Tetrahedron. Vol. 24, pp. 1503 to 1506. Pergamon Press 1968 Printed in Great Britain

TETRANORTRITERPENOIDS—VI[1]

[BICYCLONONANOLIDES IV]

SWIETENOLIDE—THE FUNCTIONAL GROUPS

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(*Received in UK* 23 *July* 1967; *accepted for publication* 15 *August* 1967)

Abstract—The part formulations A and B have been deduced for swietenolide obtained from the seeds of *Swietenia macrophylla.*

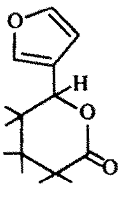
WE HAVE previously described[2] the isolation of the bitter principle swietenolide from the seeds of *Swietenia macrophylla.* This and the following paper are concerned with its functional groups, constitution and stereochemistry.

Swietenolide, crystallized from ethyl acetate, has m.p. 218–222°, $[\alpha]_D$ $-126°$ ($CHCl_3$). It is hygroscopic, but carefully dried material gave microanalyses in good agreement with the composition $C_{27}H_{34}O_8$. Kuhn–Roth oxidation detected 2·54 C-Me groups, a modified Zeisel determination[3] 0·96 O-Me groups. The presence of 2·26 active hydrogens was demonstrated by the Zerewitinoff method.

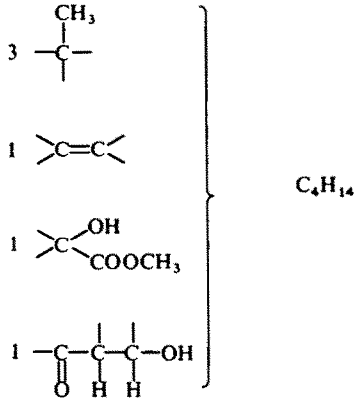
Swietenolide consumed one equivalent of base when kept in 0·05N NaOH (H_2O/EtOH; 1:1) at 20° and was regnerated on acidification. When heated at 95° with 0·1N NaOH (H_2O/EtOH; 1:1) for 5 hr two equivalents of base were consumed and acidification afforded desmethylisoswietenolide (II), $C_{26}H_{32}O_8$, m.p. 182–184°, $[\alpha]_D$ $-129°$, p*K* 4·68 (*v. infra*). Methylation with ethereal diazomethane did not regenerate swietenolide but instead afforded 3-episwietenolide (see Part VII).

Hydrogenation of swietenolide with 10% Pd–C in acetic acid gave hexahydroswietenolic acid (III), m.p. 232–235°, $[\alpha]_D$ $-59°$, p*K* 5·93, with a negative Cotton curve [R.D. in methanol: $[\phi]_{589}$ -320, $[\phi]_{310}$ -5800, $[\phi]_{277\cdot5}$ $+10{,}300$]. The derived methyl ester IIIa had m.p. 198–200°, $[\alpha]_D$ $-35°$.

Swietenolide, desmethylisoswietenolide and hexahydroswietenolic acid do not form an oxime, semicarbazone or 2,4-dinitrophenylhydrazone, but they have in the UV λ_{max} 284–288 nm ($\varepsilon \sim 50$), characteristic of a ketonic CO group, as are the Cotton curves of swietenolide (Experimental) and of the hexahydro-acid (*v. supra*). The IR spectrum of carefully dried swietenolide showed ν_{max} ($CHCl_3$) 3628 (free OH), 3535 (bonded OH) and ν_{max} (CCl_4) 1751 (δ-lactone), 1740 (methyl ester) and 1721 (cyclohexanone) cm^{-1}. The β-substituted furan ring and the associated δ-lactone are characterized in the NMR spectrum of swietenolide by singlets (1H each) at τ 2·42, 2·49 (α-furan), 3·51 (β-furan) and 4·45 (H-17), and the part structure (A), analogous to the situation in mexicanolide[4] is, as there, supported by the results of hydrogenation and hydrogenolysis (*v. supra*). Again the double bond, which survives hydrogenation, must be isolated and tetrasubstituted for the reasons already given in the case of mexicanolide.[4] Its location βγ with respect to the lactonic CO function is perhaps suggested by the positive Tollens reaction given by swietenolide and the hexahydro-ester, but not by the hexahydro-acid (crotonic and fumaric esters give the Tollens test, but the free acids do not).



A



B

While swietenolide (I) and hexahydroswietenolic acid (III) do not react with sodium periodate and consume lead tetra-acetate only slowly, desmethylisoswietenolide (II) consumes one molecular equivalent rapidly. The amorphous LAH reduction product of swietenolide rapidly reacted with periodate, generating formaldehyde (chromotropic acid). These observations suggest the presence of an α-hydroxy acid function in desmethylisoswietenolide (II), pK 4·68 and therefore an α-hydroxy-ester in swietenolide.

Two reactions which provide important clues to the constitution of swietenolide will now be briefly referred to. They are examined in detail in the following paper. Oxidation of swietenolide with potassium dichromate in acetic acid, chromium trioxide in pyridine or sodium hypobromite afforded dehydroswietenolide, (IV), $C_{27}H_{32}O_8$, m.p. 246–248°, $[\alpha]_D$ −127°, ν_{max} ($CHCl_3$) 3597 (α-hydroxy ester), ν_{max} (CCl_4) 1755 (δ-lactone), 1739 (methyl ester) and 1710 (increased intensity compared with swietenolide; additional cyclohexanone carbonyl) cm^{-1}; λ_{max} 288 nm (log ε 2·01).

The UV spectrum of dehydroswietenolide exhibited some unforeseen properties. Thus in acidified ethanol, λ_{max} 288 nm (log ε 2·01) [end absorption at 210 nm (log ε 4·22)] was unchanged after 24 hr. However, on standing in unacidified ethanol, the intensity of the peak at 288 nm progressively increased and after 24 hr. log ε had reached 3·39. Addition to the fresh ethanolic solution of one drop of 1N NaOH produced immediately λ_{max} 288 nm (log ε 4·54) [end absorption at 220 nm (log ε 4·04)]. This did not change with time but was on acidification replaced by λ_{max} 262–264 nm (log ε 4·38). This spectroscopic behaviour suggests the formation of an enolizable β-dicarbonyl system. Moreover, failure of dehydroswietenolide to show the UV absorption of such a system until treated with alkali, suggests that the β-dicarbonyl system in dehydroswietenolide is masked and can be revealed by the action of very mild base.

Presence of a β-dicarbonyl system in dehydroswietenolide would presuppose a β-hydroxy ketone in swietenolide. Attempts to dehydrate this to the αβ-unsaturated ketone were unsuccessful with thionyl chloride and pyridine, but seemed to proceed when swietenolide was heated under reflux with sodium acetate and acetic anhydride. The crystalline acetate formed V, $C_{29}H_{34}O_8$, m.p. 198–201°, $[\alpha]_D$ +249°, corresponded in composition to the monoacetate of anhydroswietenolide and had ν_{max} (Nujol) 1685 cm^{-1} and λ_{max} 276 nm (log ε 4·18) [shoulder at 235 nm (log ε 4·10)].

The structural features of swietenolide disclosed by the foregoing evidence can be summarized in the part-expressions (A) and (B).

EXPERIMENTAL

M.ps are uncorrected and were determined in an oil bath. Alumina used for chromatography was prepared by washing Spence Type H alumina with dilute nitric acid, followed by boiling distilled water and methanol[5] and then reactivating it at 200° according to Brockmann.[6] Specific rotations refer to $CHCl_3$ solns.

Isolation of swietenolide from Swietenia macrophylla *seeds*. The extraction was carried out according to the method previously described.[1] Obtained in this way, swietenolide had m.p. 218–222°, $[\alpha]_D$ −126° (*c*, 2·09), −114° (*c*, 1·28, in MeOH); rotatory dispersion (MeOH): $[\phi]_{589}$ −570; $[\phi]_{310}$ −10,600; $[\phi]_{275}$ +8100; λ_{max} 288 nm (log ε 1·72); ν_{max} (CCl_4) 1751, 1740 and 1721 cm^{-1}; ($CHCl_3$) 3628, 3535, 1736 and 1718 cm^{-1}. [Found (for swietenolide dried to constant weight at 100°): C, 66·85, 66·7, 67·15, 66·85; H, 7·2, 7·25, 7·05, 7·0; O, 26·35; 26·1. $C_{27}H_{34}O_8$ requires: C, 66·65; H, 7·05; O, 26·3%].

Alkaline hydrolysis of swietenolide

(a) Swietenolide kept in 0·05N aqueous–alcoholic (1:1) NaOH at 20° consumed 0·98 equivs of base. Acidification furnished swietenolide in 90% yield.

(b) Swietenolide (168 mg) was refluxed with 0·1N NaOH in aqueous EtOH (1:1) for 5 hr. Back titration showed 2·06 equivs base had been used. Acidification and crystallization of the acidic product afforded *desmethyl isoswietenolide* (II; 110 mg), m.p. (from aqueous EtOH) 182–184°, $[\alpha]_D$ −129° (*c*, 0·93), p*K* 4·68; ν_{max} (Nujol) 3460, 1715, 1505, 1029 and 879 cm^{-1}. [Found: (a) dried at 140°: C, 65·8; H, 6·7. $C_{26}H_{32}O_8$ requires: C, 66·1; H, 6·85%, (b) Dried and rehydrated to constant weight: C, 64·05; H, 6·75. $C_{26}H_{32}O_8 \cdot H_2O$ requires: C, 63·65; H, 7·0%.]

Hydrogenation of swietenolide

Swietenolide (500 mg) and Pd–C (10%) were shaken with hydrogen in AnalaR AcOH (10 ml) at 20°. Hydrogen uptake appeared to be complete after 3 hr (3·78 moles absorbed). Working in the usual way afforded *hexahydroswietenolic acid*, (III), m.p. (from $CHCl_3$–MeOH) 232–235°, $[\alpha]_D$ −59° (*c*, 1·7), p*K* 5·93. [Found: C, 65·3; H, 8·3. $C_{27}H_{40}O_8$ requires: C, 65·8; H, 8·2%.] The *methyl ester* (IIIa), had m.p. (from $CHCl_3$–ether) 197–200°, $[\alpha]_D$ −35° (*c*, 1·48). [Found: C, 66·05; H, 8·4. $C_{28}H_{42}O_8$ requires: C, 66·4; H, 8·35%.]

Oxidation of swietenolide: Dehydroswietenolide (IV)

(a) *With potassium dichromate*. Swietenolide (240 mg) was kept in 0·1N $K_2Cr_2O_7$ in AcOH (50 ml) for 16 hr at 20°. Working up in the usual way and crystallization of the product from EtOAc–light petroleum afforded *dehydroswietenolide* (IV; 85 mg), m.p. 246–248°, $[\alpha]_D$ −127° (*c*, 1·02). [Found: C, 66·65; H, 6·5. $C_{27}H_{32}O_8$ requires: C, 66·9; H, 6·65%.]

(b) *With chromium trioxide in pyridine*. Oxidation of swietenolide (200 mg) under standard Sarett conditions afforded dehydroswietenolide (30 mg), m.p. and mixed m.p. with material obtained in (a) 245–247°.

(c) *With sodium hypobromite*. Swietenolide (300 mg) was kept in MeOH (15 ml) and 0·1N NaOH (12 ml) at 20°. After 1 hr the MeOH was removed *in vacuo* and NaOBr soln [0·5 g Br_2 in 10 ml 4% NaOHaq] added. The product obtained on acidification after ½ hr was separated into acid and neutral fractions. The latter on working afforded dehydroswietenolide (30 mg), m.p. 234–240°, rising to 246–248° on further crystallization and then undepressed with material obtained in (a). Methylation of the acidic product afforded a further 32 mg, m.p. 246–248°, undepressed with dehydroswietenolide.

Acetylation of swietenolide: *The anhydro-acetate* (V)

Swietenolide (300 mg) and freshly fused NaOAc (1·3 g) were refluxed in Ac_2O (10 ml) for 5 hr. The product, obtained in the usual way, was adsorbed on acid alumina (Grade IV; Woelm) from benzene. Elution with ether–benzene (1:9) afforded the *anhydroacetate* (V) (36 mg), m.p. (from $CHCl_3$–ether) 198–201°, $[\alpha]_D$ +249° (*c*, 1·06). [Found: C, 68·1; H, 6·5. $C_{29}H_{34}O_8$ requires: C, 68·2; H, 6·7%.]

Lead tetraacetate oxidations of swietenolide, desmethyl isoswietenolide and hexahydroswietenolic acid

To each compound (0·04 mmole) in AcOH (2 ml) was added lead tetraacetate in AcOH (60 mg/2 ml) and the soln made up to 5 ml with AcOH. The solns were kept at 36°, 1 ml aliquots withdrawn and each added to 3 ml of a soln prepared by dissolving NaI (0·5 g) and NaOAc (5 g) in water (25 ml), and the liberated I_2 titrated with 0·02N $Na_2S_2O_3$. Blank determinations were run concurrently.

The uptake of lead tetraacetate in moles per mole of substrate after 8 hr, 21 hr and 48 hr were: Swietenolide 0·1, 0·2, 0·4; hexahydroswietenolic acid, 0·05, 0·1, 0·2; desmethylisoswietenolide: 1·0, 1·3, 1·7. 1-Hydroxycyclohexanecarboxylic acid: 0·6, 0·9, 1·2.

Acknowledgement—We cordially thank Mr. W. S. Chalmers, Assistant Conservator of Forests, Port of Spain, Trinidad for supplies of S. macrophylla seeds.

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