15 minutes at various temperatures and the products were separated by preparative TLC into two tetrahydroxyketones, (IIIa), mp 249°(decomp.), $C_{20}H_{30}O_5$, $[\alpha]_D^{25}$ -102° (c 0.22, ethanol), and (IIIb), mp 254°(decomp.), $C_{20}H_{30}O_5$, $[\alpha]_D^{25}$ -18°(c 0.21, ethanol). While the total yields were always above 95%, the ratio of IIIa to IIIb decreased remarkably with the rise of temperature, 93:7 at -20°, 50:50 at 25° and 0:100 at 65°. In the last condition, IIIa was converted into IIIb quantitatively. The two products, IIIa and IIIb, were acetylated with acetic anhydride-pyridine to give respective tetraacetates, (IVa), mp 147°, $C_{28}H_{38}O_9$, and (IVb), mp 152°, $C_{28}H_{38}O_9$. On oxidation with chromic acid-65% acetic acid, IIIa and IIIb gave tetraketones, (Va), mp 228°(decomp.), $C_{20}H_{24}O_5$, and (Vb), mp 232°(decomp.), $C_{20}H_{24}O_5$, respectively. These results indicate that the isomerization reaction is of an intramolecular aldol condensation type forming C_1-C_6 bond and also that the two products, IIIa and IIIb, are epimeric each other at C_1.

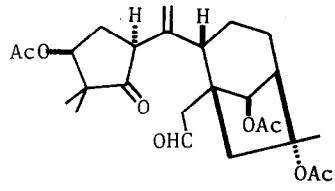
While merely two diastereoisomers, IIIa and IIIb were obtained from the

secoketone(I), all four possible stereoisomers were obtained as follows. On oxidation with lead tetraacetate, Grayanotoxin-II triacetate (1) gave secoketone triacetate(II), mp 129°, $C_{26}H_{36}O_8$. The ethereal solution of II was stirred with 3% aqueous sodium hydroxide at 0° for 15 minutes and the oily products were separated on silica gel column into four compounds, (VIa-1), mp 170°, (VIa-2), mp 190°, (VIb-1), mp 161°, and (VIb-2), mp 177°, in a ratio of 60:19:13:8, total yields 90%. All of them showed the same molecular formula, $C_{26}H_{36}O_8$, by elemental analysis and exhibited similar spectral features, i.e., IR absorptions at ca. 3500(OH), 1640 and 890 cm^{-1}(=CH_2), UV absorption at ca. 300 mμ(ε 30-90) and NMR absorptions of five protons at δ($CDCl_3$) 3.5-5.5(=$C\underline{H}_2$ and three $\underline{H}\dot{C}OR$). Since two of the four products, VIa-1 and VIb-1 could be acetylated to the tetraacetates, IVa and IVb respectively, they proved to be the respective triacetates of IIIa and IIIb. Both VIa-1 and VIa-2 were oxidized to an identical diketone(VIIa), mp 167°, $C_{26}H_{34}O_8$, and also both VIb-1 and VIb-2 to another diketone(VIIb), mp 183°, $C_{26}H_{34}O_8$. Consequently the two compounds(suffix 1 and 2) in either group(suffix a or b) must be epimeric each other at C_6, and each group should be opposite in the configuration of C_1. The existence of β-diketone moiety in VIIa was demonstrated by successive alkaline hydrolysis of VIIa, lactonization with acid and ultimate acetylation to give an authentic specimen of acetyl-α,β-unsaturated keto-γ-lactone(VIII) (2) together with its C_9-epimer, mp 156°.

The absolute configurations of the isomerization products were determined as follows. Treatment of the tetrahydroxyketone(IIIb) with diethylacetal and catalytic amounts of p-toluenesulfonic acid in isopropyl ether gave a diacetal (IX), mp 223°(decomp.), $C_{24}H_{34}O_5$, no hydroxyl absorption in IR spectrum; this reverted to IIIb on hydrolysis with acetic acid-water. Since one of the two acetal groups is attached to C_3 and C_6, the C_6-carbinol group must be cis to 3β-hydroxyl group with respect to ring A, thus the C_1-configuration of b-group is determined as R. Since Horeau's asymmetric synthesis (3) applied to the triacetate(VIa-1) gave dextrorotatory α-phenylbutyric acid(esterification yield 38%, optical yield 44%), its C_6-configuration can be determined as R, accordingly that of VIa-2 as S. In the NMR spectrum of VIb-2 the signal of C_6-hydroxyl proton was observed as a doublet(J=2.2 cps) at an exceptionally lower



(I)



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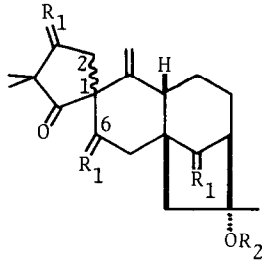
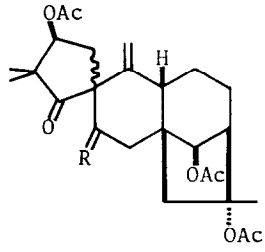




(IIIa*), (IIIb*): R_1= , R_2=H

(IVa), (IVb): R_1= , R_2=Ac

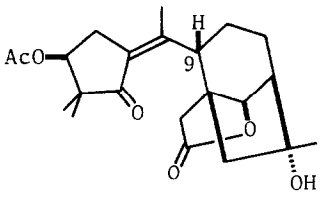
(Va), (Vb): R_1=O, R_2=H

(VIa-1), (VIb-1): R=

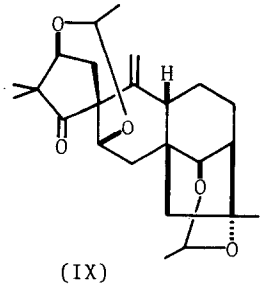
(VIa-2), (VIb-2): R=

(VIIa), (VIIb): R=O

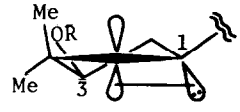
*in III-VII,
suffix a: C_1""C_2
suffix b: C_1—C_2



(VIII)



(IX)



(X)

field, $\delta(CDCl_3)$ 4.15, and that of C_6-proton as a multiplet at $\delta(CDCl_3)$ 3.81. On deuterium exchange, the former disappeared and the latter turned into a triplet (J=2.7 cps). These NMR data indicate that the B ring is a chair form with the C_6-proton in an equatorial position and also that the C_6-hydroxyl group forms such a rigid intramolecular hydrogen-bond with the C_5-carbonyl group that makes the hydroxyl proton coupled to the C_6-proton; the C_6-configuration of VIb-2 is thus determined as S.

The C_1-S isomers obtained predominantly at low temperature can be regarded as those produced through a kinetically controlled process, while the C_1-R isomer as a product owing to its thermodynamic stability. The stereoselectivity of the former depends on the stereochemistry of the intermediate carbanion. The C_1-carbanion moiety produced by the attack of base on secoketones may take either planar or tetrahedral conformation. In the former case, the A ring becomes nearly coplanar and the C_6-aldehyde group would approach it from the opposite side of 3β-substituent to give C_1-S configuration (4). If a tetrahedral conformation is provided, the most stable conformation for the A ring would be such a half chair form with the two C_1- and C_3-substituents in a cis-relationship and in diequatorial position(X) as shown by J.Jacques in a 4,4-dimethyl-1,3-disubstituted cyclopentan-5-one (5). Then the anionic electron pair occupies an axial position and gives again the C_1-S configuration. Furthermore this axial electrons would be stabilized by the conjugation with the C_5-carbonyl group as shown by E.J.Corey (6).

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