The Constitution of Mexicanolide. A Novel Cleavage Reaction in a Naturally Occurring Bicyclo[3,3,1]nonane Derivative

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WE have obtained from *Cedrela mexicana* a crystalline lactone, $C_{27}H_{32}O_7$, m.p. 222—227°, $[\alpha]_D$ −90°, which we name mexicanolide and formulate as (I)* on the following evidence.†

The key to the constitution of mexicanolide is contained in its exceedingly ready reaction with base. Thus, the end-absorption in the u.v. spectrum shown by mexicanolide in neutral ethanol ($\lambda_{max.}$ 209 mμ; ε 10,850) is immediately supplanted by an intense new maximum at 287 mμ (ε 31,700) on addition of two drops of 4N-aqueous sodium hydroxide, and this in turn yields on acidification to a less intense maximum at 264 mμ (ε 20,800) with a shoulder at 285 mμ. The product of this irreversible base-catalysed transformation was isolated as the crystalline β-diketone (IIa or IIIa), $C_{27}H_{32}O_7$, m.p. 164—166°, $[\alpha]_D$+250°; $\lambda_{max.}$ 264 mμ (ε 25,300; shoulder at 285 mμ) in neutral ethanol, $\lambda_{max.}$ 287 mμ (ε 37,500) in alkaline ethanol; vinyl protons at τ 4·09 (multiplet, C–9) and 4·02 (singlet, C–15). This was further characterised as the enol acetate (IIb or IIIb), m.p. 172—173°, $[\alpha]_D$+299°; $\lambda_{max.}$ 238 mμ (ε 15,000), 277 mμ (ε 13,900) in neutral ethanol and as for the parent β-diketone in alkaline ethanol, and the enol methyl ether (IIc or IIIc), m.p. 164—166°, $[\alpha]_D$+337°; $\lambda_{max.}$ 210 mμ (ε 9,100), 262 mμ (ε 23,200), shoulder at 282 mμ, in neutral and alkaline ethanol.

The constitution of the new β-diketone (IIa or IIIa) was suggested by the appearance of (1) a secondary methyl group (τ 8·74; 3H, doublet, J = 7 c./sec.), replacing one quaternary methyl group in mexicanolide, and (2) an enolisable β-dicarbonyl system, such as is not present in mexicanolide. When these observations are referred on the one hand to the functional groups of mexicanolide as revealed by its spectroscopic properties and on the other to the framework and oxygenation pattern of swietenine (IV),[1] an explanation suggests itself in terms of (*a*) initial isomerisation of the isolated double bond in mexicanolide (I) to position 14,15, followed by (*b*) retro-Michael fission of the resulting pentenolide [(Ia) → (IIa or IIIa); arrows]. A major product (I; 3β–OH), m.p. 194—196°, $[\alpha]_D$−141°, from the reduction of mexicanolide with sodium borohydride, was unchanged under the conditions which effected C–9—C–10 cleavage in mexicanolide. Evidently the resonance stabilisation of the enolisable β-dicarbonyl system obtainable from mexicanolide is required to render the retro-Michael reaction irreversible. On the other hand the derived acetate (I; 3β–OAc), m.p. 166—168°, $[\alpha]_D$−185°, $\lambda_{max.}$ 213 mμ (ε 10,700), very readily underwent C–9—C–10 cleavage and β-elimination to afford the enone (IIId), m.p. 187—189°, $[\alpha]_D$+207°, $\lambda_{max.}$ 236 mμ (ε 12,700) and 278 mμ (ε 14,600) in ethanol, $\nu_{max.}$ (in carbon tetrachloride) 1683 ($\Delta^{\alpha\beta}$-cyclohexenone), 1730, 1745 cm.$^{-1}$ (shoulder) ($\Delta^{\alpha\beta,\gamma\delta}$-δ-lactone and methyl ester); vinyl protons at τ 3·73 (diffuse singlet, C–3), 3·89 (multiplet, C–9), and 4·21 (singlet, C–15).

The constitution (I) of mexicanolide, postulated to account for the observed changes, receives compelling support from a detailed analysis of its

* The suggested stereochemistry is at present based on the assumption that mexicanolide is biosynthetically related to swietenine.[1]

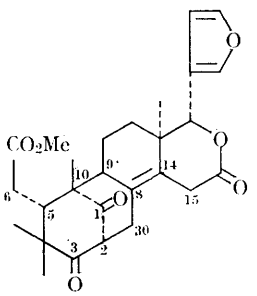
† The analytical and spectroscopic data are entirely in accord with the suggested constitution and do not merit further comment here.

[1] J. D. Connolly, R. Henderson, R. McCrindle, K. H. Overton, and N. C. Bhacca, *Tetrahedron Letters*, 1964, 2593; A. T. McPhail and G. A. Sim, *ibid.*, 2599.

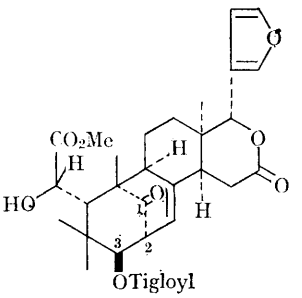
n.m.r. spectrum. Thus, double resonance experiments[2] at 100 Mc./sec. resolve the region between τ 6·3 and 7·8 into two spin-coupled systems: (i) an ABX system, attributable to the three protons attached to C–2 and C–30 [AB region τ 6·65–6·85, X at τ 7·69. $|J_{AX}| = 14$, $|J_{AB}| = 3$, $|J_{BX}| = 5{\cdot}5$ c./sec. J_{AX} and J_{BX} are of opposite sign, hence most reasonably $J_{AX} = -14$ (geminal coupling of C–30 H_2), $J_{BX} = +5{\cdot}5$ (vicinal coupling of C–2 H and one C–30 H), $J_{AB} = +3$ (vicinal coupling of C–2 H and other C–30 H) c./sec.]. The X proton shows a small bisallylic coupling with one proton at C–15 (τ 6·48). (ii) an AB_2 system, attributable to the three protons at C–5 and C–6 [A at τ 7·21, B_2 at τ 7·46; $J_{AB} = 6{\cdot}5$ c./sec.]. The remaining protons can be accommodated unequivocally.

We have observed[3] an analogous cleavage with the diketone (I; 6–OH) derived from swietenolide,[4] and for this and other reasons we favour the constitution (I; 3β,6-dihydroxy) for swietenolide.

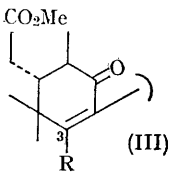
The position of the isolated double bond plays a critical role in determining the point of cleavage of the heavily encumbered bicyclo[3,3,1]nonane system in the compounds being considered. Thus, base-promoted cleavage of 1,3-dioxygenated derivatives in the swietenine (IV) series proceeds,



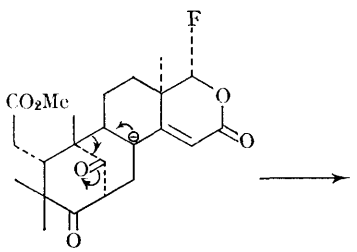
(I)



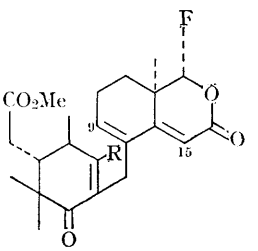
(IV)



(III)



(Ia)



(II)

a; R = OH
b; R = OAc
c; R = OMe
d; R = H

invariably in our experience[1,5] (by dealdolisation or β-dicarbonyl cleavage) through rupture of the C–2—C–3 bond. By contrast, in the mexicanolide (I) and swietenolide (I; 3β,6-dihydroxy) series, where the (biogenetically more readily acceptable) position of the isolated double bond at position 8(14) makes possible C–9—C–10 cleavage, this supervenes. We have yet to encounter the alternative fission of the C–2—C–30 bond, whose closure we have invoked[1] in the formation in nature of the bicyclononanolides.

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[2] We warmly thank Drs. A. Melera and U. Scheidegger, Zurich, for carrying out these experiments.
[3] J. D. Connolly, R. McCrindle, K. H. Overton, and W. Warnock, unpublished results.
[4] S. S. Guha Sircar and T. Chakrabartty, *J. Indian Chem. Soc.*, 1951, **28**, 207. T. Chakrabartty, Ph.D. Thesis, Edinburgh, 1959.
[5] R. Henderson, Ph.D. Thesis, Glasgow, 1964.