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TETRANORTRITERPENOIDS—VII[1, 2]

[BICYCLONONANOLIDES—V]

THE CONSTITUTION AND STEREOCHEMISTRY OF SWIETENOLIDE

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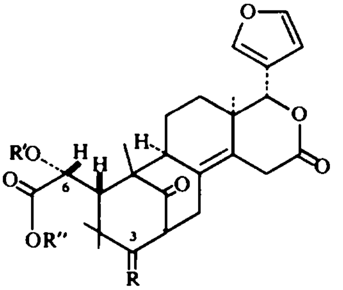
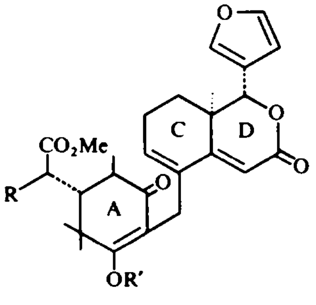
Abstract—The constitution and stereochemistry of swietenolide (I) are deduced from its spectroscopic and chemical properties and confirmed by cleavage of the β-diketone VIIa or VIIIa (R = OH) to the mono- and di-carboxylic acids corresponding to XIII and XIV. The absolute configuration of swietenolide as in I follows from the CD of XIII.[4]

In the preceding paper[2] we have summarized the evidence which leads to the functional groups contained in the part-expressions (A) and (B)* for swietenolide.

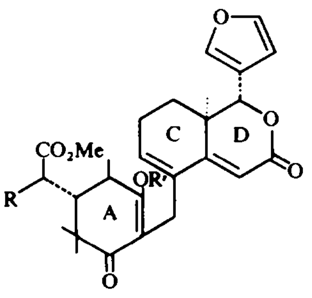
The NMR spectra of swietenolide (I)* and its simple diacetate (VI) provide further support for these proposals. The diacetate (VI) has four distinct singlets (3H each,



I: R = β-OH, H; R' = H; R'' = Me
II: R = α-OH, H; R' = R'' = H
VI: R = β-OAc, H; R' = Ac; R'' = Me
IV: 3-dehydro-(I)
XVI: R = α-OH, H; R' = H; R'' = Me
XVII: 3,6-bisdehydro-(I)
XXI: R = α-OAc, H; R' = Ac; R'' = Me



VII



VIII

a: R' = H
b: R' = Ac
c: R' = Me

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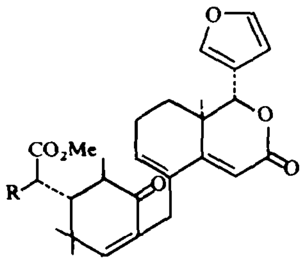
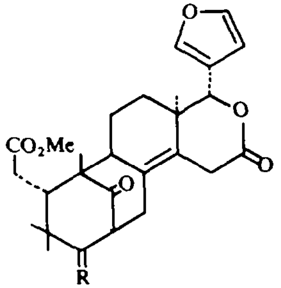
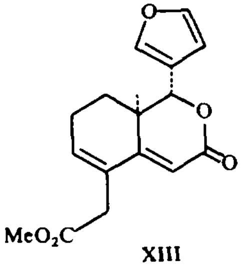
* The numbering of formulae in this and the preceding paper is continuous.



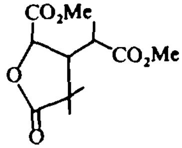
IX : R = OAc
X : R = H
XX : R = OH

XI : R = β-OAc. H
XII : R = O
XXII : R = βOH. H

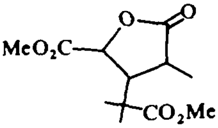




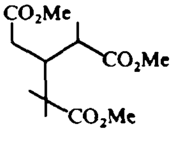
XIII



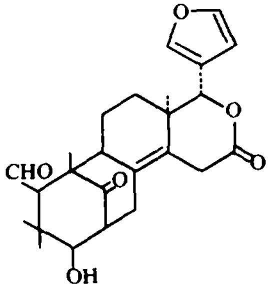
XIV



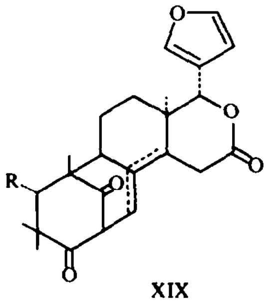
XIVa



XV



XVIII



XIX

tertiary methyls) at τ 8·84, 8·93, 8·96 and 9·16, a singlet (6H, 2-$OCOCH_3$) at τ 7·85, and a singlet (3H, methyl ester) at τ 6·24. It also shows a sharp doublet (1H, J = 10 Hz, $\overset{|}{\underset{|}{-C}}-C\underline{H}OAc-CH-$) at τ 5·12 and a diffuse singlet (1H, $-C\underline{H}OAc-CO_2Me$) at τ 4·43. No attempt is made here to analyse in detail the region between τ 6·0 and 8·5 in the NMR spectra of swietenolide or its derivatives. Such an analysis for the case of mexicanolide appears in Part V.[3] However, reference to Figs 1 and 2 will show the additional structural information to be extracted from the NMR spectra of swietenolide diacetate and 3-dehydroswietenolide. The assignments shown are supported by double resonance experiments.

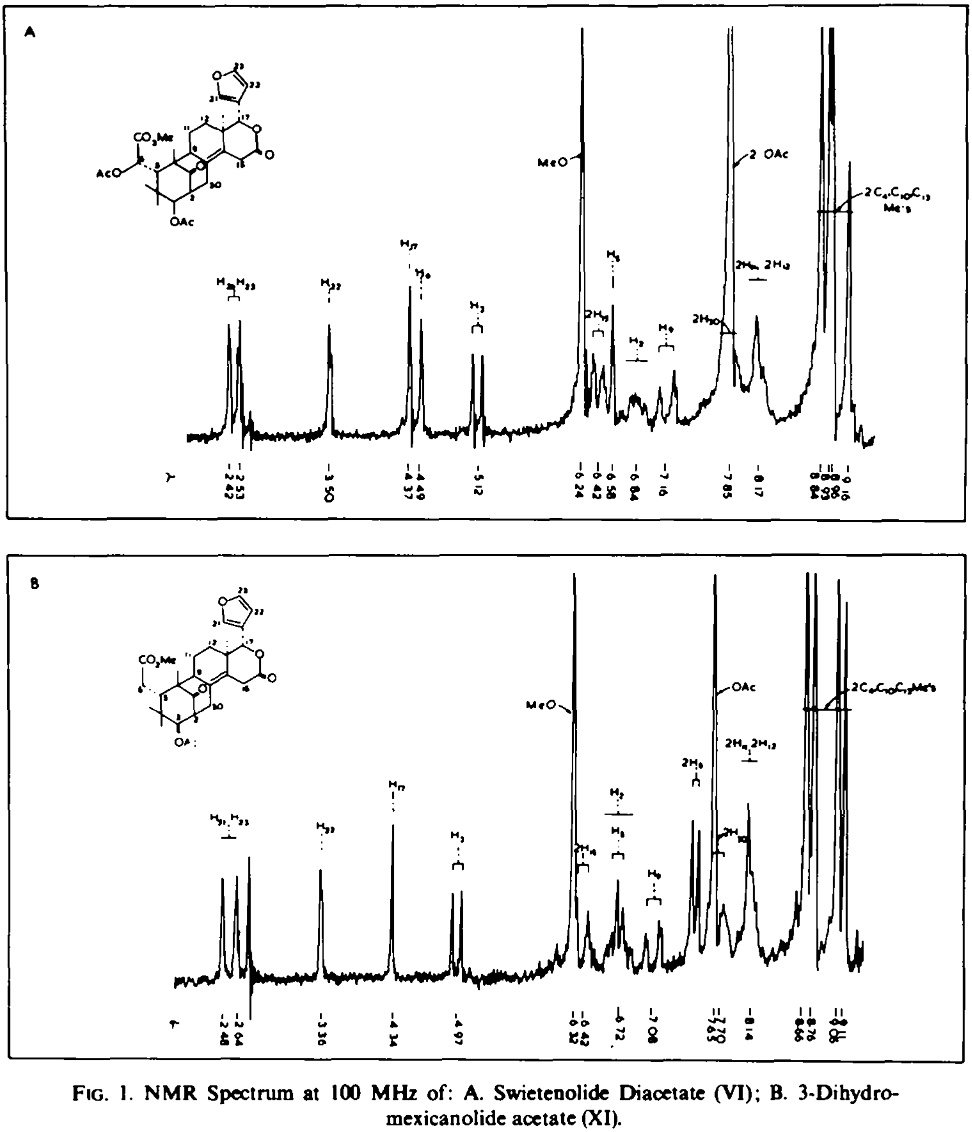


FIG. 1. NMR Spectrum at 100 MHz of: A. Swietenolide Diacetate (VI); B. 3-Dihydromexicanolide acetate (XI).

Our encounter with the structurally revealing spectroscopic properties of mexicanolide (see Part IV)[4] recalled the strikingly similar behaviour of 3-dehydroswietenolide (IV) [see Part VI,[2] and *v. infra* for further discussion of its spectroscopic properties] when treated with base. Indeed, it was possible here also to isolate the product VIIa or VIIIa (R = OH), $C_{27}H_{32}O_8$, $[\alpha]_D$ +122°. Moreover, the previously mentioned acetate (V) ≡ (IX) obtained from swietenolide with sodium acetate in refluxing acetic anhydride, very closely resembled in its UV, IR and NMR spectra the αβ-unsaturated ketone X derived from mexicanolide. The properties of these two pairs of compounds are compared in Table 1.

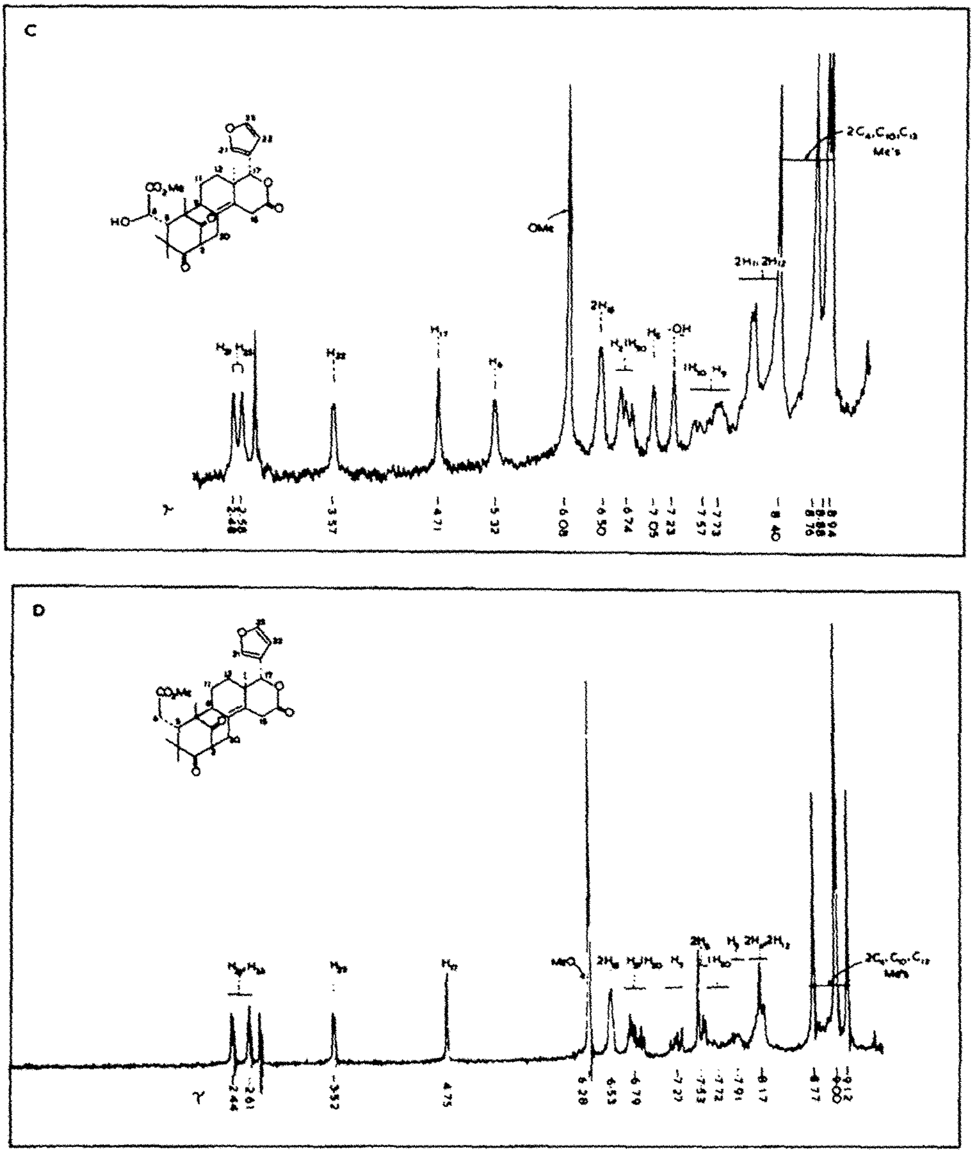


FIG. 2. NMR Spectrum at 100 MHz of: C. 3-Dehydroswietenolide (IV); D. Mexicanolide (XII).

When the similarities summarized in Table 1 are taken in conjunction with the functional groups established for swietenolide [expressions (A) and (B), Part VI[2]], then it becomes evident that 3-dehydroswietenolide must be 6-hydroxymexicanolide (IV). Comparison of the NMR spectra of (i) swietenolide diacetate (VI) and mexicanolide reduction product monoacetate XI[4] (Fig. 1) and of (ii) 3-dehydroswietenolide (IV) and mexicanolide (XII)[4] (Fig. 2) provides very compelling support for this supposition. This is further substantiated by the CD and ORD curves shown for compounds I, IV, XII and XXII (Figs 3 and 4).

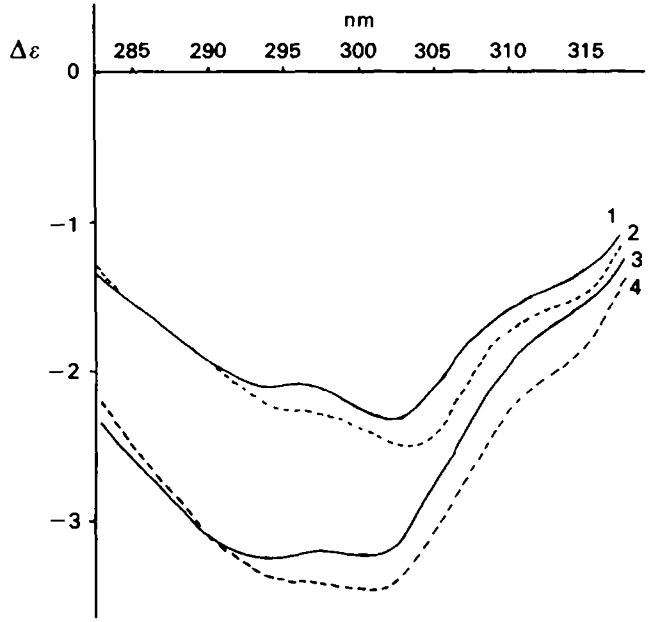


FIG. 3. CD Curves of: 1. 3-Dehydroswietenolide (IV); 2. Mexicanolide (XII); 3. Swietenolide (I); 4. 3-Dihydromexicanolide (XXII).

Definitive support for the structure of swietenolide (and also that of mexicanolide) came from a reaction which has already been alluded to (see Part IV)[4] and will now be discussed in detail.

Cleavage by sodium periodate of an enolizable 1,3-diketone, bearing an alkyl substituent at the 2-carbon atom, $RCO{-}CR'{=}C(OH)R''$, results in the formation of three carboxylic acids, RCO_2H, $R'CO_2H$ and $R''CO_2H$.[5] If the 1,3-diketones arising from base-catalyzed cleavage of 3-dehydroswietenolide and mexicanolide are represented as in VIIa (R = OH) and VIIa (R = H), respectively, then cleavage with sodium periodate should result, without loss of carbon, in *two different* tricarboxylic acids, reflecting the different side chains attached to ring A, but the *same* monocarboxylic acid, representing the common rings C and D.

This prediction was borne out in practice. Moreover, the fragments obtained were uniquely defined by their analytical and spectroscopic properties. Thus both diones VIIa (R = OH) and VIIa (R = H) afforded, after methylation of the oxidation

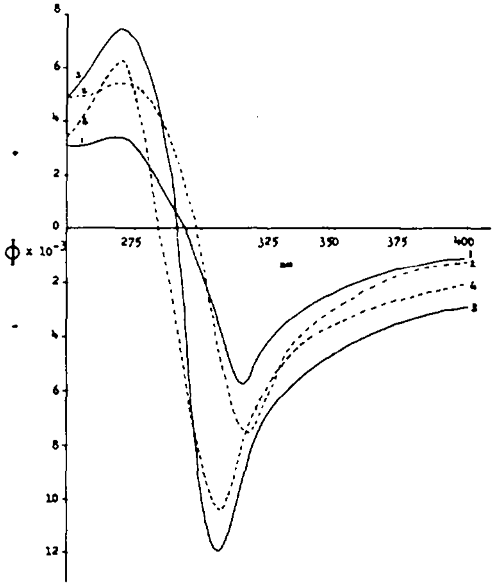


FIG. 4 ORD curves of: 1. 3-Dehydroswietenolide (IV); 2. Mexicanolide (XII); 3. Swietenolide (I); 4. 3-Dihydromexicanolide (XXII).

products, the *same* monocarboxylic ester (XIII), $C_{17}H_{18}O_5$, m.p. 147–149°, $[\alpha]_D$ +387°, λ_{max} (EtOH) 272 nm (log ε 4·18) and 212 nm (log ε 3·95), ν_{max} (CCl_4) 1740 (methyl ester) and 1730 (doubly unsaturated δ-lactone) cm^{-1}. The NMR spectrum had well-separated signals at τ 2·5 (2H, diffuse *s*, α furans), 3·5 (1H, diffuse *s*, β furan), 3·75 (1H, *m*, H-9), 4·17 (1H, *s*, H-15), 4·82 (1H, *s*, H-17), 6·27 (3H, *s*, methyl ester), 6·70 (2H, broadened *s*, 2H-30), 7·6 (2H, *m*, 2H-11), 8·5 (2H, *m*, 2H-12), 8·92 (3H, *s*, 3H-18).

The fragments representing ring A and its substituents differed, as anticipated, in the two cases. The dione VIIa (R = OH) from swietenolide furnished the oily γ-lactone dimethyl ester (XIV), $C_{12}H_{18}O_6$, $[\alpha]_D$ −8°, ν_{max} (CCl_4) 1743 (methyl esters) and 1798 (γ-lactone) cm^{-1}; NMR signals (in benzene) at τ 5·68 (1H, *d*, *J* = 8 Hz, H-6), 6·70 (6H, two closely spaced *s*, methyl esters), 7·15 (1H, *q*, *J* = 8, 9 Hz, H-5), 7·70 (1H, *m*, H-10), 8·88, 9·08 (3H each *s*, tertiary methyls), 9·04 (3H, *d*, *J* = 6 Hz, secondary methyl). Since only one lactone is formed, we prefer the structure of the less crowded isomer XIV to the alternative XIVa.

The dione VIIa (R = H) from mexicanolide afforded the oily triester (XV), $C_{13}H_{22}O_6$, $[\alpha]_D$ −26°, ν_{max} (CCl_4) 1738 cm^{-1}; NMR signals (in $CDCl_3$) at τ 6·30 (9H, *s*, methyl esters), 7·0–7·7 (4H, *m*, H-5, 2H-6, H-10), 8·8 (6H, *s*, two tertiary Me's), 8·95 (3H, *d*, *J* = 6 Hz, secondary Me).

Several reactions which did not contribute directly to the structure elucidation of swietenolide can now be interpreted. Hydrolysis of swietenolide with a 5% solution of potassium hydroxide in refluxing ethanol for 1 hr afforded the previously mentioned desmethyl isoswietenolide (II).[2] On methylation with diazomethane this afforded 3-episwietenolide, (XVI), $C_{27}H_{34}O_8$, m.p. 213–217°, $[\alpha]_D$ −114°, which on oxidation with Jones reagent led to the same 3-dehydro- (IV) and 3,6-bisdehydro- (XVII) swietenolides (*v. infra*), as were obtained from swietenolide. Epimerization at

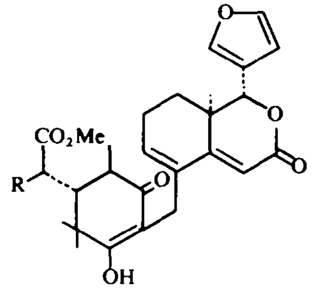
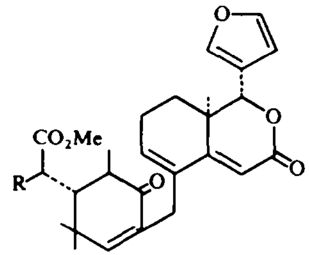
C-3 by de- and realdolization involving the C-1 carbonyl group has previously been encountered with swietenine.[6] It appears that, as in the case of swietenine, the C-3 oxygen substituent in the naturally occurring compound has the less stable β-configuration and on reaction with base is completely transformed into the more stable α-epimer.

This is clearly seen in the NMR spectrum of the simple diacetate (VI), $C_{31}H_{38}O_{10}$, m.p. 224–228°, $[\alpha]_D$ −129°, obtained from swietenolide under conditions less vigorous than are needed for the formation of the monoacetate (IX). In the diacetate, H-3 appears as a clean doublet, $J_{2,3} = 10$ Hz, centred at τ 5·12. The observed coupling constant accords with the dihedral angle $\theta_{2,3} \cong 0°$ when the C-3 hydroxyl group is β-oriented. In 3-episwietenolide diacetate (XXI), $C_{31}H_{38}O_{10}$, the H-3 resonance showed as a doublet, $J_{2,3} = 3$ Hz, centred at τ 5·69. The dihedral angle $\theta_{2,3} \cong 120°$.

Oxidation of swietenolide (and 3-episwietenolide) with Jones reagent afforded, depending on the conditions (Experimental), either the previously mentioned 3-dehydroswietenolide (IV) or 3,6-bisdehydroswietenolide (XVII), $C_{27}H_{30}O_8$, m.p. 183–185°, $[\alpha]_D$ −4°. The latter was transformed into the former by the action of zinc dust in boiling acetic acid.

Brief reference was made in Part VI[2] to the fact that desmethyl isoswietenolide rapidly consumes one equivalent of lead tetraacetate. The product of this reaction was subsequently isolated as the nor-aldehyde (XVIII), $C_{25}H_{30}O_6$, m.p. 194–197°, $[\alpha]_D$ −31°. Its NMR spectrum showed a doublet ($J = 6$ Hz) centred at 0·15 τ

TABLE 1

				
	R = H	R = OH	R = H	R = OAc
UV λ_{max} (nm) in EtOH	Neutral: 264 (log ε 4·40) (shoulder at 285) Basic: 287 (log ε 4·57)	Neutral: 265 (log ε 4·17) (shoulder at 285) Basic: 287 (log ε 4·53)	236 (log ε 4·10) 278 (log ε 4·16)	235 (log ε 4·10) 280 (log ε 4·19)
IR ν_{max} (cm^{-1})	1734, 1710, 1626 ($CHCl_3$)	1729, 1711, 1630 ($CHCl_3$)	1741, 1728, 1678 (CCl_4)	1755, 1729, 1680 (CCl_4)
NMR τ in $CDCl_3$	4·02 (*s*, H-15) 4·09 (*m*, H-9) 8·74 (*d*, C-19 Me)	3·96 (*s*, H-15) 3·97 (*m*, H-9) 8·80 (*d*, C-19 Me)	3·73 (*s*, H-3) 3·89 (*m*, H-9) 4·21 (*s*, H-15)	4·08 (*s*, H-3) 3·93 (*m*, H-9) 4·37 (*s*, H-15)

(—C$\underline{H}$O), arising from coupling with H-5 (τ 7·41, *d*, $J = 6$ Hz). The IR spectrum ($CHCl_3$) had ν_{max} 3623 (free OH), 1741 (δ-lactone), 1718 (superimposed aldehyde and cyclohexanone) cm^{-1}.

One point not readily accessible from direct evidence is the configuration at C-6 in swietenolide. We base our preference for the (R)-configuration on the established[7] configuration at the corresponding centre in swietenine for the following reasons. Removal of the asymmetric centre C-6 in the 3,6-dioxoswietenolide and 3,6-dioxoswietenine series (XIX) during transformation of the α-hydroxy ester into (a) the pyruvate ($—CHOH—CO_2Me \rightarrow —CO—CO_2Me$) and (b) the nor-aldehyde ($—CHOH—CO_2Me \rightarrow —CHO$) results in the following molecular rotation changes:[8] swietenolide $[\phi]_D$ (a) +129°; $[\phi]_D$ (b) +411°. Swietenine $[\phi]_D$ (a) +596°; $[\phi]_D$ (b) +483°.

The absolute configuration of swietenolide, as depicted in I, follows from the circular dichroism of the monocarboxylic ester XIII.[4]

EXPERIMENTAL

For general experimental see Part I.[6]

Acetylation of swietenolide

The diacetate (VI). Swietenolide (80 mg) was dissolved in dry pyridine (2 ml) and Ac_2O (2 ml). The soln was heated at 60° for 4 hr and worked up by addition of water and extraction into $CHCl_3$. The product was separated by prep. TLC (2% MeOH–$CHCl_3$) affording (from $CHCl_3$–Et_2O–light petroleum) *swietenolide diacetate* (VI; 28 mg), m.p. 225–228°; $[\alpha]_D$ −129° (*c*, 1·1). (Found: C, 65·3; H, 6·7. $C_{31}H_{38}O_{10}$ requires: C, 65·3; H, 6·7%.)

Treatment of swietenolide with strong alkali

The enone (XX). Swietenolide (200 mg) was refluxed in a 3% soln of NaOMe in dry MeOH for 4½ hr. The product, obtained by dilution, acidification and extraction into $CHCl_3$, was esterified with ethereal diazomethane and separated by prep. TLC (2% MeOH-$CHCl_3$; EtOAc–light petroleum (1:1)) to give the non-crystalline enone dienelactone (XX), λ_{max} (EtOH) 235 nm (log ε 4·15), 278 nm (log ε 4·20); ν_{max} (CCl_4) 3520 (OH), 1730, (1738 shoulder) (dienelactone, methyl ester), 1680 (enone) cm^{-1}; NMR signals ($CDCl_3$) at τ 3·83 (1H, diffuse *s*, H-3), 3·90 (1H, diffuse *t*, H-9), 4·27 (1H, diffuse *s*, H-15), 8·99 (3H, *d*, $J = 6$ Hz, C-10 Me). (Found: C, 69·2; H, 7·2. $C_{27}H_{32}O_7$ requires: C, 69·2; H, 6·9%.) Acetylation as above afforded the anhydroacetate (V), m.p. and m.m.p. 198–200°, indistinguishable by TLC.

3-*Dehydroswietenolide* (IV)

(a) Swietenolide (99 mg) in acetone (100 ml) and Jones reagent (1 ml) was kept at −20° for 5 min. Chromatography of the product obtained in the usual way afforded 3-*dehydroswietenolide* (50 mg), m.p. (from $CHCl_3$–light petroleum) 241–244°. (Found: C, 66·7; H, 6·8. $C_{27}H_{32}O_8$ requires: C, 66·9; H, 6·7%.)

(b) 3-Episwietenolide (50 mg) oxidized as in (a) afforded 3-dehydroswietenolide (20 mg), m.p. and m.m.p. 240–244°.

(c) 3,6-Bisdehydroswietenolide (see below) (250 mg) and AnalaR Zn dust (3 g) were refluxed in AnalaR AcOH (20 ml) for 1½ hr. Solids were removed by filtration, solvent by evaporation under reduced press and the product extracted from water into $CHCl_3$, furnishing 3-dehydroswietenolide (180 mg), m.p. (after prep. TLC and crystallization) 240–244°, undepressed on admixture with material obtained in (a).

3,6-*Bisdehydroswietenolide* (XVII)

(a) To swietenolide (97 mg) in acetone (50 ml) Jones reagent (5 ml) was added dropwise and the mixture kept at 20° for 3 min. The reaction was then poured into water and the product recovered in the usual way. Prep. TLC (2% MeOH–$CHCl_3$) afforded as the major product (69 mg) 3,6-*bisdehydroswietenolide* (XVII), m.p. (from $CHCl_3$–light petroleum) 183–185°, $[\alpha]_D$ −4° (*c*, 1·00). (Found: C, 67·0; H, 6·0. $C_{27}H_{30}O_8$ requires: C, 67·2; H, 6·25%.)

(b) 3-Episwietenolide (XVI; 93 mg) oxidized under comparable conditions gave 3,6-bisdehydroswietenolide (66 mg) m.p. (from $CHCl_3$–light petroleum) 182–185°.

Alkali treatment of 3-dehydroswietenolide

The *β-diketone* VIIa or VIIIa (R = OH): Compound IV (250 mg) was kept in a mixture of EtOH (50 ml) and 1N NaOH (1 ml) at 20° for 2 min. The product (170 mg), obtained on acidification, dilution with water and extraction into $CHCl_3$, was isolated by prep. TLC (2% MeOH–$CHCl_3$) as the non-crystalline *β-diketone* VIIa or VIIIa (R = OH), $[\alpha]_D$ +122°. (For UV, IR and NMR spectra see Table 1.) (Found: C, 66·7; H, 6·6. $C_{27}H_{32}O_8$ requires: C, 66·9; H, 6·7%.)

Periodate cleavage of the β-diketones (a) VIIa *or* VIIIa (R = OH) *from swietenolide and* (b) VIIa *or* VIIIa (R = H) *from mexicanolide*

(a) The β-diketone obtained above (170 mg) in water (20 ml) containing NaOH (1 equiv) and sodium metaperiodate (380 mg; 5 equivs) was kept for 18 hr at 20°. Separation of the product as usual afforded acidic (48 mg) and neutral (108 mg) fractions. Esterification of the acid fraction in MeOH (5 ml) with ethereal diazomethane afforded, on prep. TLC: (i) the *γ-lactone diester* (XIV; 21 mg) which was distilled at 160°/0·1 mm, $[\alpha]_D$ −8° (*c*, 1·20). (Found: C, 55·8; H, 6·8. $C_{12}H_{18}O_6$ requires: C, 55·8; H, 7·05%.) (ii) The *diene lactone* (XIII; 20 mg), m.p. (from $CHCl_3$–Et_2O) 147–149°, $[\alpha]_D$ +387°. (Found: C, 67·35; H, 6·2. $C_{17}H_{18}O_5$ requires: C, 67·55; H, 6·0%.)

(b) To the β-diketone VIIa or VIIIa (R = H; 900 mg) in t-butanol (100 ml) was added sodium metaperiodate (10 g) in water (30 ml) and the mixture stirred for 72 hr at 20°. The product was separated in the usual manner into acidic (200 mg) and neutral (520 mg) fractions. Methylation of the acid fraction and separation by prep. TLC afforded (i) the diene lactone XIII (60 mg), identical with the lactone obtained in (a) (m.p., m.m.p. and NMR) and (ii) the *triester* (XV; 50 mg), $[\alpha]_D$ −26°, which was distilled at 155°/0·05 mm. (Found: C, 56·15; H, 7·95. $C_{13}H_{22}O_6$ requires: C, 56·9; H, 8·1%.)

3-*Episwietenolide* (XVI). Swietenolide (1·0 g) in ethanolic KOH (100 ml; 5%) was refluxed in a N_2 atm for 1 hr. Acidification, dilution and extraction into $CHCl_3$ afforded acidic ($NaHCO_3$-soluble) material (930 mg), desmethyl 3-episwietenolide, m.p. (from EtOH–H_2O) 178–184°. Methylation with ethereal diazomethane, followed by prep. TLC (2% MeOH–$CHCl_3$), afforded 3-*episwietenolide* (XVI; 410 mg), m.p. (from $CHCl_3$–light petroleum) 213–217°, $[\alpha]_D$ −114° (*c*, 1·32). (Found: C, 66·5; H, 7·05. $C_{27}H_{34}O_8$ requires: C, 66·7; H, 7·05%.)

3-*Episwietenolide diacetate* (XXI). 3-Episwietenolide (46 mg) was treated with Ac_2O–pyridine as for swietenolide (see above). The least polar constituent obtained by prep. TLC was an amorphous white solid. (Found: C, 65·0; H, 6·8. $C_{31}H_{38}O_{10}$ requires: C, 65·3; H, 6·7%.)

Lead tetraacetate oxidation of desmethyl 3-episwietenolide

The noraldehyde (XVIII). Desmethyl 3-episwietenolide (480 mg) and lead tetraacetate (650 mg) in AnalaR AcOH were stored for 58 hr in the dark at 20°. Dilution and extraction into $CHCl_3$ afforded a product (430 mg) which was twice chromatographed by prep. TLC ($CHCl_3$) and then furnished the *noraldehyde* (XVIII; 130 mg), m.p. (from $CHCl_3$–light petroleum) 194–197°, $[\alpha]_D$ −31° (*c*, 1·04). (Found: C, 70·2; H, 7·3. $C_{25}H_{30}O_6$ requires: C, 70·4; H, 7·1%.)

Acknowledgement—We cordially thank Dr. G. Snatzke, Bonn, and Prof. W. Keyne, London, for the CD and ORD measurements.

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[4] Part IV. J. D. Connolly, R. McCrindle and K. H. Overton, *Ibid.* **24**, 1489 (1968).

[5] M. L. Wolfrom and J. M. Bobbitt, *J. Am. Chem. Soc.* **78**, 2489 (1956). We are indebted to Professor R. A. Raphael, F.R.S., for bringing this reaction to our notice.

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[8] Values taken in part from R. Henderson, Ph.D. Thesis, Glasgow, 1964.