CHEMISTRY LETTERS, pp. 773-776, 1973. Published by the Chemical Society of Japan

PYRROLIZIDINE ALKALOIDS. THE ABSOLUTE CONFIGURATIONS OF LATIFOLIC ACID AND ITS STEREOISOMERS

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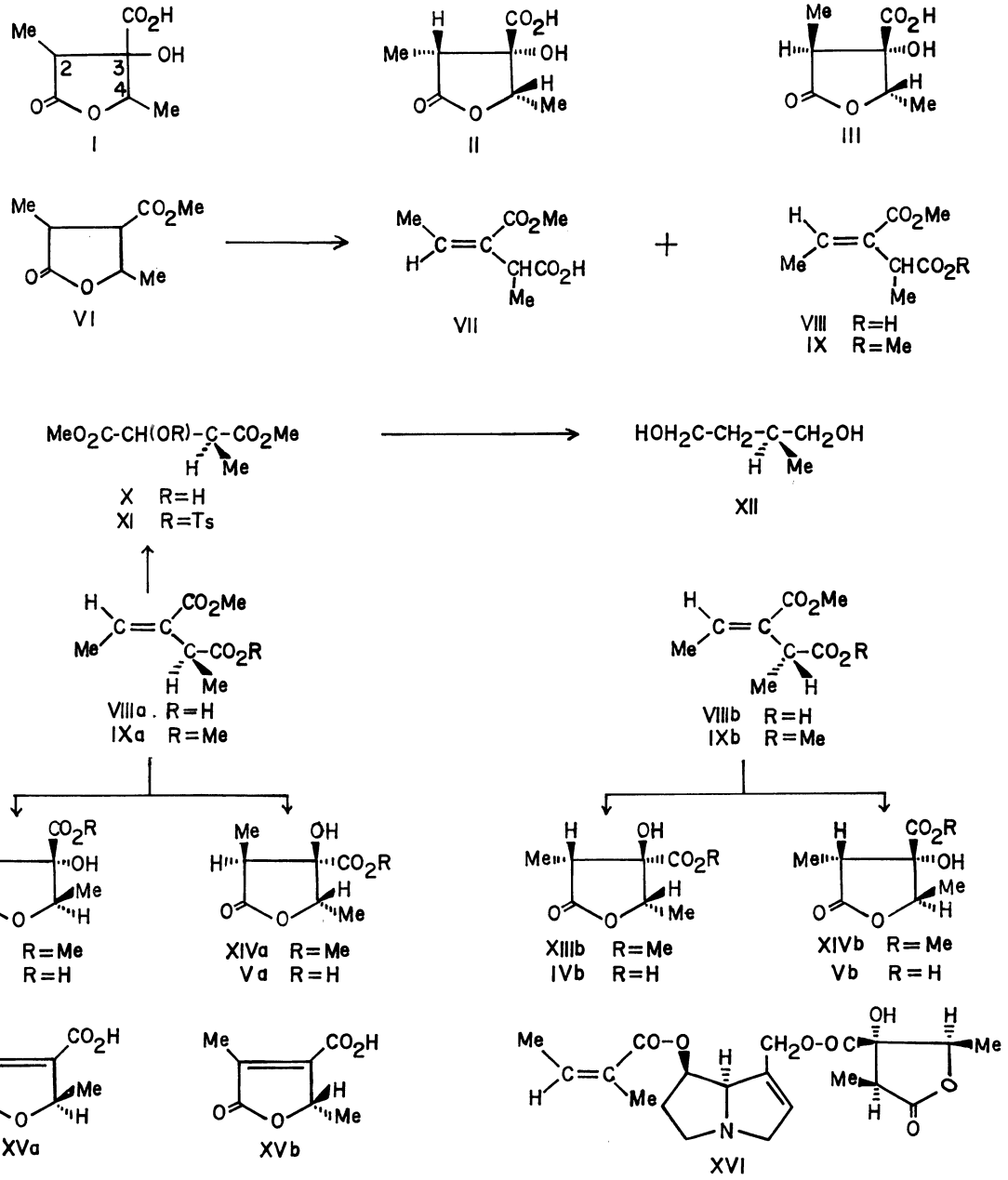
The absolute configurations of latifolic acid (IVa) and its stereoisomers (IVb, Va, and Vb) have been elucidated. (S)(+)-3-Methoxycarbonyl-2-methyl-cis-3-pentenoic acid (VIIIa), correlated to (S)(-)-2-methyl-1,4-butanediol (XII), was converted to latifolic acid (IVa: 2S,3S,4R) and Va (2S,3R,4S). Similarly, the enantiomer (VIIIb) was also converted to IVb (2R,3R,4S) and Vb (2R,3S, 4R). The CD spectra of these butyrolactones were also examined.

Latifolic acid, 3-carboxy-2,4-dimethyl-3-hydroxybutyrolactone (I), was isolated as a necic acid from latifoline, a pyrrolizidine alkaloid of Cynoglossum latifolium R. Br., by Crowley and Culvenor.[1] Eight stereoisomers are possible for I. However, since the stereochemistry of latifolic acid was not reported, the present authors attempted the total synthesis of the stereoisomers to confirm the proposed structure and to elucidate the stereochemistry of the natural acid. In a previous communication,[2] we reported on the synthesis of four diastereomeric racemates (II, III, IV, and V) for I and suggested that the configuration of latifolic acid is represented as IVa (2S,3S,4R) or its enantiomer IVb (2R,3R,4S). This communication will describe the synthesis and absolute configurations of the optically-active latifolic acid and its stereoisomers. Treatment of a mixture of diastereomeric (±)-2,4-dimethyl-3-methoxycarbonylbutyrolactones (VI)[2] in dry ether with sodium hydride and a small amount of methanol afforded a mixture of (±)-3-methoxycarbonyl-2-methyl-trans-3-pentenoic acid (VII) and its (±)-cis isomer (VIII), which by recrystallization from ether-petroleum ether gave VIII; mp 109-110°C ; NMR: 1.34 (d, J=7 Hz, $-\overset{1}{C}HC\underline{H}_3$), 1.86 (d, J=7 Hz, $=CHC\underline{H}_3$), 3.67 (q, J=7 Hz, $-\underline{C}\overset{1}{H}CH_3$), 3.71 (s, $-CO_2C\underline{H}_3$), 6.93 (q, J=7 Hz, $=\underline{C}HCH_3$). The cis-configuration in VIII was assigned by its NMR spectrum. That is, VIII showed

a signal of a vinyl proton at δ 6.93, suggesting the presence of a cis-methoxycarbonyl group relative to the vinyl proton, because the trans-isomer (VII) would be expected to show the corresponding signal at δ ca. 6.0.[2] This assignment was further confirmed by conversion of VIII to the methyl ester (IX), the IR spectrum of which was identical with that of an authentic methyl (±)-3-methoxycarbonyl-2-methyl-cis-3-pentenoate.[2] The half-ester (VIII) in acetone was successfully resolved by means of brucine, and one of the diastereomeric salts (mp 157-159°C) was decomposed with dilute hydrochloric acid to give VIIIa, mp 46-47°C, $[\alpha]_D$ + 117° ($CHCl_3$). The mother liquor, after the separation of the above brucine salt, gave another salt, mp 78° (sinter). This was also treated with dilute hydrochloric acid to give VIIIb, mp 47-48°C, $[\alpha]_D$ - 114° ($CHCl_3$). Methylation of VIIIa and VIIIb with diazomethane gave the corresponding esters; IXa, $[\alpha]_D$ + 109° ($CHCl_3$), and IXb, $[\alpha]_D$ - 107° ($CHCl_3$), respectively. For elucidation of the absolute configurations of these isomers, conversion of IXa to 2-methyl-1,4-butanediol was carried out. Ozonization of IXa in methanol at - 60°C, followed by reduction of the resulting ozonide with sodium borohydride gave dimethyl 3-methylmalate (X); $[\alpha]_D$ + 10.3° ($CHCl_3$); NMR: 1.25 (d, J=7 Hz, $-\dot{C}H\underline{C}H_3$), 2.98 (dq, J=4 and 7 Hz, $-\dot{C}\underline{H}CH_3$), 3.64 and 3.73 (each s, $2\text{-}CO_2\underline{C}H_3$), 4.29 (d, J=4 Hz, $-\dot{C}\underline{H}OH$). Two stereoisomers (threo and erythro) are possible for X. However, since the present work aimed at destroying the asymmetry at C-2, the crude X was immediately subjected to the next reaction. Tosylation of X in pyridine with p-toluenesulfonyl chloride gave the corresponding tosylate (XI); $[\alpha]_D$ + 23.5° ($CHCl_3$); NMR: 1.19 (d, J=7 Hz, $-\dot{C}H\underline{C}H_3$), 2.45 (s, $-C_6H_4\underline{C}H_3$), 3.08 (m, $-\dot{C}\underline{H}CH_3$), 3.62 and 3.67 (each s, $2\text{-}CO_2\underline{C}H_3$), 5.08 (d, J=6 Hz, $-\dot{C}\underline{H}O-$), 7.33 and 7.82 (each d and J=8 Hz, $-C_6\underline{H}_4CH_3$). Subsequently, XI was reduced with lithium aluminum hydride in dry ether to give the known (S)(-)-2-methyl-1,4-butanediol (XII);[3,4] $[\alpha]_D$ - 12.3° (acetone); NMR: 0.93 (d, J=6 Hz, $-\dot{C}H\underline{C}H_3$), 1.5-2.0 (m, $-C\underline{H}_2\dot{C}\underline{H}CH_3$), 3.30 (s, 2-O<u>H</u>), 3.3-3.8 (m, $2\text{-}C\underline{H}_2OH$). Thus, the absolute configurations of C-2 in VIIIa (or IXa) and VIIIb (or IXb) were identified as S and R respectively. Cis-hydroxylation of IXa in methanol with an aqueous solution of potassium permanganate and magnesium sulfate at - 25 ~ - 20°C gave the butyrolactones; XIIIa, mp 86-87°C, $[\alpha]_D$ + 99.0° ($CHCl_3$), and XIVa, mp 67-68°C, $[\alpha]_D$ - 107° ($CHCl_3$). The relative configurations of these lactones were easily determined on the comparisons of their spectra with those of the corresponding racemate.[2] Further, since no configurational change at C-2 of IXa would be expected in the above oxidation, the absolute configurations of XIIIa and XIVa were identified as 2S,3S,4R and 2S,3R,4S respectively. Hydrolysis of XIIIa with dilute hydrochloric acid gave the corresponding acid (IVa), mp 164-165°C, $[\alpha]_D$ + 86.7° (EtOH), along

with an α,β-unsaturated derivative (XVa), mp 186-188°C, $[\alpha]_D$ + 29.7° (EtOH). The IR spectrum of the synthetic IVa was identical with that of natural latifolic acid (mp 165-166°C, $[\alpha]_D$ + 94° (EtOH)).[1] Since methylation of IVa with diazomethane gave XIIIa, the absolute configuration of latifolic acid was identified as 2S,3S,4R. A similar hydrolysis of XIVa with dilute hydrochloric acid gave Va (2S,3R,4S), mp 129-130°C, $[\alpha]_D$ - 102° (EtOH), along with an α,β-unsaturated derivative (XVb), mp 186-188°C, $[\alpha]_D$ -32.4° (EtOH), and an epimeric acid (IVb: 2R,3R,4S), mp 164-165°C, $[\alpha]_D$ -86.6° (EtOH). The absolute configurations of C-4 in the enantiomeric XVa and XVb were also assigned as R and S respectively. Subsequently, IXb was oxidized with potassium permanganate to



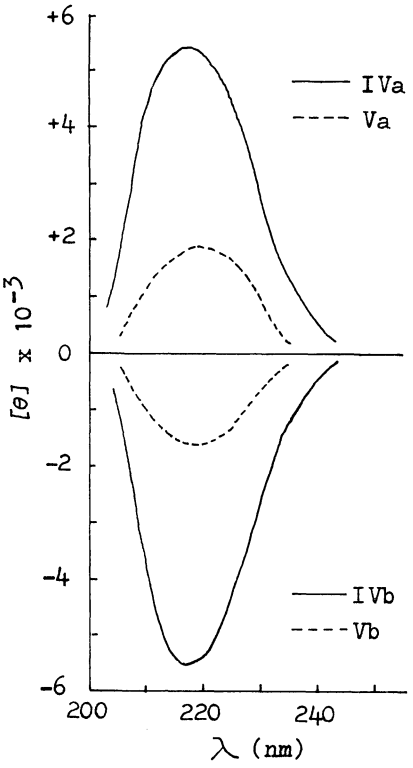


Fig. 1. The CD spectra of IVa,b and Va,b in ethanol

give XIIIb (2R,3R,4S), mp 86-87°C, $[\alpha]_D$ - 100° ($CHCl_3$), and XIVb (2R,3S,4R), mp 67-68°C, $[\alpha]_D$ + 106° ($CHCl_3$). Hydrolysis of XIIIb with dilute hydrochloric acid gave IVb, $[\alpha]_D$ - 86.8° (EtOH), along with XVb, $[\alpha]_D$ - 26.2° (EtOH), and Va, $[\alpha]_D$ - 98.5° (EtOH). Similarly, XIVb was also hydrolyzed to give Vb, $[\alpha]_D$ + 98.0° (EtOH), XVa, $[\alpha]_D$ + 32.4° (EtOH), and latifolic acid (IVa), $[\alpha]_D$ + 86.8° (EtOH). Further, Va and Vb were also obtained by the resolution of (±)-V with cinchonidine. From the above experiments, the absolute configuration of latifoline was fully elucidated as XVI.

It is of interest to know the relationship between the sign of the Cotton effect in CD spectra and the absolute configurations of the butyrolactone-acids possessing a carboxyl group at C-3. As shown in Fig. 1, the sign of the observed Cotton effect associated with the lactone n-π^* transition is not influenced by the substituents at C-3 and C-4, but the sign depends upon the configuration of C-2, as has been noted by Kinoshita et al.[5]

Acknowledgment. The authors are grateful to Dr. C. C. J. Culvenor, Division of Organic Chemistry, C.S.I.R.O. Chemical Research Laboratories, Melbourne, for his gift of natural latifolic acid.

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NMR spectra were taken on a Hitachi Model R-20 (60 MHz) using $CDCl_3$ as solvent and Me_4Si as an internal standard. Their chemical shifts are presented in terms of δ values; s: singlet, d: doublet, q: quartet, dq: double quartet, m: multiplet.

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(Received June 13, 1973)