The Constituents of *Ecballium elaterium* L. XVI. Stereochemical Problems in the Cucurbitacins[1,2]

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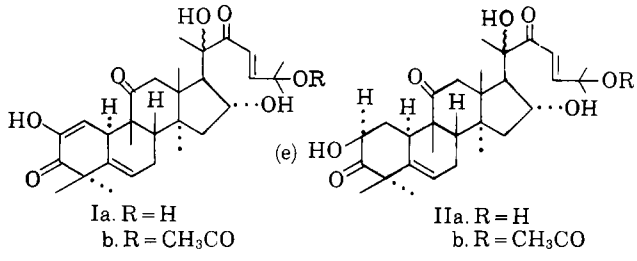
The configuration of the various asymmetric centers of elatericin A and cucurbitacin B as well as the hydrogenated derivatives of elatericin B and elaterin (cucurbitacin E) are presented and discussed.

In the preceding paper[2b] of this series, complete structures were proposed for elatericin B (Ia), elaterin (cucurbitacin E) (Ib), elatericin A (IIa), and cucurbitacin B (IIb). In the present paper experiments are described which contribute toward the elucidation of the stereochemistry of several asymmetric centers in these tetracyclic triterpenes and their derivatives.[4]

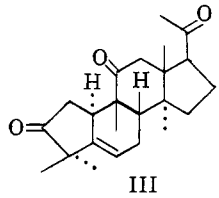
In order to determine the stereochemistry at carbon atom 10, the contribution of the ketone group in ring A of compound III[2b] to the optical rotatory dispersion was determined by drawing the difference curve of the two substances III and IV. The latter substance was obtained through the preparation of the bisethylene ketal of the ketone groups at 3 and 20 of compound III by the usual procedure[2b] and the subsequent selective hydrolysis of the C-20 ketal, using a dilute solution of acetic acid during a limited period of time. By substracting the optical rotatory dispersion curve of IV from III, the contribution of the two carbonyl groups at C-11 and C-20 were eliminated and the resultant curve ($[\alpha]_{320}$ −3837°, $[\alpha]_{280}$ +4710°) showed a strong negative Cotton effect whose large amplitude, due to the strain of the five-membered ring bearing the ketone group in ring A, was comparable but opposite in sign to that found in the curve obtained with 4,4-dimethyl-A(2)-nor-cholestenone.[5] Since the latter has a β-substituent at the C-10 position, it was concluded that the corresponding hydrogen in compounds III, IV, and elatericin A, from which they derive, has the α-orientation. The substitution in the latter products of a hydrogen by a methyl group should not influence the sign of the curve. In view of the presence of the methyl group at C-9, this α-orientation could have been anticipated biogenetically in the cucurbitacins. With this observation in mind, the previous stereochemical assignments of the C-2 hydroxyl groups in elatericin A (IIa) and in cucurbitacin B (IIb) should be revised.[6]

In our previous studies we erroneously had assumed a β-oriented methyl group at C-10.[7] The relationship existing between dihydroelatericin A (Va) (double bond of the side chain reduced) and tetrahydroelatericin B (VIa) (double bonds in side chain and ring A reduced) has now to be clarified. These two derivatives have already been reported to differ in physical properties (melting points, optical rotations, and solubilities); they are epimers at C-2.[7]



Ia. R = H
b. R = CH_3CO

IIa. R = H
b. R = CH_3CO



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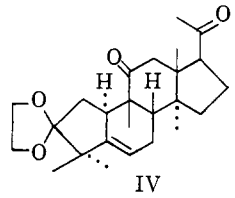

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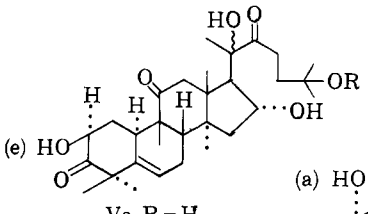

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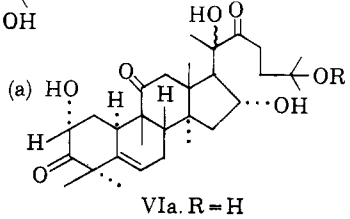
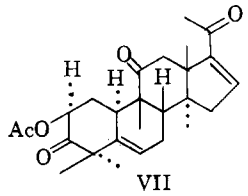
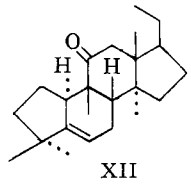
b. R = CH_3CO



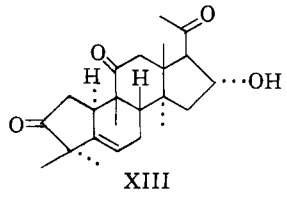
VIa. R = H
b. R = CH_3CO



VII



XII



XIII

The conformations of the hydroxyl group at C-2 in the compounds possessing a 1,2-hydroxy ketone were determined using several spectroscopic measurements.

A. In the infrared spectra it was found that dihydroelatericin A (Va) and dihydrocucurbitacin B (Vb)

(1) This investigation was supported by a research grant CY-2810 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) (a) A previous version of this paper which was already in print, June, 1960, was withdrawn from publication in order to avoid misinterpretations in the literature. Various subsequent communications have been published meanwhile; however, for the sake of continuity, we have kept the numbering of the original version; (b) Part XV, D. Lavie, Y. Shvo, O. R. Gottlieb, and E. Glotter, *J. Org. Chem.*, **27**, 4546 (1962).

(3) On leave of absence from the Instituto de Química Agrícola, Ministério da Agricultura, Rio de Janeiro; O. R. G. acknowledges support from the Conselho Nacional de Pesquisas, Brazil.

(4) Presented in part before the 2nd International Symposium on the Chemistry of Natural Products, Prague, 1962; *cf. Bull. Res. Council Israel*, **11A**, 34 (1962).

(5) R. Hanna and G. Ourisson, *Bull. soc. chim. France*, (**5**), 1945 (1961).

(6) D. Lavie, Y. Shvo, and O. R. Gottlieb, *Tetrahedron Letters*, No. **22**, 23 (1960).

(7) D. Lavie and O. R. Gottlieb, *Chem. Ind.* (London), 929 (1960).

as well as elatericin A (IIa) and cucurbitacin B (IIb), have bands at 1125 cm.$^{-1}$, while in tetrahydroelatericin B (VIa) and in tetrahydroelaterin (VIb) that band is at 1100 cm.$^{-1}$. The frequency of the C–OH stretching band for secondary alcohols is at about 990–1065 cm.$^{-1}$, and it has been found to be *higher* for the equatorial hydroxyl than for the axial partner.[8] The effect of a neighboring carbonyl is to displace these bands in both cases to higher frequencies. The hydroxyl group then should be equatorial in substances Va and Vb and axial in VIa and VIb. A careful study of the spectrum of the carbonyl region using a calcium fluoride prism, corroborated these findings. A band at 1712 cm.$^{-1}$ was observed in the two dihydroderivatives (V) as well as in elatericin A (IIa) and cucurbitacin B (IIb). We correlate this band to the increased stretching frequency of the carbonyl at C-3, an increase which is due to the adjacent equatorial hydroxyl at C-2. In the two tetrahydroderivatives (VI) the band was recorded at about 1705 cm.$^{-1}$, it was somewhat lower due to the smaller effect of the vicinal axial hydroxyl. Such a relative lowering effect of an axial hydroxyl on the frequency of the carbonyl has been described previously.[8]

B. The ultraviolet spectra were consistent with these observations,[9] acetylation of the equatorial hydroxyl at C-2 of V shifted the weak carbonyl maximum to longer wave lengths, while acetylation of the axial hydroxyl of VI resulted in a shift to shorter wave lengths.

C. Part of the n.m.r. spectrum of elatericin A diacetate[10] shown in Fig. 1a indicates a series of signals which are due to the two protons at C-2 and C-16. They are composed of a triplet of lines in higher field originating from the C-16 proton and of a quartet in lower field which is due to the C-2 proton. There is an overlapping of two neighboring signals resulting in the appearance of the first higher peak. The pattern of four signals related to the C-2 proton is clearly visible in Fig. 1b, for 16-desoxyhexanorelatericin A monoacetate (VII).[11] This pattern is the result of a large coupling constant due to axial–axial interaction (13.6 c.p.s.) and of a small coupling constant due to axial–equiatorial interaction (4.2 c.p.s.). This characteristic pattern[12] of the C-2 hydrogen implies an axial conformation for this hydrogen. The acetoxy group has therefore an equatorial conformation in this derivative of elatericin A. The similarity of the two quartet patterns of lines in Fig. 1a and 1b ascertains the unaltered nature of the stereochemistry at carbon 2 in 16-desoxyhexanorelatericin A monoacetate which is obtained following a series of reactions from elatericin A diacetate.

It can be deduced from the various evidences presented, that in elatericin A (IIa) and cucurbitacin B (IIb) (as well as in their dihydroderivatives V) the conformation of the hydroxyl group at C-2 is equatorial, while in tetrahydroelatericin B (VIa) and tetrahydroelaterin (VIb) this group is axial. In view of the α-orientation of the hydrogen at C-10, determined earlier in this presentation, the configuration at C-2 should be β for the equatorial and α for the axial epimer. In the tetrahydro derivatives (VI) the α-axial configuration is, therefore, the result of a frontal approach to the molecule during the process of hydrogenation of the enolic double bond of ring A in I.

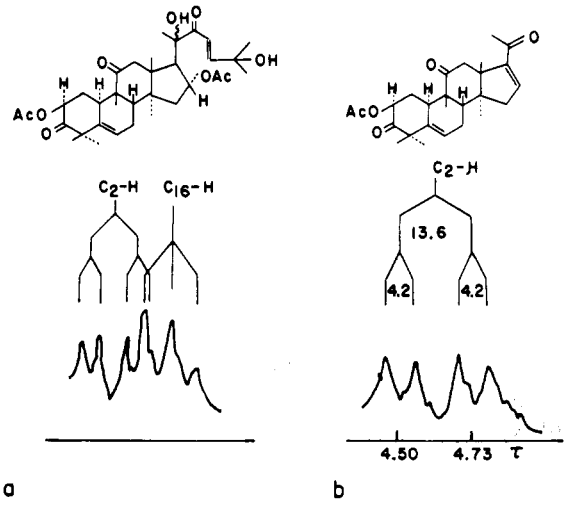


Fig. 1.—Part of n.m.r. spectra in chloroform-*d* of: a, elatericin A diacetate; b, 16-desoxyhexanorelatericin A acetate.

It is noteworthy that in agreement with these observations, the optical rotatory dispersion curves measured on dihydroelatericin A (Va) and tetrahydroelatericin B (VIa), which are both positive, display a remarkable difference in amplitude. It has been reported[13] that in steroids, as well as in triterpenes, the contribution to the size of the optical rotation in 1,2-hydroxy ketones is stronger for an axial than for an equatorial hydroxyl. In a β-configuration at C-10, the 2,β-axial hydroxyl group falls in a positive octant (lower right) and its contribution is, therefore, positive. When the configuration at C-10 is α the contribution of the 2-α-axial hydroxyl falling in a negative octant (lower left) is negative. Indeed, we have observed that in tetrahydroelatericin B (2,α-axial OH) the Cotton effect is smaller at the peak $[\alpha]_{325}$ +1550° than in dihydroelatericin A (2,β-equatorial OH) $[\alpha]_{325}$ +2200°.

With the stereochemistry of the asymmetric centers in ring A determined, a study of the various optical rotation values of several cucurbitacins and their derivatives leads to some novel and interesting observations. These values are reported in Table I. It can be seen that the substances possessing a 1,2-hydroxy ketone in ring A, as for example elatericin A, cucurbitacin B, and their dihydro derivatives as well as tetrahydroelatericin B and tetrahydroelaterin, have positive optical rotation values, while the cucurbitacins in which a diosphenol system occurs in ring A, *e.g.* elatericin B, elaterin, and their respective dihydro derivatives, have negative rotations. The sign of the optical rotations of the cucurbitacins is thus consistent with their structures, and it can, therefore, be used to make a distinction between the two major groups, differing in the nature of the substituents in ring A. This fact fitted conclusively for the substances obtained during the hydrogenation of the substances with the diosphenol

(8) The carbonyl absorption in the infrared of epimeric 1,2-hydroxy ketones was reported by A. R. H. Cole and G. T. A. Müller, *J. Chem. Soc.*, 1224 (1959), and by R. B. Bates, G. Büchi, T. Matsuura, and R. R. Shaffer, *J. Am. Chem. Soc.*, **82**, 2327 (1960).

(9) *Cf.* D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, **10**, 44 (1956).

(10) D. Lavie and Y. Shvo, *J. Am. Chem. Soc.*, **81**, 3058 (1959).

(11) D. Lavie and Y. Shvo, *ibid.*, **82**, 966 (1960).

(12) K. L. Williamson and W. S. Johnson, *ibid.*, **83**, 4623 (1961).

(13) W. Klyne, *Tetrahedron*, **13**, 29 (1961).

TABLE I

OPTICAL ROTATIONS, $[\alpha]_D$, OF THE CUCURBITACINS ARRANGED ACCORDING TO THE FUNCTIONAL GROUPS OF RING A

Diosphenols		1,2-Hydroxy ketones		1,2-Diols
Elaterin[a] (Ib) −58°	Dihydroelaterin −46°	2-Epicucurbitacin B[b] +41°	Tetrahydroelaterin (VIb) +21°	Hexahydroelaterin +54°
		Cucurbitacin B (IIb)[c] +87°	Dihydrocucurbitacin B (Vb)[c] +57°	
Elatericin B (Ia)[d] −52°	Dihydroelatericin B −44°		Tetrahydroelatericin B (VIa) +59°	Hexahydroelatericin B[c] +49°
		Elatericin A (IIa)[e] +48°	Dihydroelatericin A (Va)[e] +83°	Tetrahydroelatericin A[e] +31°

[a] See ref. 14. [b] See ref. 16. [c] See ref. 17. [d] See ref. 15. [e] See ref. 10.

in ring A, namely elatericin B and elaterin, the sign of the optical rotation becoming positive when a 1,2-hydroxy ketone was formed. This was true for tetrahydroelatericin B[15], which has now been prepared in a carefully purified form, as well as for tetrahydroelaterin.[18] Furthermore it can be seen that in each pair of epimeric 1,2-hydroxy ketones, those possessing an equatorial hydroxyl group show higher rotation values than the axial partner. Thus cucurbitacin B > 2-epicucurbitacin B, dihydrocucurbitacin B > tetrahydroelaterin, and dihydroelatericin A > tetrahydroelatericin B.

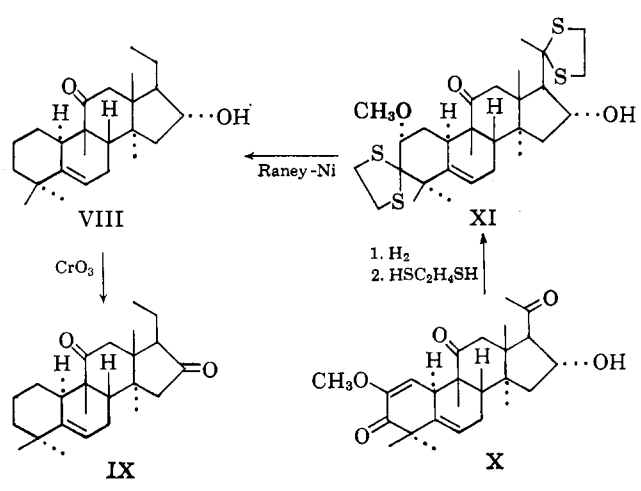
We report in Table I, for further reference, the cucurbitacin derivatives in which the carbonyl functions in ring A have been converted to 1,2-diols. Their optical rotations are all positive.

The occurrence of 2-epicucurbitacin B has been recently[16] reported in *Luffa echinata*. In this naturally occurring substance the conformation of the hydroxyl group at C-2 has been found to be identical with the conformation of this group in tetrahydroelaterin; it is, therefore, *α-axial*. This is the first instance of an α-axial 2-alcohol occurring in nature in this series of substances. Furthermore the optical rotation of 2-epicucurbitacin B is positive as expected, and finds its place among the 1,2-hydroxy ketones in Table I.

(14) D. Lavie and S. Szinai, *J. Am. Chem. Soc.*, **80**, 707 (1958).
(15) D. Lavie and D. Willner, *ibid.*, **80**, 710 (1958).
(16) D. Lavie, Y. Shvo, O. R. Gottlieb, R. B. Desai, and M. L. Khorana, *J. Chem. Soc.*, 3259 (1962).
(17) W. O. Eisenhut and C. R. Noller, *J. Org. Chem.*, **23**, 1984 (1958); A. Meleira, W. Schlegel, and C. R. Noller, *ibid.*, **24**, 291 (1959).
(18) The catalytic hydrogenation of elaterin (Ib) has led to controversial results.[19] A reinvestigation of the reduction sequence was therefore undertaken. Elaterin (Ib) in tetrahydrofuran solution, with palladium on carbon as catalyst, was reduced very rapidly to dihydroelaterin, the double bond of the side chain being saturated. For this purpose, the reaction had to be discontinued when one mole of hydrogen was absorbed. That only the double bond of the side chain had been reduced, was shown by the spectroscopical and chemical evidences. When the hydrogenation was allowed to proceed, a second mole of hydrogen was absorbed at a much lower rate, to yield tetrahydroelaterin. During this process, the diosphenol system in ring A (I) was reduced to the 1,2-hydroxy ketone (VI). Chemically this transformation was indicated by a negative reaction with ferric chloride, and a positive reaction with triphenyltetrazolium chloride (red precipitate of formazan). With bismuth oxide in acetic acid solution, black bismuth was precipitated.[20] Spectroscopically, the disappearance of the diosphenol chromophore was clearly indicated by the infrared, no bands at 1660 and 1413 cm.$^{-1}$, and by the ultraviolet absorption spectrum, the λ_{max} 267 mμ having faded away.[14] Hexahydroelaterin has been prepared by the hydrogenation of tetrahydroelaterin in acetic acid solution using platinum as catalyst. No more than one mole of hydrogen was absorbed under these conditions. During this process, the carbonyl at C-3 was reduced to the corresponding alcohol forming thereby the 1,2-diol. Thus, hexahydroelaterin did not react with the specific oxidizing reagents for 1,2-hydroxy ketones mentioned previously. Furthermore a band at 1705 cm.$^{-1}$ in the infrared spectrum of tetrahydroelaterin, which is related to the C-3 carbonyl, was not present in hexahydroelaterin.
(19) (a) J. N. T. Gilbert and D. W. Mathieson, *Tetrahedron*, **4**, 302 (1958); (b) D. Lavie and D. Willner, *J. Am. Chem. Soc.*, **82**, 1668 (1960), see Note Added in Proof.
(20) W. Rigby, *J. Chem. Soc.*, 793 (1951).

In order to study the stereochemistry of the C/D rings fusion, the optical rotatory dispersion of a C-16 ketone derivative was studied. The corresponding curve was obtained by substracting the data of the monoketone (VIII) from the diketone (IX), thereby eliminating the contribution of the C-11 carbonyl in the over-all system. The resulting curve showed a negative Cotton effect with a very large amplitude $[\alpha]_{325}$ −3770°, $[\alpha]_{280}$ +4108°. Such sign and amplitude are characteristic for a 13β,14α orientation in steroids as well as in tetracyclic triterpenes[21] and, therefore indicates a lanostane type fusion in the cucurbitacins. We have proposed[6] previously such a stereochemistry between rings C and D on the basis of a study of molecular rotation differences between the C-16 ketone derivative and its corresponding alcohol.

The preparation of the diketone (IX) is shown in the following sequence of reactions. It involves the methylation of the enolic C-2 hydroxyl group in ring A of hexanorelatericin B,[11] the reduction of the double bond in the obtained X and the straightforward elimination of the C-2 and C-20 carbonyl groups through thioketalization (XI) and reduction with Raney nickel; it is noteworthy to observe the concomitant hydrogenolysis of the 2-methoxy group which occurred during the desulfurization (VIII). The monohydroxy derivative was then oxidized to the required diketone (IX).



The orientation of the side chain attached at C-17 was studied using the Cotton effect associated with the C-20 keto group which has been studied on various

(21) C. Djerassi, O. Halpern, V. Halpern, and B. Riniker, *J. Am. Chem. Soc.*, **80**, 4001 (1958) (compound LXXV).

steroids.[22] In our series of derivatives two substances were selected for measurement: in order to eliminate the effect of the carbonyl group of ring A-nor, the rotatory dispersion curve of the monoketone (XII)[2b] was substracted from the monoketal IV eliminating thereby the effect due to the C-11 ketone. The drawn resultant showed a positive Cotton effect with a small peak $[\alpha]_{310}$ +663°. The Cotton effect in steroids with a methyl ketone β-oriented at C-17 is positive and strong ($[\alpha]_{310}$ +2400°) while, if α-oriented, the effect is opposite in sign (−1200°). Although small, the definite positive shape of the observed curve induced us to accept the β-orientation of the side chain. It should be kept in mind that in all known tetracyclic triterpenes the side chain has the same orientation as the C-13 substituent, which is also the same in the present substances. It should be noted that the triketone (III)[2b] used in our measurements was the product of the hydrogenation of the double bond Δ^{16} which was formed during the elimination of the C-16 hydroxyl group. In order to ascertain that no changes in configuration had occurred at the C-17 asymmetric center during dehydration and hydrogenation, the dispersion curve of the triketone (III) was compared with the curve of the corresponding 16-hydroxy triketone (XIII).[11] The two curves were found identical and almost superimposable, a clear and unequivocal indication that no configurational alterations had taken place at carbon 17.

The orientation of the hydroxyl at C-16 of the cucurbitacin molecule could now be determined. Although the results of our calculations have already been reported,[6] for the sake of completeness we shall repeat them briefly here. The molecular rotation of elatericin B (Ia) is $[M]_D$ −267° while the rotation of elatericin B diacetate is $[M]_D$ −492°.[15] From the two acetoxy groups, only the C-16 positive will contribute to a variation in value, the acetate at C-2 being enolic. The difference between these values is $\Delta[M]_D$ −225° which is the shift due to acetylation of the C-16 hydroxyl. Compared to similar shifts in the acetylation of C-16 hydroxyl group in steroids,[23] the sign and value of the difference ($\Delta[M]_D$ −239°) is in complete accordance with α-orientation. The reported value for β-oriented groups is $\Delta[M]_D$ +64°. A supporting evidence on the opposite orientation of the side chain and the C-16 hydroxyl group is found in the inability of this group to form a hemiketal with the C-22 carbonyl group. Such cyclizations have been reported in the literature[24] to occur readily upon heating with acid. No cyclization was observed when treated under the same conditions of reaction.

The α configuration of the C-16 hydroxyl group is also indicated by the triplet of lines in the n.m.r. spectrum[25] of elatericin A diacetate shown in Fig. 1a. This triplet can better be studied in dihydroelatericin B[15] (dihydro-Ia) (Fig. 2c). In both alternate orientations the C-16 proton is coupling its spin with the C-17,α, C-15,β, and C-15,α protons according to the two patterns drawn in Fig. 2a and 2b for C-16,β-H and

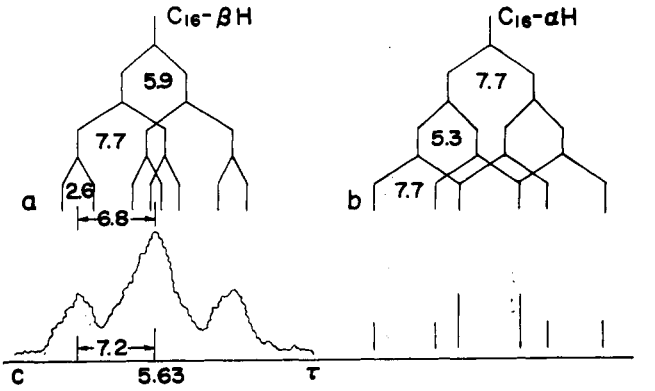


Fig. 2.—Calculated and observed n.m.r. spectra for C-16 proton in dihydroelatericin B: a, C-16, β-H epimer; b, C-16, α-H epimer; c, part of observed spectrum in chloroform-*d*.

C-16,α-H, respectively. The dihedral angles observed are: for C-16,β-H with C-17,α-H, ϕ = 137° (J = 5.9 c.p.s.); with C-15,β-H, ϕ = 10° (J = 7.7 c.p.s.); and with C-15,α-H, ϕ = 115° (J = 2.6 c.p.s.). The resulting pattern gives rise to a triplet in the ratio of 1:2:1. In the C-16,α-H alternative the respective angles and coupling constants are: ϕ = 10° (J = 7.7 c.p.s.), ϕ = 132° (J = 5.3 c.p.s.), and ϕ = 10° (J = 7.7 c.p.s.) resulting in a multiplet which probably would form a quartet in a ratio of 1:3:3:1. The observed spectrum of dihydroelatericin B in Fig. 2c, displayed a triplet of lines centered at τ = 5.63 with a peak spacing of 7.2 c.p.s. which agrees well with the pattern shown in Fig. 2a and eliminates the alternate possibility.

The angles for these calculations were measured on Dreiding models and the coupling constants are as calculated by Karplus.[26] It has already been shown that five-membered ring coupling constants agree very well with those expected from Karplus' work.[27]

The stereochemistry of the B/C rings fusion was studied using the optical rotatory dispersion curve of the monoketone XII[2b]; the Cotton effect was positive, $[\alpha]_{320}$ +3806°, $[\alpha]_{275}$ −4085°. To our knowledge, this observed large amplitude is unusual for a C-11 ketone[28] and could not be compared to previously recorded data. Of the four possible configurations at C-8 and C-9 we favor on biogenetic grounds, a β-orientation for the C-9 methyl group, in view of the occurrence of an α-oriented hydrogen at C-10. In order to decide on the configuration at C-8, the two remaining alternatives were built using models and they were observed in the light of the octant rule. With the 8β and 9β orientations, almost the entire molecule was found to fall into positive octants. This fact could very well account for the observed strong positive Cotton effect of the C-11 ketone.[28]

It is noteworthy that in the structures recently proposed for cucurbitacin A and C, it was deduced from certain chemical reactions described there,[29] that the configuration of the B/C ring fusion is *cis*

(22) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 51.

(23) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 179.

(24) St. Kaufman and G. Rosenkranz, *J. Am. Chem. Soc.*, **70**, 3503 (1948).

(25) We thank a referee for pointing out this observation.

(26) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

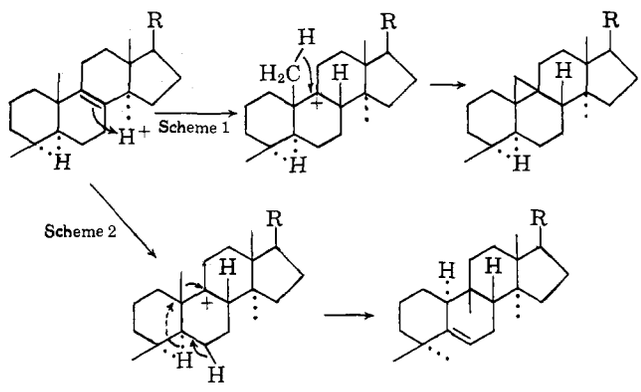
(27) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

(28)(a) C. Djerassi, "Optical Rotatory Dispersion," (ref. 22, p. 44). (b) NOTE ADDED IN PROOF.—Meanwhile the optical rotatory dispersion of a steroidal C-11 ketone having rings B/C *cis* fused and the hydrogens β-oriented was reported. The recorded data agree very well with ours. See C. Djerassi and W. Klyne, *J. Chem. Soc.*, 4929 (1962), for compound XLVII.

(29) W. T. de Koch, P. R. Enslin, K. B. Norton, D. H. R. Barton, B. Sklarz, and A. A. Bothner-By, *Tetrahedron Letters*, 309 (1962).

in these compounds. No relationships between cucurbitacin A and C and the compounds dealt with in this paper have yet been determined; however, their structural similarities are striking.

In view of the stereochemistry of the cucurbitacins presented herewith, it could be assumed that these substances would originate in the plant by a secondary series of concerted stereospecific shifts from a lanostane like skeleton. Biogenetically the triterpenoids possessing a 9,10-cyclopropane ring can be regarded as intermediates between the lanostane and the cucurbitane type compounds. By β protonation at C-8 of a lanostane and formation of a "carbonium like ion" at C-9, scheme 1 would lead to a cycloartane triterpenoid, while scheme 2 to a cucurbitane skeleton. It is noteworthy that all triterpenoids possessing a 9,10-cyclopropane ring have in common a β-oriented C-8 hydrogen.



Experimental

Melting points were taken on a Kofler hot-stage microscope and are corrected. All optical rotation measurements were carried out in chloroform solution. Ultraviolet absorption spectra were done on a Unicam Model S.P. 500 spectrophotometer in methanol solution. Infrared spectra were recorded on a Perkin-Elmer Infracord Model 137 spectrometer equipped with a sodium chloride prism and, when specified, on a Perkin-Elmer single-beam Model 12C equipped with a calcium fluoride prism. Unless otherwise stated infrared spectra were determined in chloroform solution in 5–10% concentration. Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Varian High resolution n.m.r. spectrometer, Model V-4300B, operating at 60 Mc. The spectra were determined in deuterated chloroform solutions of about 5–10% concentration and containing tetramethylsilane as internal standard; calibration was done by side-band technique; the line positions given are τ values. Optical rotatory dispersion curves were measured on a Rudolph spectropolarimeter in dioxane solution.

16-Desoxy-A(2)-norhexanorelatericin A (III).[2b]—M.p. 179–181°; RD $[\alpha]_{589}$ +95° (*c* 1.54), $[\alpha]_{335}$ +574°, $[\alpha]_{325}$ +201°, $[\alpha]_{305}$ +2347°, $[\alpha]_{267.5}$ −538°, $[\alpha]_{250}$ +94° (*c* 0.08).

3-Monoethylene Ketal of III. (IV).—3,20-Bisethylene ketal of III[2b] (450 mg.) was dissolved in ethanol (28 ml.) and a 70% aqueous acetic acid solution (12 ml.) was added. The mixture was kept at room temperature (~25°) for the period of 8 hr., then worked up by pouring into dilute sodium bicarbonate solution, extracted with chloroform, washed with water, and dried over sodium sulfate. Evaporation of the solvent left a crude residue which was chromatographed through alumina (Alcoa F20, 40 g.). Following elution with a benzene–ether mixture 4:1 there emerged first the unchanged bisethylene ketal followed by the monoketal (102 mg.). The product crystallized from acetone–hexane, m.p. 158–161°; ν_{max}^{KBr} 1704 (overlapping of C-11 and C-20 carbonyls); RD $[\alpha]_{600}$ +103°, $[\alpha]_{589}$ +115°, $[\alpha]_{320}$ +4235°, $[\alpha]_{270}$ −5139°, $[\alpha]_{260}$ −4661° (*c* 0.13).

Anal. Calcd. for $C_{28}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.99; H, 9.10.

Dihydroelaterin.—Elaterin (Ib)[14] (556 mg.) in tetrahydrofuran solution (30 ml.) was added to a suspension of 5% palladium-on-carbon catalyst (100 mg.) in tetrahydrofuran and hydrogenated at atmospheric pressure. The hydrogenation was discontinued after 10 min., when the calculated amount for 1 mole of hydrogen (22.5 ml.) had been adsorbed. The catalyst was filtered and the solvent evaporated under reduced pressure. The amorphous residue was dissolved in methanol and water added to turbidity, yielding 530 mg. of crystals, m.p. 170–172°. Recrystallizations from aqueous methanol and drying at 60° under vacuum afforded long needles, m.p. 174–176°, $[\alpha]_D$ −46° (*c* 1.00); λ_{max} 266 mμ (ε 6970); ν_{max} 1724 and 1720 (ester), 1700, 1694 (C-22 and C-11 carbonyls), and 1664 cm.$^{-1}$ (diosphenol) (calcium fluoride prism). In ethanol, coloration was produced with ferric chloride. No formazan precipitate was formed with triphenyltetrazolium chloride.

Anal. Calcd. for $C_{32}H_{46}O_8 \cdot H_2O$: C, 66.64; H, 8.39; one CH_3CO, 7.47. Found: C, 67.00; H, 8.44; CH_3CO, 7.83.

The substance was dried at 110° under vacuum to constant weight.

Anal. Calcd. for $C_{32}H_{46}O_8$: C, 68.79; H, 8.30; one CH_3CO, 7.70. Found: C, 68.56; H, 8.21; CH_3CO, 8.02.

This substance was found identical in all respects to **dihydroelaterin** previously[19b] obtained by the hydrogenation of elaterin in acetic acid solution with platinum as catalyst.

Tetrahydroelaterin (VIb).—Dihydroelaterin (558 mg.) was hydrogenated overnight in ethanol solution (30 ml.) over 5% palladium-on-carbon catalyst (100 mg.). One mole of hydrogen was absorbed. The catalyst was removed by filtration, and the product precipitated from its solution by adding water, 339 mg., m.p. 220–231°. Recrystallizations from aqueous methanol and drying at 60° under vacuum afforded rods, m.p. 231–233°, $[\alpha]_D$ +21° (*c* 0.96); λ_{max} 272 mμ (ε 857), λ_{min} 247 mμ (ε 510), high terminal absorption at 225 mμ (ε 1340); ν_{max} 1724 (ester), 1705 and 1702 (C-3 and C-22 carbonyls) and 1696 cm.$^{-1}$ (C-11 carbonyl) (calcium fluoride prism), and 1100 cm.$^{-1}$ (for C-2 axial hydroxyl). In ethanol, no coloration was produced with ferric chloride. A dark red crystalline precipitate of formazan was obtained with triphenyltetrazolium chloride.

Anal. Calcd. for $C_{32}H_{48}O_8$: C, 68.54; H, 8.63; one CH_3CO, 7.68. Found: C, 68.57; H, 8.54; CH_3CO, 7.35.

The same compound was obtained in lower yield if elaterin (556 mg.) in acetic acid solution (30 ml.) was added to platinum catalyst (100 mg.) in acetic acid (5 ml.). Hydrogenation was discontinued (17 min.) when the calculated amount for 2 moles of hydrogen (45 ml.) had been absorbed.

Hexahydroelaterin.—Tetrahydroelaterin (VIb) (560 mg.) in acetic acid solution (30 ml.) was added to platinum catalyst (100 mg.) in acetic acid (5 ml.) and hydrogenated at atmospheric pressure overnight. One mole (22.5 ml.) of hydrogen was absorbed. The catalyst was filtered and the solvent evaporated under reduced pressure. The amorphous residue was dissolved in benzene and purified by chromatography on acid-washed alumina (Merck). Small quantities of starting material were eluted with benzene–ether 1:1. The main fraction (308 mg.) was obtained with ether–methanol 3:1 as an amorphous solid which crystallized upon addition of ether, m.p. 212–215°. Recrystallization from ether and drying at 110° in vacuum afforded hexagonal plates, m.p. 221–223°, $[\alpha]_D$ +54° (*c* 0.96); λ_{max} 271 mμ (ε 393), λ_{min} 241 mμ (ε 194), high terminal absorption at 218 mμ (ε 850); ν_{max} 1724 (ester), 1702 and 1696 cm.$^{-1}$ (C-22 and C-11 carbonyls) (calcium fluoride prism). In ethanol, no coloration was produced with ferric chloride. No formazan precipitate was obtained with triphenyltetrazolium chloride.

Anal. Calcd. for $C_{32}H_{50}O_8$: C, 68.30; H, 8.96; one CH_3CO, 7.66. Found: C, 67.87; H, 8.82; CH_3CO, 6.95.

Tetrahydroelatericin B (VIa).—Elatericin B (Ia)[15] (10.24 g.) in ethanol solution (250 ml.) was hydrogenated over 10% palladium-on-carbon catalyst (1 g.) at atmospheric pressure until 1.8 moles were absorbed. The filtered solution was evaporated and the residue dissolved in chloroform. The solution was treated with cold 4% aqueous sodium hydroxide (to eliminate unreacted material), washed with water, and dried over sodium sulfate. Evaporation of the solvent under reduced pressure yielded crude tetrahydroelatericin B (VIa) (8.7 g.) that gave negative ferric chloride and positive triphenyltetrazolium chloride tests. The product was crystallized twice from ether–methanol, prismatic needles, m.p. 174–176°, $[\alpha]_D$ +59° (*c* 0.88); λ_{max} 278 mμ (ε 180), λ_{min} 256 mμ (ε 130); ν_{max} 1705 (broad band) and 1694 (C-11 carbonyl) (calcium fluoride prism), and 1100 cm.$^{-1}$ (for C-2 axial hy-

droxyl). RD $[\alpha]_{589}$ +59°, $[\alpha]_{450}$ +70°, $[\alpha]_{350}$ +440° (*c* 0.04); $[\alpha]_{325}$ +1550°, $[\alpha]_{312}$ +800°, $[\alpha]_{308}$ +910°, $[\alpha]_{305}$ −580° (*c* 0.02).

Dihydroelatericin B.—In order to prepare a purified sample of dihydroelatericin B, the crude hydrogenation product of elatericin B[15] (one mole of hydrogen) was extracted in 4% aqueous sodium hydroxide solution, which was then acidified and re-extracted in chloroform. The residue crystallized from a solvent mixture of ether–benzene–hexane, m.p. 158–160° dec. (sinters ~135°); $[\alpha]_D$ −44° (*c* 0.91).

Acetylation of Tetrahydroelatericin B.—Tetrahydroelatericin B (VIa) (8.80 g.) was acetylated in a mixture of acetic anhydride (50 ml.) and dry pyridine (50 ml.) overnight at room temperature. The solution was decomposed with ice–water. The precipitate of tetrahydroelatericin B diacetate (9.64 g.) was filtered and washed with water. The amorphous solid was dried in vacuum at 60°, $[\alpha]_D$ −24° (*c* 1.07); λ_{infl} at 270 mμ (ε 250); ν_{max} 1724 (esters) and 1700 cm.$^{-1}$ (overlapping of C-11 and C-22 carbonyls).

Anal. Calcd. for $C_{34}H_{52}O_9$: C, 67.75; H, 8.36; two CH_3CO, 14.28. Found: C, 67.21; H, 8.38; CH_3CO, 14.92.

Acetylation of Dihydroelatericin A.—Dihydroelatericin A (Va)[10] (100 mg.) was acetylated in a mixture of acetic anhydride (1 ml.) and pyridine (1 ml.) overnight at room temperature. The solution was decomposed with ice–water. The amorphous solid was dried in vacuum at 60°, $[\alpha]_D$ −11° (*c* 1.16); λ_{max} 284 mμ (ε 240), λ_{min} 254 mμ (ε 170); ν_{max} 1724, 1700, 1240, and 1025 cm.$^{-1}$.

Anal. Calcd. for $C_{34}H_{52}O_9$: C, 67.75; H, 8.36; two CH_3CO, 14.28. Found: C, 67.15; H, 8.53; CH_3CO, 14.78.

Dihydroelatericin A (Va).[10]—RD $[\alpha]_{589}$ +83° (*c* 1.27); $[\alpha]_{400}$ +300°, $[\alpha]_{350}$ +732° (*c* 0.045); $[\alpha]_{325}$ +2200°, $[\alpha]_{302}$ −1870°, $[\alpha]_{290}$ −3130° (*c* 0.011).

Ultraviolet Absorption Spectra.—In order to indicate the effect of acetylation on the ultraviolet absorption, the following data are presented: dihydroelatericin A (Va), λ_{infl} 273 mμ (ε 300); dihydroelatericin A diacetate, λ_{max} 284 mμ (ε 240), λ_{min} 254 mμ (ε 170); tetrahydroelatericin B (VIa), λ_{max} 278 mμ (ε 180), λ_{min} 256 mμ (ε 130); and tetrahydroelatericin B diacetate, λ_{infl} 270 mμ (ε 250).

Dihydrohexanorelaterin-2-methyl Ether-3,20-Bisethylenedithioketal (XI).—Hexanorelaterin-2-methyl ether (X)[19b] (680 mg.) was hydrogenated in ethanol solution (50 ml.) over 10% palladium-on-carbon catalyst. The filtered solution was evaporated *in vacuo* to dryness to give the **dihydro X** derivative which was crystallized from ether, m.p. 166–168°, $[\alpha]_D$ +165° (*c* 1.21); ν_{max} 1728 and 1705 cm.$^{-1}$.

To a mixture of dihydro X (400 mg.) and 1,2-ethanedithiol (0.5 ml.) in an ice bath, boron trifluoride etherate (0.2 ml.) was added as catalyst. The solution was stirred for 5 min. and then left at room temperature for 5 hr. Chloroform was added and any unchanged dithiol was removed by shaking with a 10% sodium hydroxide aqueous solution. Upon evaporation of the solvent the residue crystallized, it was collected (450 mg.) and washed with ether, m.p. 215–225°; ν_{max} 1698 cm.$^{-1}$.

Desulfurization of XI to VIII.—To the substance XI (440 mg.) in dioxane solution (100 ml.), Raney nickel (prepared from 25 g. of alloy) in dioxane suspension was added. The mixture was stirred and maintained at reflux temperature overnight. The Raney nickel was removed and the filtrate evaporated *in vacuo* leaving an oily residue. It was crystallized several times from ether, m.p. 161–170°, and then sublimed at 140° (0.5 mm.), ν_{max} 1698 cm.$^{-1}$. RD $[\alpha]_{589}$ +182° (*c* 1.69); $[\alpha]_{322.5}$ +4043°, $[\alpha]_{280}$ −3436°, $[\alpha]_{270}$ −3120° (*c* 0.083).

Oxidation of VIII to IX.—To a stirred ice-cooled solution of VIII (150 mg.) in purified acetone (50 ml.), 0.3 ml. of a chromium trioxide solution (68 g. of chromium trioxide and 57 ml. of concentrated sulfuric acid diluted to 250 ml. with water) was added dropwise during 30 min. The excess oxidant was destroyed with methanol, water was added, and the product extracted with chloroform. The solution was washed and dried. Evaporation of the solvent left a residue which crystallized from ether, m.p. 184–187°; ν_{max}^{KBr} 1750 and 1698 cm.$^{-1}$. RD $[\alpha]_{589}$ +55° (*c* 0.9); $[\alpha]_{360}$ +212°, $[\alpha]_{330}$ −99°, $[\alpha]_{320}$ +1147°, $[\alpha]_{315}$ +500°, $[\alpha]_{307.5}$ +1448°, $[\alpha]_{280}$ +672° (*c* 0.116).

Anal. Calcd. for $C_{24}H_{36}O_2$: C, 80.85; H, 10.18. Found: C, 80.50; H, 9.93.

Monoketone XII.[2b]—RD $[\alpha]_{589}$ +127° (*c* 0.94); $[\alpha]_{358}$ +1000°, $[\alpha]_{320}$ +3806°, $[\alpha]_{275}$ −4085°, $[\alpha]_{260}$ −3484° (*c* 0.14).

A(2)-Norhexanorelatericin A (XIII).[11]—RD $[\alpha]_{589}$ +66° (*c* 1.65); $[\alpha]_{335}$ +461°, $[\alpha]_{322.5}$ +303°, $[\alpha]_{305}$ +2091°, $[\alpha]_{270}$ −856°, $[\alpha]_{250}$ −371° (*c* 0.13).

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Neighboring Group Reactions. VIII. Reactions of 3-(ω-Bromoalkyl)-3-phenyl-2-benzofuranones with Ammonia and Primary Amines

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Reactions of a series of ω-bromoalkylbenzofuranones I (*n* = 0–2) with ammonia and primary amines are described. The first member of the series (I, *n* = 0) reacts with ammonia and cyclohexylamine to give the α-amino amide V. With ammonia the two other homologs (I, *n* = 1,2) form only the rearranged amide VI (*n* = 1,2). Primary amines, however, yield appreciable quantities of a second product in addition to the rearranged amide VI (*n* = 1,2). From the bromomethyl homolog (*n* = 1), β-aminopropionamides VII are obtained and from the bromoethyl derivative (*n* = 2) five-membered ring imidates VIII are secured. Relative yields of the two products are found to depend on the amine used and on the solvent system. Both amino amides V and VII are weak bases ($pK_a \sim 4$) and acylate preferentially on the phenolic oxygen atom. Evidence is presented in support of a mechanism for the formation of VII which involves the intermediacy of the four-membered cyclic imidate A.

A previous paper[1] of this series described the reactions of 3-(ω-haloalkyl)-3-phenyl-2-benzofuranones (I) with secondary amines. Depending on the length of the haloalkyl side chain, the amine used, the temperature, and solvent, any one or several of three products was formed. With morpholine, for example, the bromomethyl homolog I (*n* = 1) under all conditions, gave only the rearranged amide II. The three extreme members of the series (*n* = 0,3,4), formed only the product III of direct halogen displacement. In excess morpholine at room temperature, the bromoethyl homolog I (*n* = 2) gave exclusively the trapped tetrahedral intermediate IV; but at raised temperatures (95–100°), or in dimethylformamide or dimethyl sulfoxide solution at room temperature, only the displacement product III (*n* = 2) was obtained. With other secondary amines more basic than morpholine, the bromoethyl derivative I (*n* = 2) gave varying amounts of the re-

(1) H. E. Zaugg, F. E. Chadde, and R. J. Michaels, *J. Am. Chem. Soc.*, **84**, 4567(1962).