Tetranortriterpenoids. Part XV.[1] Base-induced Fragmentation of Some Swietenine Derivatives

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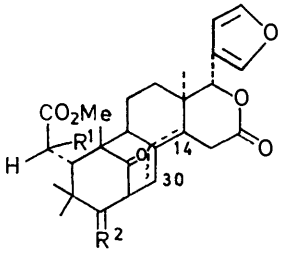
The swietenine derivatives (3). (9). and (22) are transformed under basic conditions. with rearrangement. into the acids (4). (10). and (23). respectively whose structures are supported spectroscopically and by mechanistically reasonable modes of formation. The rearrangements are initiated by β-dicarbonyl fission at C(2)–C(3) [or C(1)–C(2)] of the bicyclononane system of swietenine. Attention is drawn to the structural diversity and unpredictability of the products.

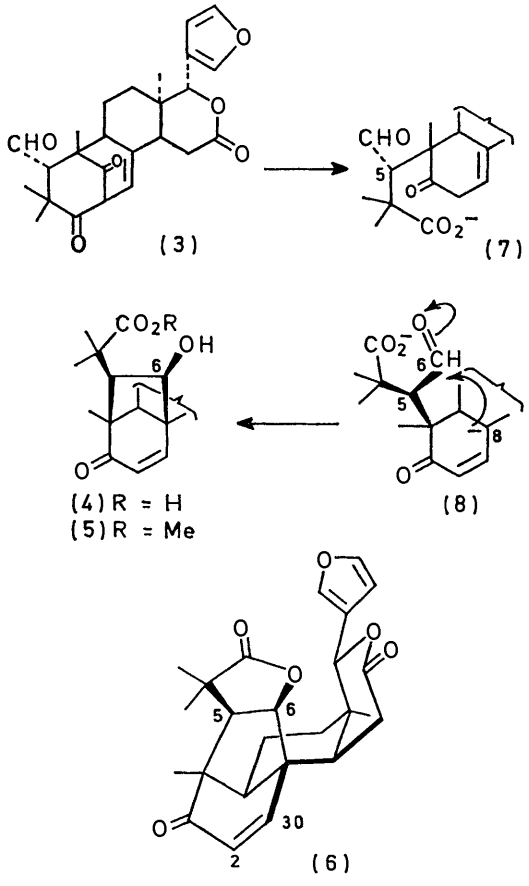
THE bicyclononane system of natural bicyclononanolides such as swietenine (1) and mexicanolide (2) undergoes ready base-induced fragmentation, the particular mode



(1) R^1 = OH, R^2 = β-O-tigloyl, H, $\Delta^{8(30)}$
(2) R^1 = H, R^2 = O, $\Delta^{8(14)}$

of fragmentation depending upon the presence and location of substituents that direct hydroxide ion attack to a particular site. We have previously exemplified this fact in the course of elucidations of the structures of swietenine [2] and mexicanolide,[3] and now report the products of base-catalysed cleavage of some further derivatives of swietenine which illustrate how critically dependent upon substitution and unpredictable in outcome is the course of such fragmentations.

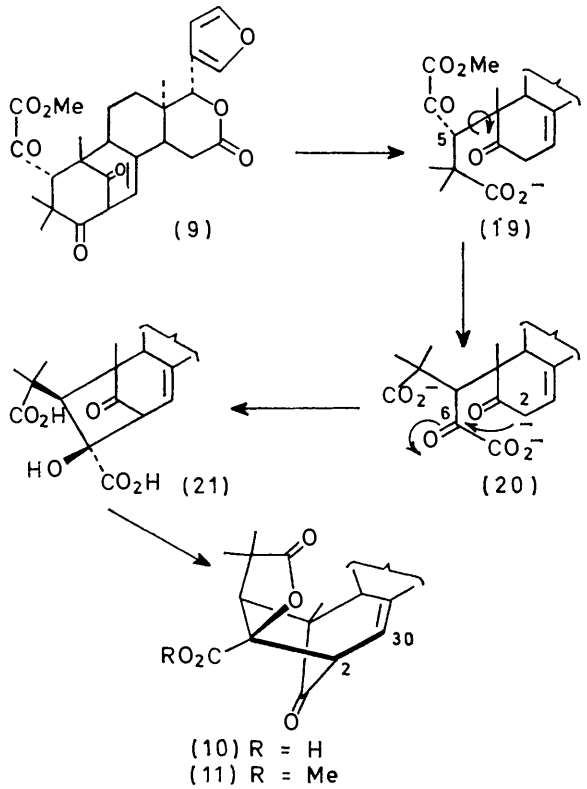
The diketo-aldehyde (3) [≡ (XV) [2]], when treated with aqueous ethanolic sodium hydroxide at reflux, was converted in high yield into the acid (4), characterised as its methyl ester (5), $\nu_{max.}$ ($CHCl_3$) 3620, 3583 (unbonded and bonded OH), 1733, 1687 (ester + δ-lactone and enone CO) cm^{-1}. Both acid and ester were insoluble in deuteriochloroform. An n.m.r. spectrum of the ester in trifluoroacetic acid was of limited value, but



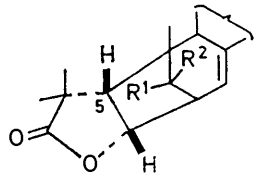
(3) (7)
(4) R = H
(5) R = Me
(8)
(6)

[1] Part XIV, J. D. Connolly and D. A. H. Taylor, *J.C.S. Perkin I*, 1973, 686.
[2] J. D. Connolly, R. Henderson, R. McCrindle, K. H. Overton, and N. S. Bhacca, *J. Chem. Soc.*, 1965, 6935.
[3] J. D. Connolly, R. McCrindle, and K. H. Overton, *Tetrahedron*, 1968, **24**, 1489.

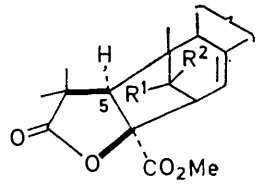
that of the lactone (6), freely soluble in deuteriochloroform, was much more useful. The lactone was obtained when the sodium salt of acid (4) was treated with oxalyl chloride during attempts to prepare a derivative for *X*-ray structure analysis, and showed $\nu_{max.}$ (Nujol) 1780 (γ-lactone), 1742 (δ-lactone), and 1685 (enone) cm^{-1}. N.m.r. (single- and double-resonance) data supported the formulation (6) as follows: (*a*) AB quartet at δ 6·75 and 6·07 (*J* 10·5 Hz), H-2 and H-30; (*b*) doublet (*J* 11·5 Hz) at δ 4·84, H-6; (*c*) doublet (*J* 11·5 Hz) at δ 2·31, H-5. H-2 and H-5 do not show any additional coupling, thus supporting the two isolated AB systems of formulation (6). The doublets arising from H-6 and H-30 do show a slight diminution in height when compared with the doublets arising from their respective AB partners ($J_{1,4}$ between H-6 and H-30?). We suppose that the enone acid (4) is formed as follows. Hydroxide attack at C-3, β-dicarbonyl fission and double-bond conjugation [(3) ⟶ (7) ⟶ (8)] is followed by epimerisation at C-5 and vinylogous anion addition of C-8 to C-6 [(8) ⟶ (4)]. We favour the configuration in which the γ-lactone ring in the dilactone (6) is *syn* with respect to the cyclohexenone (this requires inversion of the original configuration at C-5), since this is much less congested than the alternative *anti*-configuration [the steps leading to the acid (4) are reversible].



Another interesting base-catalysed transformation concerns the triketo-ester (9) [≡ (XII) [2]]. This gives, in high yield, an acid (10) whose methyl ester we formulate as (11), $\nu_{max.}$ ($CHCl_3$) 1787 (γ-lactone), 1764 (bicyclo[3.2.1]octenone + α-acyloxy-ester), and 1735 (δ-lactone) cm^{-1}. These bands are very similar to those for the γ-lactone (12) [≡ (XVII) [2]] but for the substantially greater intensity of the band at 1764 cm^{-1}. In the n.m.r. spectrum the H-2 signal appears as a clean doublet (*J* 16 Hz) at δ 3·08, coupled only with H-30 at δ 5·58, which in turn shows the characteristic allylic coupling seen in swietenine.[2] Borohydride reduction of the ketone (11) led to the two isomeric alcohols (13) and (14). Of these the less polar alcohol (13) showed in dilute ($CHCl_3$) solution a strongly H-bonded (to ester CO) OH band at 3465 cm^{-1}, whereas the more polar oily alcohol (14) showed a weakly H-bonded [to $\Delta^{8(30)}$] OH band at 3575 cm^{-1}, comparable to a band at 3587 cm^{-1}



(12) R^1R^2 = O
(15) R^1 = H, R^2 = OH
(18) R^1 = H, R^2 = OAc



(13) R^1 = OH, R^2 = H
(14) R^1 = H, R^2 = OH
(16) R^1 = OAc, R^2 = H
(17) R^1 = H, R^2 = OAc

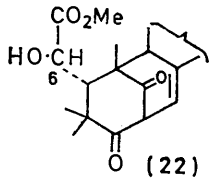
in the spectrum of the lactone (15) [≡ (XVI) [2]]. Both alcohols formed crystalline acetates, (16) and (17), whose n.m.r. spectra accorded with the assigned structures. In particular, $J_{1,2}$ is <1 Hz for the acetate (16) and 6 Hz for the acetate (17). Comparison with chemical shifts and coupling constants for the acetate (18) [≡ (XVIa) [2]] shows general correspondence, except for the chemical shift of H-5 [δ 3·27 for (16), 2·72 for (17), 2·52 for (18)]. This and the strong H-bond in the alcohol (13) support the configuration (11) for this ester, in which the ester function is *syn* to the C-1 bridge. The *anti*-configuration is mechanistically attainable by inversion at C-5 before condensation.

We suppose that the γ-lactone (11) arises by dicarbonyl fission [(9) ⟶ (19)] as before, followed by C-2 ⟶ C-6 bond formation and lactonisation [(20) ⟶ (21) ⟶ (10)]. A transition state for the carbanion addition in which the two carboxylate groups are *anti* is clearly preferable. Hydrolysis of either acetate (16) or (17) and oxidation of the products regenerated the ketone (11).

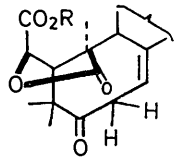
Reduction of the triketo-ester (9) with zinc and acetic acid specifically reduced the C-6 carbonyl group to furnish the hydroxy-diketone (22), m.p. 221—223°, $[\alpha]_D$ −254°, as evidenced by its n.m.r. spectrum. In particular, there is a new carbinol signal for H-6 at δ 4·68 (*cf.* δ 4·34 in swietenine) and the H-5 signal moves upfield from δ 4·68 in the triketone (9) to δ 3·20 in the reduction product (22). This is analogous to reduction under the same conditions of 6-dehydroswietenine (26) [≡ (V) [2]] which, in that case stereoselectively, restores the 6*R*-configuration of swietenine.

Treatment with base of the reduction product (22)

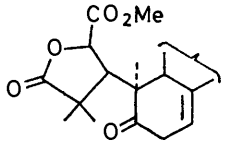
affords an acid (23) whose crystalline methyl ester (24), m.p. 260—263°, $[\alpha]_D$ +113°, has $\nu_{max.}$ ($CHCl_3$) 1783 (γ-lactone), 1738 (methyl ester + δ-lactone), and 1717 (cycloalkanone) cm^{-1}. The n.m.r. spectrum showed one olefinic proton (δ 5·43, broad s), and a low-field doublet



(22)



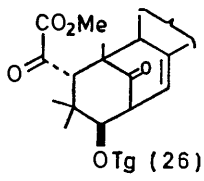
(23) R = H
(24) R = Me



(25)

(*J* 0·8 Hz) at δ 4·60 [–C*H*(CO_2Me)·O·CO–]. Of the possible formulations (24) and (25) for this lactone, arising from the two alternative modes of β-dicarbonyl fission and γ-lactonisation, we marginally prefer the cyclo-octenone structure (24), as this more convincingly accounts for the observed absence of conjugated enone. Attainment of coplanarity of the enone chromophore is in this case made impossible by prohibitive transannular interactions. The high cycloalkanone carbonyl frequency may be associated with angle strain in the optimal conformation.

It is instructive to compare the very different reaction paths followed in the foregoing examples in response to apparently minor changes in constitution of the substances reacting. Contrast, for instance, the conversion under similar conditions of the hydroxy-aldehyde (27) [≡ (VI) [2]] and the corresponding diketo-aldehyde (3), respectively, into compounds (15) and (4), presumably *via* the similar initial products of cleavage, (28) and (7). It is also stimulating, but probably unprofitable at this stage, to speculate on the reasons for these observed differences, apart from recognising that there is available a multiplicity of reversible base-promoted processes (*e.g.* de- and re-aldolisation, β-dicarbonyl fission, enol-mediated epimerisation, Cannizzaro-type hydride transfer) which will result in a sequence of steps that must depend critically upon the conformational and stereoelectronic properties of all possible intermediates and products.



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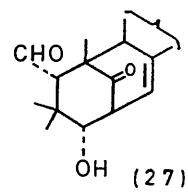

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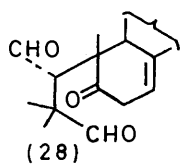

(28)

EXPERIMENTAL

For general experimental directions see ref. 2. N.m.r. spectra were obtained with a Varian HR 100 spectrometer.

The Enone Methyl Ester (5).—The diketo-aldehyde (3) [2] (71 mg) dissolved in ethanol (3 ml) and 0·5N-sodium hydroxide (3 ml) was heated at 95° for 1 h. Dilution with water, acidification, and extraction into ethyl acetate, and separation with sodium hydrogen carbonate into acid and neutral portions, afforded an acid fraction (60 mg). Methylation and chromatography over Grade IV acidic alumina (3 g) afforded [elution with chloroform–benzene (3 : 7 to 2 : 3)] the *enone methyl ester* (5) (48 mg), m.p. 285—287°, $[\alpha]_D$ +25° (*c* 0·56), δ (CF_3·CO_2H) 7·39 (2H, m, α-furan protons), 6·96 and 6·06 (each 1H, d, *J* 17 Hz, H-30 and H-2), 6·38 (1H, m, β-furan H), 5·98 (1H, s, H-17), 4·95 (1H, d, *J* 12 Hz, H-6), 2·33 (1H, d, *J* 12 Hz, H-5), and 1·40 and 1·31 (3H each) and 1·02 (6H) (methyls) (Found: C, 67·2; H, 7·15. $C_{26}H_{32}O_7$,0·5H_2O requires C, 67·1; H, 7·15%).

The ester (5) was recovered unchanged from (i) attempted oxidation with excess of Jones reagent at 20°; (ii) attempted acetylation with sodium acetate and acetic anhydride under reflux for 1 h; (iii) attempted dehydration with phosphoryl chloride–pyridine at 20° for 3 days.

The γ-Lactone (6).—The acid (4) (20 mg) in ethanol (3 ml) was neutralised with sodium hydrogen carbonate (5 mg) and solvents were removed at 0·1 mmHg and 40° for 16 h. The sodium salt was suspended in redistilled oxalyl chloride (2 ml) and shaken at 20° for 10 h. Removal of solids and excess of oxalyl chloride, and preparative layer chromatography of the residue (23 mg) on silica gel [methanol–chloroform (3 : 97)] afforded the γ-lactone (6) (14 mg), m.p. 295—298° (from ether–chloroform), δ 1·32, 1·29, 1·15, and 1·02 (3H each, methyls).

The Ester (11).—The triketo-ester (9) [2] (200 mg) was kept in dioxan (4 ml) and methanolic 5% potassium hydroxide (4 ml) at 20° for 30 min. Work-up as usual afforded an acidic product which was methylated with diazomethane to afford the *ester* (11) (155 mg), m.p. 297—299° (from ether–chloroform), $[\alpha]_D$ +43° (*c* 1·08 in $CHCl_3$), $\Delta\varepsilon_{310}$ +5·59 $\Delta\varepsilon_{270}$ −5·35, δ 7·69, 7·41, and 6·42 (each H, m, α- + β-furan protons), 5·58 (1H, d, *J* 16 Hz, H-30), 5·47 (1H, s, H-17), 3·83 (3H, s, CO_2Me), 3·08 (1H, d, H-2), and 1·52, 1·33, 1·25, and 1·09 (each 3H, Me) (Found: C, 66·05; H, 6·3. $C_{27}H_{30}O_8$ requires C, 66·0; H, 6·35%).

Sodium Borohydride Reduction of the Ester (11). *The Alcohols* (13) *and* (14).—The ester (11) (150 mg) and sodium borohydride (450 mg) were kept in methanol (35 ml) for 12 h. The product (145 mg) obtained with chloroform from the acidified mixture consisted of two compounds more polar than the starting material (t.l.c.). Chromatography over Grade III acidic alumina (6 g) [chloroform–benzene (3 : 7 to 2 : 3)] afforded the *alcohol* (13) (56 mg), m.p. 313—317° (from chloroform–light petroleum), $[\alpha]_D$ −72° (*c* 1·00 in pyridine), $\nu_{max.}$ ($CHCl_3$) 3465, 1783, and 1720 cm^{-1} (Found: C, 66·75; H, 6·65. $C_{27}H_{32}O_8$ requires C, 66·9; H, 6·65%). Elution with chloroform–benzene (1 : 1 to

3 : 2) afforded the alcohol (14) (84 mg) as an oil, homogeneous by t.l.c., $\nu_{max.}$ ($CHCl_3$) 3620, 3575, 1783, 1756, and 1732 cm^{-1}. Acetylation of the alcohol (13) with acetic anhydride–pyridine afforded the *acetate* (16), m.p. 142—144° (from chloroform–light petroleum), $[\alpha]_D$ −82 (*c* 1·22 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 1780 and 1737 cm^{-1}, δ 7·92, 7·76, and 6·42 (1H each, α- and β-furan protons), 5·64 (1H, d, *J* 9 Hz, H-30), 5·39 (1H, s, H-17), 4·73 (1H, s, H-1), 3·79 (3H, s, CO_2Me), 3·27 (1H, s, H-5), 3·03 (1H, d, *J* 9 Hz, H-2), 2·17 (3H, s, Ac), and 1·45, 1·30, 1·18, and 1·08 (each 3H, s, Me) (Found: C, 65·35; H, 6·55. $C_{29}H_{34}O_9,0{\cdot}5H_2O$ requires C, 65·05; H, 6·6%). Acetylation of the alcohol (14) afforded the *acetate* (17), m.p. 259—262° (from chloroform–light petroleum), $[\alpha]_D$ −13° (*c* 1·12 in $CHCl_3$), δ 7·68, 7·36, and 6·42 (α- + β-furan protons), 5·36 (1H, s, H-17), 5·34 (1H, d, *J* 9 Hz, H-30), 4·92 (1H, d, *J* 6 Hz, H-1), 3·86 (3H, s, CO_2Me), 3·22 (1H, q, *J* 9 and 6 Hz, H-2), 2·72 (1H, s, H-5), 2·03 (3H, s, Ac), and 1·47, 1·27, 1·18, and 1·13 (each 3H, s, Me) (Found: C, 66·05; H, 6·4. $C_{29}H_{34}O_9$ requires C, 66·15; H, 6·5%).

Reduction of the Triketo-ester (9) *with Zinc and Acetic Acid.*—The triketo-ester (9) (110 mg) and AnalaR zinc dust (1·2 g) were refluxed in AnalaR acetic acid (15 ml) for 2 h. Work-up as usual afforded a gum (110 mg) which was dissolved in chloroform (10 ml) and percolated through Grade IV acidic alumina (15 g) to afford the *ester* (22) (78 mg), m.p. 221—223° (from ethyl acetate–light petroleum), $[\alpha]_D$ −254° (*c* 1·63 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3611, 3538, 1739, and 1716 cm^{-1}, $\Delta\varepsilon_{320}$ −7·93, $\Delta\varepsilon_{270}$ +7·69, δ 7·52, 7·43, and 6·34 (each 1H, m, α- + β-furan protons), 5·74 (1H, dt, *J* 8 Hz, H-30), 5·43 (1H, s, H-17), 4·65 (1H, s, H-6), 3·72 (3H, s, CO_2Me), 3·66 (1H, d, *J* 8 Hz, H-2), 3·17 (1H, s, H-5), and 1·57, 1·15, 1·08, and 0·97 (each 3H, s, Me) (Found: C, 66·45; H, 6·95. $C_{27}H_{32}O_8$ requires C, 66·95; H, 6·65%). Oxidation of the ester (22) with an excess of Jones reagent regenerated the triketo-ester (9) (i.r., m.p. and mixed m.p., and R_F value).

The Ester (24).—The ester (22) (42 mg) was stored in dioxan (0·8 ml) and methanolic 5% potassium hydroxide (0·8 ml) for 30 min at 20°. The usual work-up afforded an acidic product (36 mg) which was methylated with diazomethane. Chromatography of the product over Grade IV acidic alumina afforded [with chloroform–benzene (1 : 4)] the *ester* (24) (30 mg), m.p. 259—262° (from chloroform–light petroleum), $[\alpha]_D$ +113° (*c* 0·91 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 1783, 1738, and 1717 cm^{-1}, $\Delta\varepsilon_{330}$ +1·58, $\Delta\varepsilon_{275}$ +0·09, δ 7·37 (2H, m), 6·31 (1H, m) (α- + β-furan protons), 5·41 (1H, m, H-30), 5·28 (1H, s, H-17), 4·57 (1H, d, *J* 0·8 Hz, H-6), 3·83 (3H, s, CO_2Me), and 1·43, 1·34, 1·07, and 1·04 (each 3H, s, Me) (Found: C, 65·9; H, 6·8. $C_{27}H_{32}O_8,0{\cdot}5H_2O$ requires C, 65·7; H, 6·75%).

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