

TETRANORTRITERPENOID—IV^{1,2} [BICYCLONANOLIDES II]

THE CONSTITUTION AND STEREOCHEMISTRY OF MEXICANOLIDE

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Abstract—The constitution of mexicanolide (I) is deduced from two key reactions. Under very mild basic conditions mexicanolide fragments to form the diketone IVa or Va. This in turn is cleaved by periodate to the triacid X (R = H) and the monoacid XI (R = H) see Part VII. These cleavage products are uniquely defined by their spectroscopic attributes. The absolute configuration of mexicanolide follows from the CD of the diene lactones IVa or Va and XI.

THE genus *Cedrela*, which gives its name to the tribe *Cedreloideae* (Fam. *Meliaceae*), has numerous representatives that grow throughout tropical America. *Cedrela mexicana* is a commercially useful timber known in the U.K. as “Mexican” or “cigar box” cedar.

From the trunk-wood of this tree we have obtained in variable yield a new lactone, mexicanolide I, C₂₇H₃₂O₇, m.p. 222–227°, [α]_D –90°.

The part-structure II could be readily identified in the NMR spectrum by comparison with the spectra of swietenine³ and of numerous other tetranortriterpenoids which possess this feature.⁴ Thus the three furanic protons appear as separate diffuse singlets (1H each) at τ 2.44, 2.61 (α H's) and τ 3.52 (β H), and H-17 characteristically as a sharp singlet (1H) at τ 4.75. The formation of the hexahydro-acid III (R = H), (*v. infra*) also supports the part structure II. The NMR spectrum of mexicanolide further shows the presence of a methyl ester (3H, s, τ 6.28), and four tertiary Me groups [singlets at τ 8.77 (3H), 9.00 (6H) and 9.12 (3H), four clearly separated sharp singlets (3H each) can be seen in certain derivatives, e.g. VIII]. The IR spectrum supports the δ -lactone and methyl ester functions [ν_{\max} (CCl₄) 1758 and 1739 cm⁻¹ respectively]; it also suggests the presence of one or two ketonic CO groups (ν_{\max} 1712 cm⁻¹) and shows that alcoholic OH's are absent. In consequence of the functional groups just enumerated, mexicanolide, C₂₇H₃₂O₇, must have a combined total of four carbocyclic rings and ethylenic double bonds.

As is the case with swietenine,³ the hexahydroacid III (R = H) obtained by catalytic hydrogenation of mexicanolide, still contains an ethylenic double bond (tetrasubstituted, absence of vinyl hydrogens in the NMR) (*v. infra*) and mexicanolide must therefore be tricarbocyclic. The preliminary evidence, and in particular, the presence of a methyl ester function, *four* rather than *five* tertiary Me groups and a tetrasubstituted olefinic double bond, suggests, although it does not define, for mexicanolide the carbon skeleton of a bicyclonanolide.

Support for this supposition and clarification of the functional group relationships

in mexicanolide came in an unexpectedly simple manner from the changes observed when it is exposed to mild base. Thus the end-absorption in the UV shown by a neutral ethanolic solution (λ_{\max} 209 nm; $\log \epsilon$ 4.04), is immediately supplanted by an intense new max at 287 nm ($\log \epsilon$ 4.50) when two drops of 4N NaOH are added to the UV cell, and this upon acidification yields in turn to a less intense max at 264 nm ($\log \epsilon$ 4.32) with a shoulder at 285 nm.

Indeed, the product of this irreversible base-catalysed transformation could be isolated as the crystalline β -diketone IVa or Va, $C_{27}H_{32}O_7$, m.p. 164–166°, $[\alpha]_D + 250^\circ$, λ_{\max} in neutral ethanol 264 nm ($\log \epsilon$ 4.40; enolized β -diketone) with a shoulder at 285 nm (diene-lactone), λ_{\max} in alkaline ethanol 287 nm ($\log \epsilon$ 4.57; enolized β -diketone anion and diene-lactone). The NMR spectrum of the diketone showed, as expected, signals for vinyl protons at C-9 (τ 4.09, 1H *m*) and C-15 (τ 4.02, H *s*).

The β -diketone was further characterized as the enol acetate IVb or Vb, $C_{29}H_{34}O_8$, m.p. 172–173°, $[\alpha]_D + 299^\circ$; $[\lambda_{\max}$ 238 nm ($\log \epsilon$ 4.18) and 277 nm ($\log \epsilon$ 4.14) in neutral ethanol and as for the parent diketone in alkaline ethanol], and as the enol methyl ether IVc or Vc, m.p. 164–166°, $[\alpha]_D + 337^\circ$ [λ_{\max} 210 nm ($\log \epsilon$ 3.96) and 262 nm ($\log \epsilon$ 4.37) (shoulder at 282 nm) in neutral and alkaline ethanol].

Two attributes of the product obtained from the action of alkali on mexicanolide provided unmistakable clues to its constitution and therefore to the constitution also of mexicanolide. First, the NMR spectrum showed three tertiary and *one secondary* Me groups (τ 8.74; 3H *d*, $J = 7$ Hz) in place of the four tertiary Me groups in mexicanolide. Second, there is an enolizable β -dicarbonyl system such as is not present in mexicanolide. Reference to the disposition of oxygen functions in swietenine immediately suggests location of the β -diketone system at positions one and three. Clearly this is not enolizable while it is part of a bicyclo[3.3.1]nonane system, but fission of any one bond that removed this steric constraint while leaving C-1, C-2, C-3 intact, could make it so. Cleavage of C-9/C-10 would not only meet these requirements but would also effect the observed transmutation of a tertiary into a secondary Me group. We can now see that if the hitherto unplaced tetrasubstituted ethylenic linkage were to be located at C-8/C-14, then a base-catalysed cleavage process could occur either after isomerization of the olefinic double bond to C-14/C-15 (cf. VI) or possibly directly⁵ (cf. VII), and this would result in formation of IVa or Va. The observed spectroscopic properties accord with these structures.

It is interesting to note at this point that the major product VIII (*v. infra*) obtained from reduction of mexicanolide by sodium borohydride, was not changed under the conditions that led to C-9/C-10 fission in mexicanolide. Evidently the resonance stabilization of the enolizable β -dicarbonyl system derivable from mexicanolide is required to render irreversible the retro-Michael fission observed in this case. On the other hand, the acetate IX, $C_{29}H_{36}O_8$, m.p. 166–168° $[\alpha]_D - 185^\circ$, λ_{\max} 213 nm ($\log \epsilon$ 4.03), very readily underwent C-9/C-10 cleavage and β -elimination to afford the enone Vd $C_{27}H_{32}O_6$ m.p. 187–189°, $[\alpha]_D + 207^\circ$, λ_{\max} 236 nm ($\log \epsilon$ 4.10), and 278 nm ($\log \epsilon$ 4.16) in ethanol, ν_{\max} (CCl_4) 1683 ($\Delta^{\alpha\beta}$ -cyclohexenone), 1730, 1745 (shoulder) cm^{-1} ($\Delta^{\alpha\beta, \gamma\delta}$ - δ -lactone and methyl ester); vinyl protons at τ 3.73 (diffuse *s*, C-3), 3.89 (*m*, C-9) and 4.21 (*s*, C-15).

The proposed constitution (I) for mexicanolide receives compelling support from a detailed analysis of its NMR spectrum which, for the sake of clarity, is discussed separately in the following paper.⁶

Definitive evidence for the constitution of mexicanolide comes from cleavage by sodium periodate of the β -diketone IVa or Va to the triacid X (R = H) and the monoacid XI (R = H). A detailed discussion of this reaction is deferred to a subsequent paper⁷ on the chemistry of swietenolide, where it has a close parallel.

We now discuss two further reactions of mexicanolide to which we have already alluded. One is hydrogenation in solvent acetic acid in presence of a 10% Pd-C catalyst. Uptake of 2.8 mole hydrogen was complete in 1 hr at 20° and methylation of the (mainly) acidic product afforded the hexahydro-diester III (R = Me), C₂₈H₄₀O₇, m.p. 116–119°, whose NMR spectrum was devoid of signals below τ 5.6, and otherwise completely supported the proposed structure. This reaction has such ample precedent that it does not merit elaboration. However, the absence of a vinyl proton in the NMR spectrum coupled with a positive tetranitromethane reaction and end absorption in the UV ($\lambda_{220\text{nm}}$, log ϵ 3.77) indicates a tetrasubstituted double bond in the hexahydrodiester and probably also in mexicanolide. It is worth noting that under conditions which convert mexicanolide into the β -diketone IVa or Va, the diester III (R = Me) survives unchanged.

The second reaction concerns reduction of mexicanolide with an excess of sodium borohydride. Two clean products were obtained, the relative yields depending on the amount of reducing agent, and could be readily separated by prep. TLC. They were smoothly reconverted into mexicanolide by oxidation with the Jones reagent. The less polar VIII, C₂₇H₃₄O₇, m.p. 122–124°; 194–196°, $[\alpha]_D -141^\circ$ readily formed an acetate (IX), C₂₉H₃₆O₈, m.p. 166–168°. The acetate IX has in its NMR spectrum a sharp doublet ($J = 10$ Hz) at τ 4.97, assignable to H-3, which shows that the —OAc group must be β -oriented ($\theta_{2,3} = \text{approx. } 0^\circ$, assuming a quasi-boat conformation for ring A as in swietenine). The four tertiary Me groups show very clearly as separated singlets (3H each) in both the alcohol VIII (τ 8.90, 9.00, 9.21, 9.30) and the acetate IX (τ 8.66, 8.76, 9.05, 9.11). In the IR, alcohol VIII has in CCl₄ ν_{max} at 1717 (cyclohexanone), 1737 (methyl ester), 1752 (δ -lactone) and 3644 (unbonded OH) cm⁻¹. The more polar product C₂₇H₃₆O₇, m.p. 182–185°, formulated as XII shows in the IR (CCl₄) CO bands at 1713 (cyclohexanone) and 1738 (methyl ester) cm⁻¹ and OH bands at 3612 (free) and 3494 (intra-bonded) cm⁻¹, the latter being somewhat more intense.

In the NMR spectrum of the non-crystalline diacetate XIII, C₃₁H₄₀O₉, one >CHOAc signal (doublet, $J = 8$ Hz) centred at τ 5.05 matches the corresponding signal from H-3 in the monoacetate IX, while the hemiacetal acetate proton, H-16,

—O—CHOAc , appears as a quartet, centred at τ 4.13. H-17 is, as expected, diamagnetically shifted to τ 5.06. The strong and persistently intense intramolecular hydrogen bond in the IR spectrum of the hemiacetal XII (ν_{max} 3494 cm⁻¹; 0.0004M in CCl₄) must arise from interaction between the hemiacetal OH and C-3 β -hydroxyl groups. Fieser models show that these groups are very favourably placed for such interaction, provided that the C-16 OH group is β -oriented.

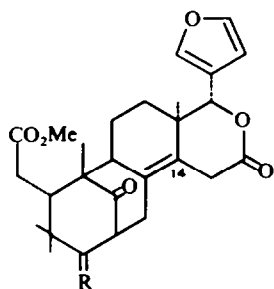
The relative configurations at C-2, C-5, C-9, C-10, C-13 and C-17 in mexicanolide are based on analogy with swietenine and a presumed common biogenetic pathway from euphol.

The absolute configuration of mexicanolide is defined as in I by the circular

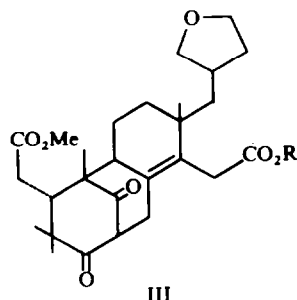
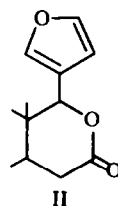
dichroism* of the diene-lactones IVc or Vc ($\Delta\epsilon_{284\text{nm}} = +20.0$) and XI ($\Delta\epsilon_{281\text{nm}} = +14.3$). The sign, magnitude and position of the maxima in both cases accord with the configurational assignments.

It has recently been proposed⁸ that the rules which relate CD to conformation in unsaturated ketones can be applied to unsaturated lactones in cases where there is a dissymmetry of the first sphere.⁹ In the lactones XI and IVc or Vc there are two possible conformations (keeping C—O—CO—C planar) for ring D; one has the furan substituent quasi-axial (this will be disfavoured because of interaction between the furan ring and the C-18 Me group), the other has it quasi-equatorial. In the latter case the rule⁸ predicts a negative CD, as is observed. Moreover, extending the conjugation, so long as the additional double bond is essentially coplanar with the first, should substantially increase the magnitude of the Cotton effect.¹⁰ In agreement with this, the size of the CD for XI and IVc or Vc is between two and three times that for the analogous singly unsaturated lactones carapin¹¹ (XV) ($\Delta\epsilon_{265\text{nm}} = +6.8$)¹² and odoratin¹³ (XVI) ($\Delta\epsilon_{263\text{nm}} = +7.04$).^{8, 13} The R-band shift of 15–20 nm to the red upon introduction of a second olefinic double bond is not unexpected. The $\alpha\beta$ -unsaturated ketone system in the enol ether (IVc or Vc) gives rise additionally to a small positive R-band ($\Delta\epsilon_{335\text{nm}} = +1.58$), and this also accords¹⁴ with a 13- α Me configuration if one assumes a planar enone chromophore and furthermore, that the secondary Me and acetic acid substituents are quasi-equatorial.

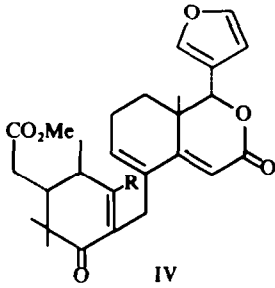
Cedrela odorata substance B has been isolated by Bevan, Taylor and their colleagues from *Cedrela odorata*¹⁵ and *Khaya grandifoliola*,¹⁶ and assigned¹⁷ structure I on the basis of an X-ray structure determination¹⁸ of the derived iodo-acetate (XIV). It is very probable that this substance [m.p. 228–232°, $[\alpha]_D +41^\circ$ (CHCl₃),¹⁵ but more recently revised to m.p. 226–230°, $[\alpha]_D -100^\circ$ (CH₂Cl₂)¹⁹] is identical with mexicanolide. If this is the case, the X-ray work completely supports the structure which we have deduced for mexicanolide.



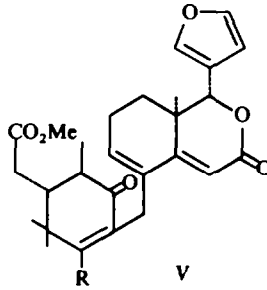
- I: R = O
 VIII: R = 3 β OH, H
 IX: R = 3 β OAc, H
 XV: Δ^{14} -(I)



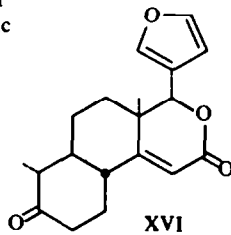
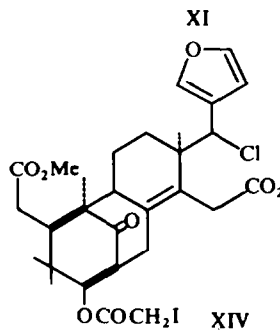
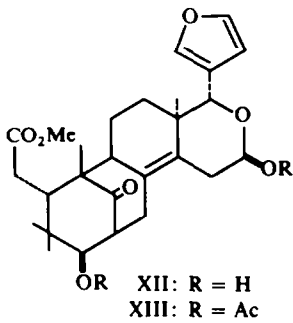
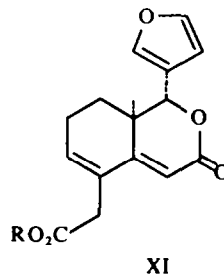
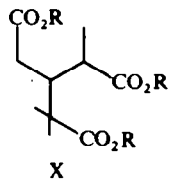
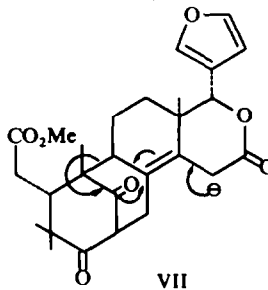
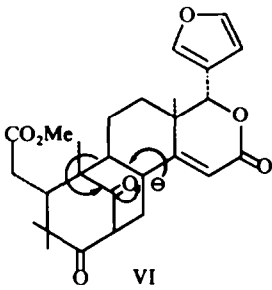
* We cordially thank Dr. Günther Snatzke, Bonn, for the discussion of the CD data.



- (a) R = OH
- (b) R = OAc
- (c) R = OMe



- (a) R = OH
- (b) R = OAc
- (c) R = OMe
- (d) R = H



EXPERIMENTAL

For General Experimental see Part I.³

Extraction of mexicanolide from Cedrela mexicana. Powdered heartwood (5 kg) of *C. mexicana* (Forest Herbarium, Forestry Division, Kumasi, Ghana) was continuously extracted for 20 hr with EtOAc (15 l). Nearly all the solvent was removed under reduced press, the residue diluted with CHCl_3 (1 l) and the insoluble material filtered off. The CHCl_3 was then evaporated and MeOH (1.5 l) added. On cooling cedrolide (7-deacetoxy-7-oxogedunin)²⁰ (4.3 g) separated and had (crystallized from CHCl_3 -MeOH) m.p. 261–264° (lit.²⁰ 262–265°). (Found: C, 71.2; H, 6.95. $\text{C}_{26}\text{H}_{30}\text{O}_6$ requires: C, 71.2; H, 6.9%). More MeOH (1.5 l) was added to the filtrate, when mexicanolide (400 mg) separated on refrigeration. Twice crystallized from CHCl_3 -MeOH, this had m.p. 222–227°, $[\alpha]_D -90^\circ$ (c 1.3). (Found: C, 69.0; H, 6.75. $\text{C}_{27}\text{H}_{32}\text{O}_7$ requires: C, 69.2; H, 6.9%). Concentration of the mother liquors afforded a mixture (2.6 g) consisting substantially (NMR) of cedrolide and mexicanolide. Attempts to separate this by either elution chromatography or TLC were unsuccessful. Another sample (12 kg) of *C. mexicana* heartwood (Forest Department, Port-of-Spain, Trinidad) on similar work-up afforded mexicanolide (10.8 g) and cedrolide-mexicanolide mixture (4.7 g).

Action of base on mexicanolide

The β -diketone IVa or Va. To mexicanolide (200 mg) in MeOH (50 ml) was added methanolic KOH (2 ml, 5%) and the soln kept at 20° for 2 hr. The MeOH was removed under reduced press, the residue diluted with water and the product extracted into CHCl_3 . Prep. TLC afforded the β -diketone (IVa or Va; 130 mg), m.p. (from aqueous MeOH) 164–166°, $[\alpha]_D +250^\circ$ (c 1.54). [Found: C, 65.55; H, 6.8. $\text{C}_{27}\text{H}_{32}\text{O}_7$ $1\frac{1}{2}$ H_2O requires: C, 65.45; H, 7.1%). The enol acetate (IVb or Vb) obtained with Ac_2O -pyridine, had m.p. (from CHCl_3 -ether) 172–173°, $[\alpha]_D +299^\circ$ (c 1.34). (Found: C, 67.75; H, 6.7. $\text{C}_{29}\text{H}_{34}\text{O}_8$ requires: C, 68.2; H, 6.7%). It was reconverted into the β -diketone by treatment with ethanolic KOH (2.5%) for 16 hr at 20°. The enol methyl ether (IVc or Vc) obtained with diazomethane, had m.p. (from CHCl_3 -ether-light petroleum) 164–166°, $[\alpha]_D +337^\circ$ (c 1.05). (Found: C, 69.45; H, 7.15. $\text{C}_{28}\text{H}_{34}\text{O}_7$ requires: C, 69.7; H, 7.1%).

Hydrogenation of mexicanolide. Mexicanolide (100 mg) and 10% Pd/C in glacial AcOH (30 ml) were shaken in an atm of H_2 for 1 hr, when the uptake (14 ml) was complete. Working in the usual way gave acidic (80 mg) and neutral (20 mg) fractions. The former was methylated with diazomethane and the product purified by prep. TLC, affording III (R = Me), m.p. (from ether-light petroleum) 116–119°, $[\alpha]_D +62^\circ$ (c 1.53). (Found: C, 68.95; H, 7.8. $\text{C}_{28}\text{H}_{40}\text{O}_7$ requires C, 68.85; H, 8.25%). The hexahydro-ester was recovered unchanged after treatment with base under conditions which transformed mexicanolide into IVa or Va.

Reduction of mexicanolide with sodium borohydride. Mexicanolide (270 mg) and NaBH_4 (500 mg) in MeOH (60 ml) were kept at 0° for 15 min. Dilution, acidification, extraction into CHCl_3 and separation by prep. TLC (2% MeOH- CHCl_3) afforded the less polar alcohol VIII; (150 mg), m.p. (from ether-water) 122–124°; 194–196°, $[\alpha]_D -141^\circ$ (c 0.70). (Found: C, 68.55; H, 7.15. $\text{C}_{27}\text{H}_{34}\text{O}_7$ requires C, 68.9; H, 7.3%). The acetate (IX) had m.p. (from CHCl_3 -ether-light petroleum) 166–168°, $[\alpha]_D -158^\circ$ (c 1.13). (Found: C, 68.2; H, 7.25. $\text{C}_{29}\text{H}_{36}\text{O}_8$ requires: C, 67.95; H, 7.1%). The more polar major band from the chromatoplate afforded the hydroxyacetal XII, (60 mg), m.p. (from ether-light petroleum) 182–185°. (Found: C, 68.60; H, 7.5. $\text{C}_{27}\text{H}_{36}\text{O}_7$ requires C, 68.6; H, 7.7%). This formed the oily diacetate XIII (Found: C, 67.8; H, 7.4. $\text{C}_{31}\text{H}_{40}\text{O}_9$ requires: C, 66.9; H, 7.25%).

Brief oxidation of both VIII and XII furnished mexicanolide as the only product.

The alcohol VIII was stable to the basic conditions which transformed mexicanolide into IVa or Va.

Action of base on the acetate (IX)

The enone Vd. The acetate IX (100 mg) in MeOH (10 ml) and 4N NaOH; (1 ml) were kept at 20° for 0.5 hr. Dilution, acidification and extraction into CHCl_3 afforded three products (TLC) which were separated by prep. TLC. These, in order of polarity, were VIII (47 mg), unchanged IX (8 mg), and the unsaturated ketone Vd (38 mg), which after repeated prep. TLC and crystallization from CHCl_3 -ether had m.p. 188–190°, $[\alpha]_D +207^\circ$ (c 1.36). (Found: C, 71.9; H, 7.5. $\text{C}_{27}\text{H}_{32}\text{O}_6$ requires: C, 71.65; H, 7.15%).

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