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REARRANGEMENTS OF THE OXIDES OF HOPENE-I AND HOPENE-II UNDER THE ACTION OF BORON TRIFLUORIDE

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Hopene-I oxide (I), a minor constituent of Polypodium vulgare, is transformed into hopa-15,17(21)-diene by HCl in ethanol (1). When the same epoxide is treated with BF_3 etherate in $CHCl_3$ solution, the reaction takes a completely different course, another diene, m.p. 167-168°, $[\alpha]_D^{20}$ + 51°,$^+$ and a ketone, m.p. 277-281°, $[\alpha]_D^{34}$ + 86.3°, being isolated in 85% and 15% yields, respectively.

Structure II has now been established for the ketone on the basis of its transformation into a benzal derivative (III), m.p. 310-312°, $[\alpha]_D^{20}$ - 1.4°, which was degraded by ozone into the anhydride IV, m.p. 265-268°, $[\alpha]_D^{25}$ + 33.3°, λ_{CO} 5.58, 5.71 μ. Reduction of II with $LiAlH_4$ gave an alcohol (V), m.p. 281-285°, $[\alpha]_D^{25}$ + 51°, which was transformed into hopene-I (VI) by $POCl_3$ in pyridine. An α configuration of the isopropyl group at C_{17} in II would be expected from a migration which is concerted with the rupture of the β-oxirane ring. The positive Cotton effect of moderate intensity of II (CD, cyclohexane, $\Delta\varepsilon_{323}$

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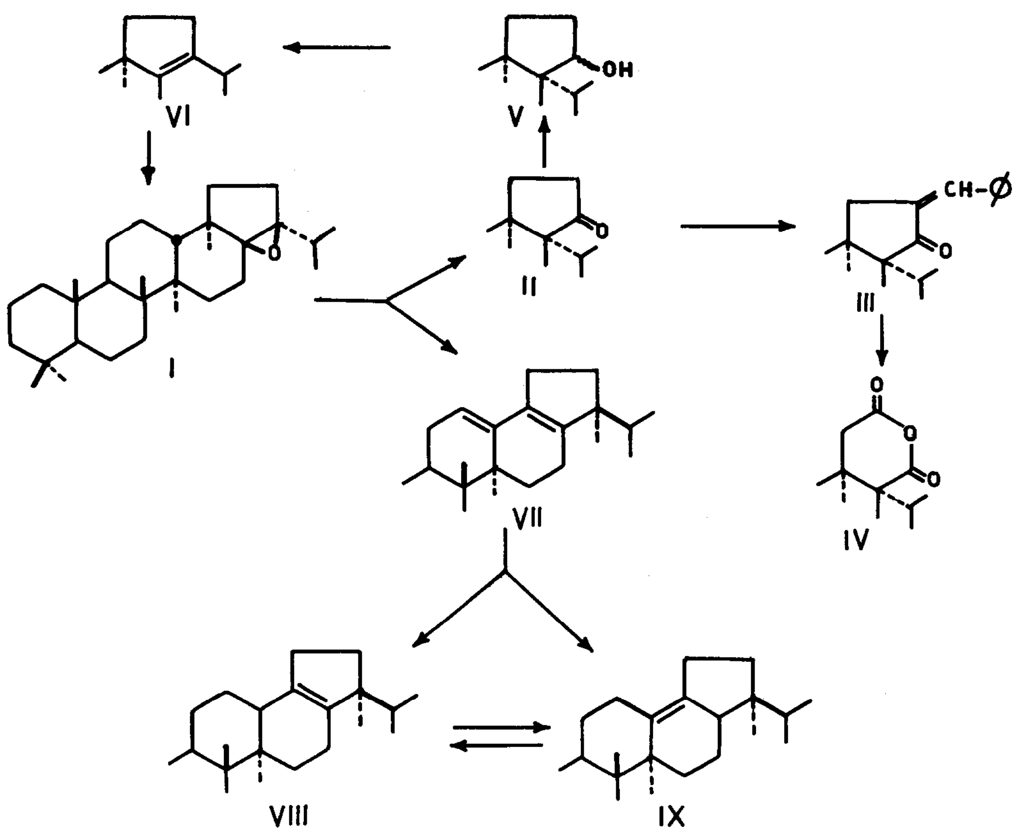
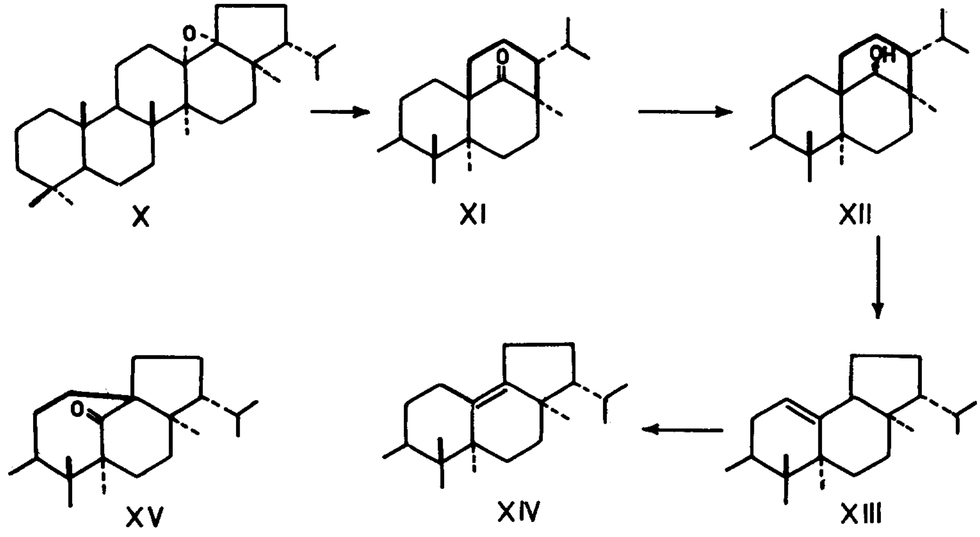
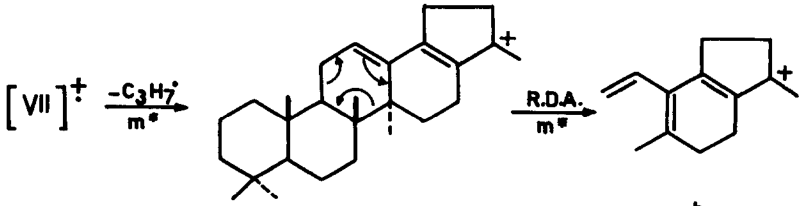
$^+$ All specific rotations were measured in $CHCl_3$.


VI
V
OH
CH-Ø
O
I
II
III
VII
IV
VIII
IX


O
OH
X
XI
XII
XV
XIV
XIII

+ 0.69, $\Delta\varepsilon_{312}$ + 1.14, $\Delta\varepsilon_{302}$ + 1.06) is in accordance with a cis junction of rings D and E, on the basis of literature data on compounds containing the cis-hydrindan-1-one system, such as 14β-androstan-17-ones and 3-oxo-A-nor-steroids (2); although the isopropyl group lies in a negative octant, the skewed nature of the cyclopentanone ring should be more important in determining the sign of the Cotton effect, than the orientation of the substituents. On the other hand the 17β-isopropyl analogue of II would be expected to exhibit a negative Cotton effect. The configuration of the hydroxyl group in V is still uncertain, but is probably α, as a determination of absolute configuration with α-phenylbutyric anhydride by the method of Horeau (3) gives an excess of (-)-acid, therefore pointing to an S configuration at C-21; this is somewhat surprising as 17-oxo-14β-steroids are reported to give the 17α-ols on hydride reduction (3c,4); however, an isopropyl in place of a methyl group may well change the stereochemistry of the reduction.

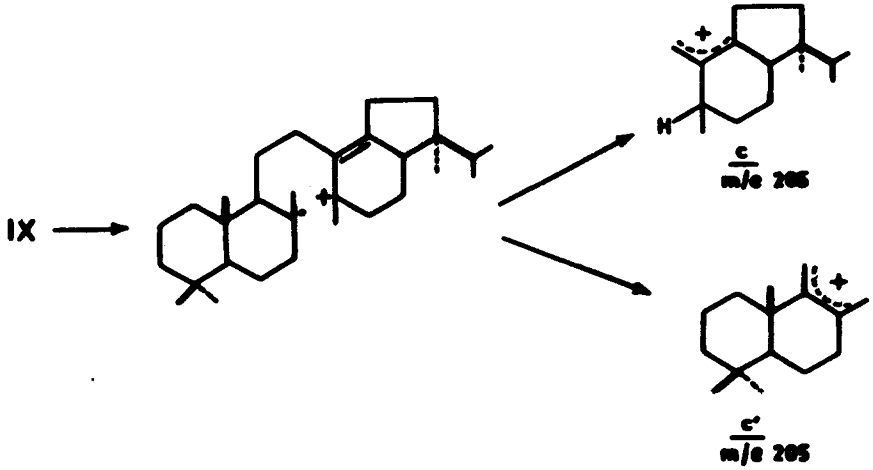
The diene obtained as the main product in the BF_3 rearrangement of I has been formulated as VII on the following grounds. Its UV spectrum (λ_{max} 237, 245, 255 mμ, ε 20,300, 23,700, 15,900) indicates its conjugated heteroannular nature. N.M.R. shows only one olefinic proton (τ 4.62). The most intense peak in the mass spectrum is m/e 365, corresponding to the loss of the isopropyl radical from the molecular ion; its intensity is six times higher than that of any other peak, while the M^+ ion is of very low abundance (5%). The high abundance of the m/e 365 ion seems to be indicative both of the position of one of the double bonds and of the quaternary nature of the isopropyl group. In most hopane derivatives the $[M - C_3H_7^{\bullet}]^+$ ion is much less abundant. In the present case the loss of the isopropyl radical leads to the formation of the stable tertiary allylic cation a, which gives rise to most of the other fragmentation peaks in the spectrum, and particularly to ion b (m/e 173) by retro-Diels-Alder cleavage; the latter peak indicates the position of the 12-13 double bond.



a
m/e 365

b
m/e 173

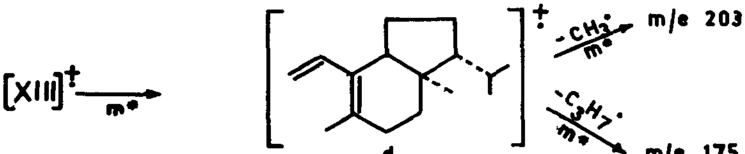
On hydrogenation over Pt VII yields two isomeric olefins, VIII, m.p. 176-179°, $[\alpha]_D^{31}$ - 11.7°, and IX, m.p. 173-179°, $[\alpha]_D^{31}$ - 4.6°, which can be separated on $AgNO_3$-containing silica, and are transformed by acid into an equilibrium mixture. The most intense peak in the mass spectrum of VIII is m/e 367, corresponding again to the loss of the C_3H_7 radical. The M^+ ion (m/e 410) is of very low abundance (< 0.5%). These features indicate the position of the 17-18 double bond. Olefin IX, in which the double bond is more distant from the isopropyl group, exhibits an intense molecular ion (49%), while the m/e 367 ion is of lower abundance (32%). The base peak, which is found at m/e 205, is characteristic for triterpenes having a 13-18 double bond (5) and has been attributed to an ion containing rings D and E, formed by allylic cleavage of the 8-14 bond, followed by the cleavage of the 11-12 bond and by a cyclic collapse with hydrogen transfer from C-9 to C-14; in our case this should give ion *c*. However, ion *c*', containing rings A and B, is isomeric with *c* and probably contributes to the m/e 205 peak. The latter peak is practically absent from the mass spectrum of VIII, while it is of high intensity in that of hopene-II (XIV), whose fragmentation pattern is extremely similar to that of IX.



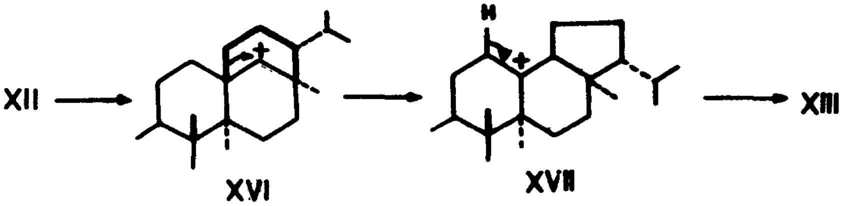
Although the transformation of hindered epoxides into dienes with acids has been observed before (6), the passage of I to VII is novel, as it involves a double migration (or 1,3-shift) of a methyl group, from C-18 to C-21. No obvious fully concerted mechanism can be suggested for this reaction. It was not possible to detect intermediates by g.l.c.; however, in the similar reaction of iso-γ-lupene oxide (7), a close analogue of I, with BF_3, two dienes can be isolated after short reaction periods, which are very probably intermediates between the oxide and the analogue of VII. This reaction is now under study and we shall discuss the mechanism of both rearrangements when our data on the latter one will be complete.

The reaction with BF_3 etherate has also been studied for hopene-II oxide (X), whose transformation into the corresponding 11,13(18)-diene with HCl has been described before (8). Here again BF_3 leads to a completely different result, no diene being formed; a ketone, m.p. 278-292°(dec.),$[\alpha]_D^{28}$ + 16.5°, is the main product (90% yield). For this compound we propose structure XI on the following grounds. No hydrogen atoms are present in position α to the CO group (NMR, resistance to attack by bromine). $LiAlH_4$ reduction gives an alcohol, m.p. 275-293°(dec.),$[\alpha]_D^{20}$ + 37.4°(XII), which is transformed by $POCl_3$ in pyridine into an alkene, m.p. 133-136°,$[\alpha]_D^{20}$ + 23.5°, formulated as XIII: N.M.R. one olefinic proton at 4.72 τ ; mass spectrum: most abundant ion at m/e 218 ($C_{16}H_{26}^{+}$), giving rise to ions m/e 203 ($-CH_3^{\cdot}$) and m/e 175 ($-C_3H_7^{\cdot}$)(metastable peaks). Therefore the m/e 218 ion must contain ring E. The high abundance of m/e 218 ion indicates that it is very probably formed by a retro-Diels-Alder fragmentation of the molecular ion, involving a 12-13 double bond ($M^{+} \xrightarrow{m^*}$ ion d). Structure XIII is also confirmed by the easy transformation into hopene-II (XIV) on short treatment with HCl in $CHCl_3$.

Of the two possible formulation of the ditertiary ketone (XI and XV) only XI can easily account for the formation of XIII from XII, through the probably concerted shifts indicated in XVI and XVII. Furthermore the ketone exhibits a positive Cotton effect (CD, cyclohexane, $\Delta\varepsilon_{314}$ + 1.19, $\Delta\varepsilon_{304}$ + 1.73, $\Delta\varepsilon_{206}$ + 1.50), which would be expected on the basis of the octant rule for XI, while XV would be more likely to give a negative Cotton effect. The transformation into XI probably requires that the epoxide ring has the α configuration, a fact that had not been established before, and that could be unexpected at first glance, as the epoxidation of XIV could be assumed to take place <u>trans</u> to the methyl groups at C-14 and C-17. Inspection of Dreiding models shows, however, that the α-epoxide should be more stable than the β-isomer, as in the latter compound the two methyl groups at C-14 and C-17 interfere whith each other much more seriously than in the former one.



d
m/e 218



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REFERENCES

1) G.Berti, F.Bottari, A.Marsili and I.Morelli, Tetrahedron Letters, 1966,979.
2) W.Klyne, Tetrahedron, 13,29(1961); P.Crabbé, Optical Rotatory Dispersion and Circular Dicroism in Organic Chemistry, p.89. Holden-Day, San Francisco (1965).
3a) A.Horeau, Tetrahedron Letters, 1961,506; b) ibid.,1962,965; c) A.Horeau and H.B.Kagan, Tetrahedron, 20,2431(1964).
4) A.F.St.André, H.B.MacPhillamy, J.A.Nilson, A.C.Shabica and C.R.Scholz, J.Am. Chem.Soc. 74,5506(1952).
5) H.Budzikiewicz, C.Djerassi and D.H.Williams, Structure elucidation of Natural Products by Mass Spectrometry, Vol.II, p.127. Holden-Day, San Francisco (1964).
6) A.Rosowski, in A.Weissberger, Editor, Heterocyclic Compounds with three- and four-membered rings, p.252. Interscience Publishers, New York (1964).
7a) R.Nowak, O.Jeger and L.Ruzicka, Helv.Chim.Acta, 32,323(1949); b) D.H.R.Barton, P.de Mayo and J.C.Orr, J.Chem.Soc. 1958,2239.
8) Y.Tsuda and K.Isobe, Tetrahedron Letters, 1965,3337.