Tetrahedron Letters No. 22, pp. 23-28, 1960. Pergamon Press Ltd. Printed in Great Britain

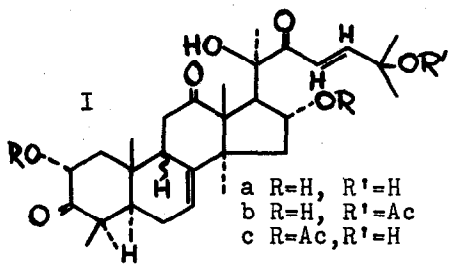
THE STEREOCHEMISTRY OF THE CUCURBITACINS[1,2]

David Lavie, Youval Shvo and Otto Richard Gottlieb[3]

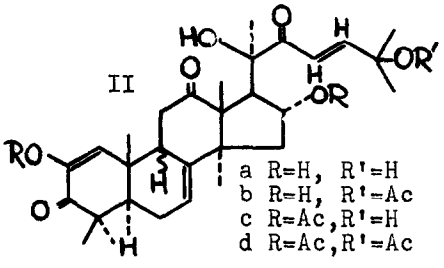
Daniel Sieff Research Institute, the Weizmann Institute of Science, Rehovoth, Israel

(Received 16 August 1960)

THE stereochemistry of ring A of some of the cucurbitacins has been discussed in a previous communication.[4] We wish to report now the experiments which led us to present most of the stereochemistry of the four naturally occurring cucurbitacins: elatericin A (Ia), cucurbitacin B (Ib), elatericin B (IIa) and elaterin (IIb), leaving only the configuration of C-9 undeter-



a R=H, R'=H
b R=H, R'=Ac
c R=Ac, R'=H



a R=H, R'=H
b R=H, R'=Ac
c R=Ac, R'=H
d R=Ac, R'=Ac

---

[1] This investigation was supported by a research grant CY-2810 (C3) from the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

[2] This communication is part XVII in the series: The Constituents of Ecballium elaterium L., part XVI. D. Lavie and O.R. Gottlieb, J.Amer.Chem.Soc. in the press.

[3] On leave of absence from the Instituto de Química Agrícola, Ministério da Agricultura, Rio de Janeiro, Brazil.

[4] D.Lavie and O.R.Gottlieb, Chem.& Ind. 929 (1960).

mined.

The configuration of the hydroxyl group at C-2 in elatericin A and cucurbitacin B, as well as in the tetrahydro-derivatives of elatericin B and elaterin has been previously presented assuming that rings A/B are trans fused.[4] That this junction is indeed trans is indicated by the fact that, in the substances possessing a diosphenol system, as for example IIa and IIb, the hydrogen reducing the double bond in ring A approaches the molecule from the rear, while in the corresponding enol acetates IIc and IId it proceeds from the front. In substances with an A/B cis junction the rear of ring A is highly hindered and only one type of product, resulting from frontal attack, should be obtained. The A/B rings junction being trans, the hydrogen at C-5 is α by convention, while the methyl group at C-10 is β-oriented.

The stereochemistry of the C-16 hydroxyl will now be presented. It is known that the molecular rotation shifts resulting from acetylation of a C-16 hydroxyl group in steroids are of opposite signs for α or β-orientation, the former being negative ($\Delta[M]_D$-239°), while the latter is positive ($\Delta[M]_D$+64°).[5] The observed difference between elatericin B diacetate (IIc, $[M]_D$-492°) and elatericin B (IIa, $[M]_D$-267°)[6] is -225°. This value is in agreement with an α-oriented hydroxyl at C-16 in the cucurbitacins, since only acetylation at this position

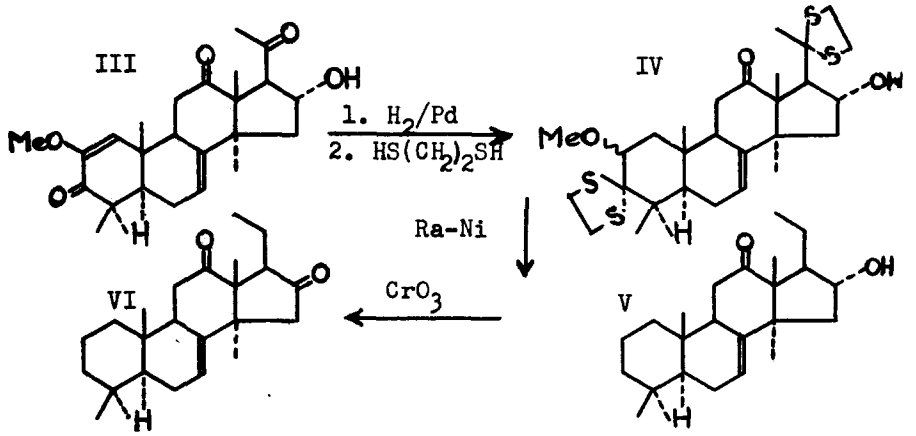
---

[5] L.F. Fieser and M. Fieser, Steroids p. 179, Reinhold Publishing Corporation, New York (1959).

[6] D. Lavie and D. Willner, J.Amer.Chem.Soc. 80, 710 (1958).

contributes to the optical rotation difference, the acetate at C-2 being enolic.

The stereochemistry of the C/D rings junction was determined using molecular rotation difference between a C-16 ketone and the corresponding secondary alcohol in substances VI and V. These substances, without oxygenated groups in the side chain, were chosen to reduce possible vicinal effects. They were prepared from III[7] by the following reaction sequence:



It is noteworthy that during treatment with Raney nickel of the ethylenedithioketal IV concomitant hydrogenolysis of the 2-methoxy group occurred with the expected desulfurisations, to yield the monohydroxy derivative V, m.p. 169-170°, $[\alpha]_D$+ 182° (c 0.93).* Oxydation of V with chromium trioxide yielded

---

[7] D. Lavie and D. Willner, J.Amer.Chem.Soc. 82, 1668 (1960).

* Melting points were taken on a Kofler hot-stage microscope and optical rotation measurements were carried out in chloroform solution.

the diketone VI, m.p. 185-187°. $[\alpha]_D$+55° (c 1.19). The molecular rotation difference between VI and V is -457°, which is in agreement with the computed $\Delta[M]_D$(CO-CHOH)-439°. This value was calculated from $\Delta[M]_D$(CO)-498° [8] and $\Delta[M]_D$(CHOH)-59° [5] given for functional groups at C-16 in similar ring systems with 13β, 14α-substituents. It can be deduced, therefore, that this is the orientation which does occur in the cucurbitacins.

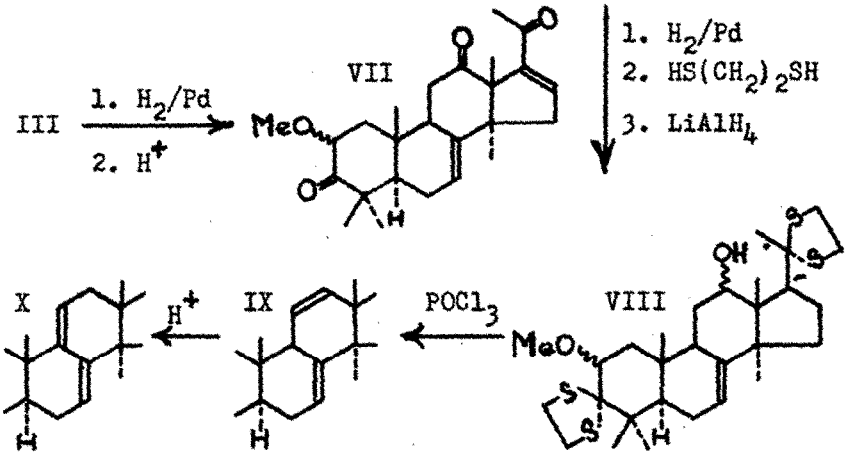
At this point we can present evidence indicating the orientation of the side chain at C-17 in the cucurbitacins. It was found that the carbonyl group at C-22 could not be induced to form a hemiketal with the 16-hydroxyl upon heating with acid. Such cyclisations have been observed to occur readily under these conditions when the side chain at C-17 and the vicinal hydroxyl at C-16 are cis.[9] It can be deduced therefore, that these substituents are on opposite sides of the cucurbitacin ring system and, since the C-16 hydroxyl was found to be α, the side chain must be β-oriented.

In accordance with the foregoing observations, the cucurbitacins belong to the lanostane type triterpenes. This conclusion was confirmed by the preparation of the heteroanular diene, X, obtained by the following sequence of reactions :

---

[8] A. Bowers, T.G. Halsall, E.R.H. Jones and A.J. Lemin, J.Chem.Soc. 2548 (1953).

[9] St. Kaufmann and G. Rosenkranz, J.Amer.Chem.Soc. 70, 3503 (1948).



The ultraviolet spectrum of X, λ_{max} 236, 244 and 251 mμ, is characteristic of 7,9(11)-dienes in the lanostane series. Analogous conjugated dienes in the euphane series exhibit maxima displaced to shorter wavelength.[10]

Finally we should like to present an argument favouring the configuration at C-20 as shown in I and II. It has been previously observed that the side chain cleavage with periodic acid is much slower in elatericin A diacetate (Ic), than in elatericin A (Ia).[11] This would indicate that the site of attack of the hydroxy-ketone becomes masked upon acetylation of the C-16 hydroxyl, while the opposite direction still does not leave free access to the oxidising agent. Inspection of

---

[10] M.C. Dawson, T.G. Halsall and R.E.H. Swayne, J.Chem. Soc. 590 (1953).

[11] D. Lavie and Y. Shvo, J.Amer.Chem.Soc. 82, 966 (1960).

a model indicated that such a possibility occurs when the methyl group at C-20 is directed towards the rear of the molecule. The stereochemistry at C-20 should be therefore as in lanostane by replacing the 20β-H with OH.[12]

With these observations in mind, we propose hereby the following structures for the four cucurbitacins investigated: 2α,16α,20,25-tetrahydroxy-3,12,22-trioxo-(9ξ-H)-lanosta-7, 23-trans-diene for elatericin A (Ia), 2α,16α,20-trihydroxy-25-acetoxy-3,12,22-trioxo-(9ξ H)-lanosta-7,23-trans-diene for cucurbitacin B (Ib), 2,16α,20,25-tetrahydroxy-3,12,22-trioxo-(9ξH)-lanosta-1,7,23-trans-triene for elatericin B (IIa) and 2,16α,20-trihydroxy-25-acetoxy-3,12,22-trioxo-(9ξH)-lanosta-1,7,23-trans-triene for elaterin (IIb).

One of the authors (O.R.G.) gratefully acknowledges support from the Conselho Nacional de Pesquisas, Brazil.

---

[12] For the nomenclature used see: S.Allard and G.Ourisson, Tetrahedron 1, 277 (1957).