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THE CHEMICAL TRANSFORMATION OF CEPHALONIC ACID

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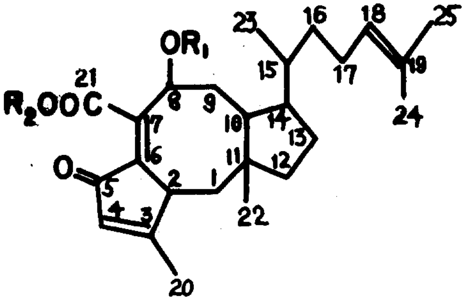
The complete structure of cephalonic acid, a minor metabolite of Cephalosporium caerulens, was elucidated by X-ray crystallographic analysis of its bromoacetate(1). We report herein the structure of the chemical transformation products of this compound as well as the chemical correlation to zizanin A isolated from another species of fungi. These are fully consistent with the results of the preceeding paper.

The ultraviolet and infrared absorptions of cephalonic acid (I) m.p. 139°, $C_{25}H_{36}O_4$, at 259 mμ (ε, 11700) and at 1690 cm^{-1}, 1610 cm^{-1}(strong) respectively are characteristic of the cisoid cyclopentadienone chromophore, and is similar to the absorption exhibited by achillin(2) and leukodin(3). The n.m.r. spectrum of I showed signals(4) at 0.85(3H, d, J=7, C_{23}-Me), 1.12(3H, s, C_{22}-Me), 1.60 and 1.68 (3H each, C_{24}-, C_{25}-Me), 2.19(3H, s, C_{20}-Me), at 6.13(1H, s, C_4-H), and at 4.44 (1H, d, J=11, C_2-H). The signals due to C_8-H and C_{18}-H overlapped and appeared together at 5.11(2H, t, J=7). An additional signal at 6.05(2H, broad s) due to a carboxylic and a hydroxylic proton disappeared on D_2O treatment.

Acetylation of I with acetic anhydride in pyridine at room temperature afforded an enol lactone acetate V, m.p. 120°, $C_{27}H_{36}O_4$(5), which showed absorption at 243 mμ (ε, 7000), 326.5 mμ (ε, 22000) in the ultraviolet and at 1790, 1778, 1747, 1647, 1615 cm^{-1} in the infrared spectrum, indicating the presence of an unsaturated enol lactone group. The n.m.r. spectrum of this compound showed the low field doublet of the exocyclic methylene group at 5.02 and 5.25. Hydrolysis of V with sodium bicarbonate in aqueous methanol gave methyl cephalonate acetate (III).

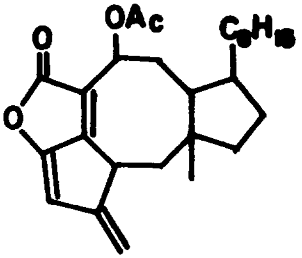


I R₁=R₂=H

II R₁=H, R₂=CH₃

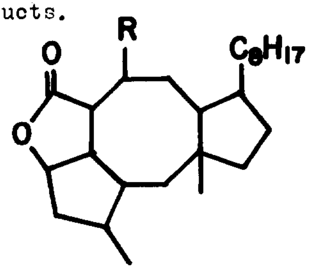
III R₁=Ac, R₂=CH₃

IV R₁=Ms, R₂=CH₃



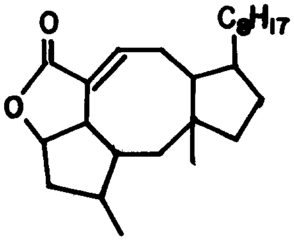
V

Hydrogenation of methyl cephalonate (II) with a platinum catalyst followed by column chromatography over silica gel afforded the three products. The major product (VI), m.p. 135°, $C_{25}H_{42}O_3$, was identified as a hydroxy-lactone. This compound showed infrared absorption at 1750 cm^{-1} (γ-lactone) and 3560 cm^{-1} (hydroxyl). Treatment of VI with potassium hydroxide in methanol gave rise to the dehydration product VIII, which also appears in the hydrogenation products. The compound VIII, m.p. 152-3°, $C_{25}H_{40}O_2$, showed ultraviolet absorption at 230 mμ, and n.m.r. signals at 6.96 due to a new olefinic proton. These spectral properties are similar to those of ophiobolin and its derivatives (6). The saturated lactone VII, m.p. 109°, $C_{25}H_{42}O_2$ (M^+=374), νmax 1767 cm^{-1}, was also isolated from the products.

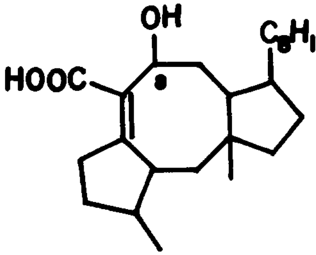


VI R=OH

VII R=H

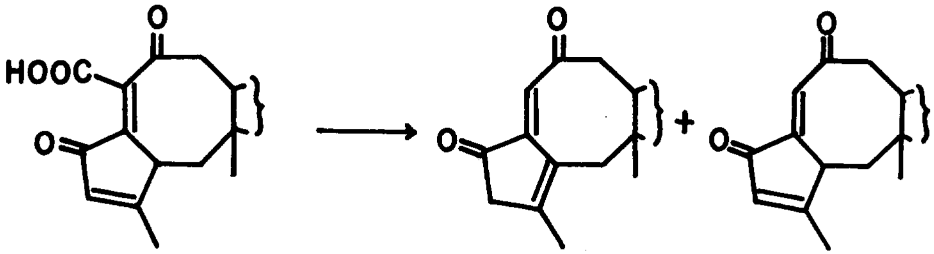


VIII

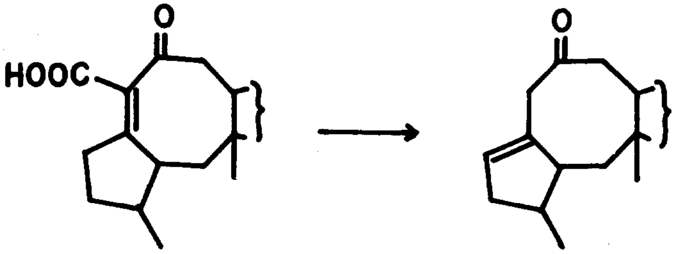


IX

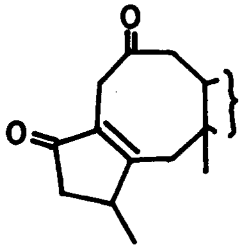
In contrast to the above results, hydrogenation of I with a palladium catalyst gave the octahydro derivative (IX), m.p. 79°, $C_{25}H_{42}O_3$(M^+=390), showing ultraviolet absorption at 231 mμ (ε, 9000) for the α,β-unsaturated carboxylic acid. The n.m.r. spectrum of this compound shows a triplet at 4.92(J=7), due to a methine proton on the carbon atom bearing a hydroxyl group which was found, from the ultraviolet absorption (λmax 227 mμ) of the oxidation product XIV, to be on C_8. Treatment of I with Kiliani reagent gave the diketo carboxylic acid X, m.p. 120-1°, νmax 1700, 1630 cm^{-1}. This compound showed ultraviolet absorption at 258.5 mμ (ε, 16000), practically identical with that of starting compound I.



X XI XII

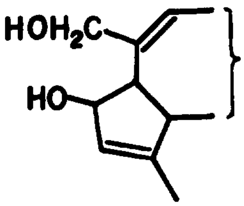


XIV XV

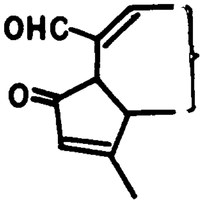


XIII

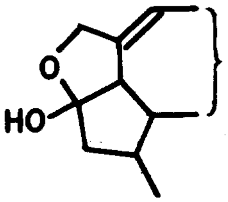
Compound X was readily decomposed upon heating at 130° to afford decarboxylated products, which were separated into two isomeric products XI, m.p. 102-3°, $C_{24}H_{34}O_2$ and XII, m.p. 89°, $C_{24}H_{34}O_2$(M^+=354). The former showed absorption in the ultraviolet at 314 mμ (ε, 9000) and bands at 1749, 1665, 1618 cm^{-1} in the infrared region, the latter, at 255.5 mμ (ε, 15500) in the ultraviolet and at 1699, 1671, 1610 cm^{-1} in the infrared region. Hydrogenation of XI gave XIII oily compd., $C_{24}H_{38}O_2$(M$^+$=358), λmax 243.5 mμ (ε, 10000), νmax 1717 cm^{-1}. The n.m.r. spectrum of XI and XII were consistent with these structures. The octahydro derivative IX was oxidised to XIV (oily compd.), whose ultraviolet absorption maximum (227 mμ (ε, 9000)) was also identical with that of the starting material. This compound also easily decarboxylates to afford the compound XV, m.p. 72-3°, $C_{24}H_{40}O$(M$^+$=344), λmax 288 (ε, Ca. 70)(n→π*), νmax 1697 cm^{-1}. The n.m.r. spectrum of XV shows a broad singlet at 5.45 (C_5-H) and AB-type quartet at 3.04 and 3.57(2H, J=14, C_7-methylene).



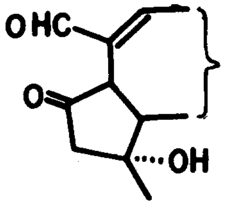
XVI



XVII



XVIII



XIX

Finally, cephalonic acid was chemically correlated to zizanin A (XIX), which has been isolated from Helminthosporium zizaniae (6). Treatment of II with methanesulfonyl chloride in pyridine gave the mesylate IV, m.p. 87°, along with a small amount of chloride. Lithium aluminium hydride reduction of IV at 0°C for a few minutes yielded the unstable dienediol XVI which was oxidised with chromium trioxide in pyridine to afford the noncrystalline keto aldehyde XVII. The compound XVII was found to be identical with the dehydration product of zizanin A (XIX) in the infrared, ultraviolet, n.m.r. and mass spectra (6). Furthermore lithium aluminium hydride reduction of XVII from both II and XIX gave the identical crystalline hemiketal XVIII, m.p. 131°, $C_{25}H_{40}O_2$(M$^+$=372). The n.m.r. spectrum of XVIII shows signals at 5.43(1H, m, C_8-H), 4.53(2H, broad s, C_{21}-methylene), 5.10(1H, t, C_{18}-H) and at 0.98(3H, d, J=6, C_{20}-methyl).

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4) Chemical shifts were expressed in δ-values from tetramethylsilane and coupling constants in c.p.s..

5) All new compounds gave satisfactory elemental analyses.

6) S. Nozoe, K. Hirai and K. Tsuda, Tetrahedron Letters, 2211 (1966).