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SENECIO ALKALOIDS. THE SYNTHESIS AND CONFIGURATION OF (±)-LATIFOLIC ACID

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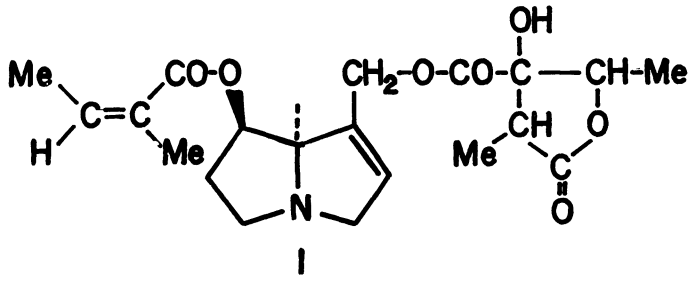
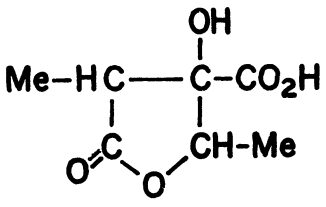
(±)-Latifolic acid and its three (±)-stereoisomers have been synthesized from dimethyl 1-acetyl-2-methylsuccinate. The synthetic (±)-2,cis-4-dimethyl-trans-3-hydroxy-cis-3-carboxybutyrolactone was shown to be identical with natural latifolic acid.

Latifoline (I) was isolated from Cynoglossum latifolium R. Br. by Crowley and Culvenor,[1] and the hydrogenolysis of I gave a new acid, named latifolic acid. On the basis of analytical and spectroscopic studies, they deduced the structure of latifolic acid to be II. Four racemic modifications are possible for II. However, since the stereochemistry of latifolic acid is as yet unknown the present authors attempted a total synthesis of latifolic acid to confirm the proposed structure and to elucidate the stereochemistry.



I

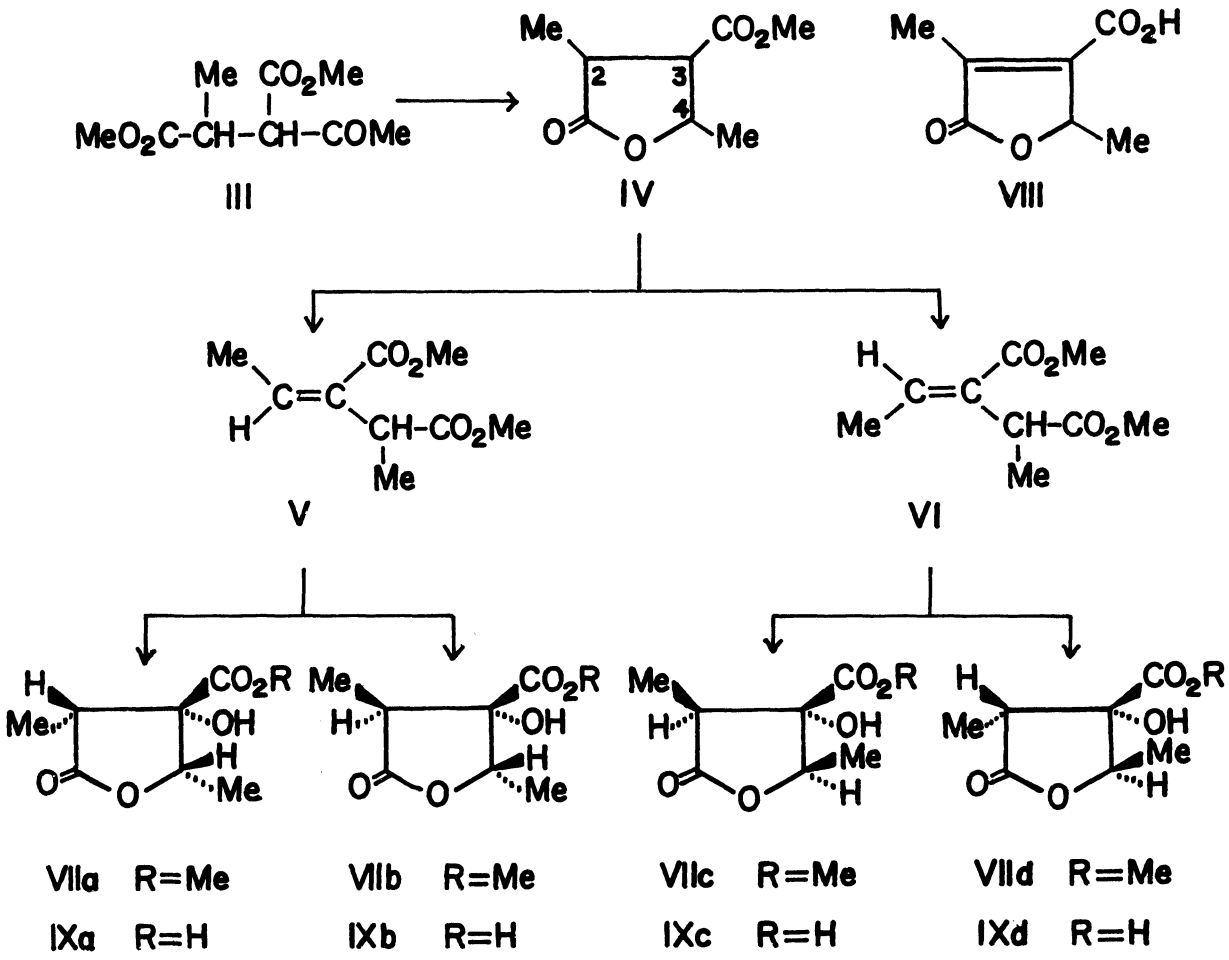


II

In this communication we wish to report a synthesis of (±)-latifolic acid and its stereoisomers. The reduction of dimethyl 1-acetyl-2-methylsuccinate (III)[2] in methanol with sodium borohydride gave a mixture of diastereomeric (±)-2,4-dimethyl-3-methoxycarbonylbutyrolactones (IV),[3] IR ($CHCl_3$): 1770, 1730 $cm.^{-1}$ The treatment of IV in dry benzene with sodium hydride and a small amount of methanol,

followed by the methylation with diazomethane gave a mixture of geometric isomers, which were then separated by means of column chromatography on silica gel into oily methyl (±)-3-methoxycarbonyl-2-methyl-trans-3-pentenoate (V), NMR in $CDCl_3$ (δ) (60 MHz): 1.25 (-CH($C\underline{H}_3$)-), 2.01 (=C($C\underline{H}_3$)-), 3.36 (-C$\underline{H}$(CH_3)-), 3.57 and 3.67 (2-$CO_2C\underline{H}_3$), 6.07 (=C$\underline{H}$-), and its (±)-cis-isomer (VI); NMR in $CDCl_3$ (δ): 1.34 (-CH($C\underline{H}_3$)-), 1.84 (=C($C\underline{H}_3$)-), 3.65 (-C$\underline{H}$(CH_3)-), 3.67 and 3.72 (2-$CO_2C\underline{H}_3$), 6.98 (=C$\underline{H}$-). The cis-hydroxylation of (±)-V in methanol with an aqueous solution of potassium permanganate and magnesium sulfate at - 25°C gave in a 7:1 ratio (±)-2,cis-4-dimethyl-cis-3-hydroxy-trans-3-methoxycarbonylbutyrolactone (VIIa); mp 139-140°C; IR ($CHCl_3$): 3540, 1780, 1735 cm^{-1} NMR in pyridine-d_5 (δ): 1.39 (C_2-$C\underline{H}_3$), 1.46 (C_4-$C\underline{H}_3$), 3.45 (C_2-$\underline{H}$), 3.74 (-$CO_2C\underline{H}_3$), 4.90 (C_4-$\underline{H}$), and (±)-2,trans-4-dimethyl-trans-3-hydroxy-cis-3-methoxycarbonylbutyrolactone (VIIb); mp 89-91°C; IR ($CHCl_3$): 3515, 1770, 1730 cm^{-1} NMR in $CDCl_3$ (δ): 1.13 (C_2-$C\underline{H}_3$), 1.37 (C_4-$C\underline{H}_3$), 2.85 (C_2-$\underline{H}$), 3.84 (-$CO_2C\underline{H}_3$), 4.67 (C_4-$\underline{H}$). The hydrolysis of (±)-VIIa with dilute hydrochloric acid gave, after chromatographic purification, (±)-α,β-unsaturated γ-lactone (VIII); mp 179-181°C; UV in EtOH: λ_{max} 226 nm (ε=12500); IR ($CHCl_3$): 3500-2500, 1760, 1700, 1660 cm^{-1} NMR in $(CD_3)_2CO$ (δ): 1.49 (-CH($C\underline{H}_3$)-), 2.12 (=C($C\underline{H}_3$)-), 5.18 (-C$\underline{H}$(CH_3)-), (±)-2,cis-4-dimethyl-cis-3-hydroxy-trans-3-carboxybutyrolactone (IXa); mp 125-126°C; IR (KBr): 3480, 3300-2600, 1750, 1720 cm^{-1} NMR in $(CD_3)_2CO$ (δ): 1.13 (C_2-$C\underline{H}_3$), 1.32 (C_4-$C\underline{H}_3$), 3.26 (C_2-$\underline{H}$), 4.78 (C_4-$\underline{H}$), and (±)-2,trans-4-dimethyl-trans-3-hydroxy-cis-3-carboxy-butyrolactone (IXb); mp 103-104°C; IR (KBr): 3480, 3300-2600, 1770, 1715 cm^{-1} NMR in $(CD_3)_2CO$ (δ): 1.15 (C_2-$C\underline{H}_3$), 1.35 (C_4-$C\underline{H}_3$), 2.86 (C_2-$\underline{H}$), 4.81 (C_4-$\underline{H}$). The methylation of (±)-IXa with diazomethane gave (±)-VIIa. Therefore, (±)-VIIa and (±)-IXa have the same configuration. The cis-configuration of the C_3-OH group relative to the C_4-CH_3 group in the above γ-lactones was assigned from the oxidation mechanism. The chemical shifts of the C_4-protons in the NMR spectra of IXa (δ 4.78 ppm) and IXb (δ 4.81 ppm) were observed respectively at the lower field than those of the corresponding IXd (δ 4.54 ppm) and IXc (δ 4.39 ppm) which are mentioned later. Therefore, it is evident that the signal of a cis-proton relative to the carboxyl group is present at the lower field than that of a trans-proton. The similar results were also reported by other workers.[4,5] Since the signals of the C_2-protons in the NMR spectra of (±)-IXa and (±)-IXb were observed at δ 3.26 ppm and at δ 2.86 ppm respectively, the configurations of the C_2-protons relative to the C_3-CO_2H groups were assigned to be cis for (±)-IXa and to be trans for (±)-IXb. The

IR spectra of (±)-IXa and (±)-IXb were different from that of natural latifolic acid. Subsequently, (±)-VI was also hydroxylated with an aqueous solution of potassium permanganate and magnesium sulfate to give two epimeric γ-lactones in an 1:4 ratio. From the reaction mechanism and spectral studies, the structures of these minor and major lactones were assigned respectively as (±)-2,cis-4-dimethyl-trans-3-hydroxy-cis-3-methoxycarbonylbutyrolactone (VIIc); mp 91-92°C; IR ($CHCl_3$): 3515, 1780, 1730 cm^{-1} NMR in $CDCl_3$ (δ): 1.15 (C_2-C$\underline{H}_3$), 1.31 (C_4-C$\underline{H}_3$), 2.95 (C_2-$\underline{H}$), 3.87 (-$CO_2C\underline{H}_3$), 4.42 (C_4-$\underline{H}$), and (±)-2,trans-4-dimethyl-cis-3-hydroxy-trans-3-methoxycarbonylbutyrolactone (VIId); mp 36-37°C; IR ($CHCl_3$): 3535, 1785, 1740 cm^{-1} NMR in $CDCl_3$ (δ): 1.24 (C_2-C$\underline{H}_3$), 1.26 (C_4-C$\underline{H}_3$), 3.13 (C_2-$\underline{H}$), 3.87 (-$CO_2C\underline{H}_3$), 4.52 (C_4-$\underline{H}$). The hydrolysis of VIIc with dilute hydrochloric acid gave (±)-VIII, (±)-2,cis-4-dimethyl-trans-3-hydroxy-cis-3-carboxybutyrolactone (IXc); mp 163-164°C; IR (KBr): 3490, 3300-2600, 1755, 1725 cm^{-1} NMR in $(CD_3)_2CO$ (δ): 1.15 (C_2-C$\underline{H}_3$), 1.32



(C_4-C$\underline{H}_3$), 2.99 (C_2-$\underline{H}$), 4.39 (C_4-$\underline{H}$), and (±)-2,trans-4-dimethyl-cis-3-hydroxy-trans-3-carboxybutyrolactone (IXd); mp 106-107°C; IR (KBr): 3300-2600, 1760, 1725 cm^{-1} NMR in $(CD_3)_2CO$ (δ): 1.18 (C_2-C$\underline{H}_3$), 1.31 (C_4-C$\underline{H}_3$), 3.23 (C_2-$\underline{H}$), 4.54 (C_4-$\underline{H}$). Similarly, (±)-VIId was also hydrolyzed with dilute hydrochloric acid to give (±)-IXc and (±)-IXd, which were converted respectively to (±)-VIIc and (±)-VIId by the methylation with diazomethane. The IR spectrum (KBr) of the synthetic (±)-IXc was superimposable with that of natural latifolic acid, while that of (±)-IXd was different.

From the present study, it is evident that the structure of latifolic acid is IXc (2S, 3S, 4R) or its mirror image (2R, 3R, 4S).

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