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A NEW PENTACYCLIC TRITERPENE ALCOHOL FROM EVODIA FRAXINIFOLIA HOOK F.[1,2]

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The occurrence of an extremely diversified series of extractives in various Evodia species has induced us to undertake a systematic chemical investigation of Evodia fraxinifolia Hook f.(Rutaceae) growing at an altitude of 4000 ft in the Himalayan Ranges.

The neutral material from the petroleum ether (b.p. 60-80°) extract of the stem-bark of the plant furnished in 0.004 p.c. yield a new pentacyclic triterpene alcohol (I) crystallising from chloroform-methanol in fine needles, m.p. 162-63°, $[\alpha]_D$ +37.2° ($CHCl_3$), $C_{30}H_{50}O$ (M^+, m/e 426), ν_{max}^{nujol} 3490 cm^{-1} (OH). Its PMR spectrum[3] shows signals (24 H) for eight methyls on saturated carbon atoms at 0.78, 0.86, 0.88, 1.01 and 1.06 ppm and a one-proton multiplet around 3.23 ppm for carbinol proton (H-C-OH). I upon treatment with Ac_2O and pyridine (25-30°, overnight) furnished a monoacetate (II), m.p. 215-16°, $[\alpha]_D$ +40° ($CHCl_3$); ν_{max}^{nujol} 1736 (acetate CO) and 1243 cm^{-1}(CO-O-C)[4]; a sharp three-proton singlet at 2.04 ppm for equatorial[4] acetate methyl. The hydroxyl group is secondary as a lone proton on the same carbon could be identified by a downfield shift by 1.28 ppm of this proton multiplet (3.23 ppm) to 4.51 ppm (CHOAc) in the acetate (II). The latter appears as a quartet having $J_{ax/ax}$ 10 c/s and $J_{ax/eq}$ 5 c/s, indicating its axial orientation. This also fits with its usual allocation at C-3 interacting with C-2 axial and equatorial protons. I forms benzoate, m.p. 199-200°, $[\alpha]_D$ +70° ($CHCl_3$) and tosylate, m.p. 160° in the usual way.

Chromic acid-pyridine oxidation of I afforded a ketone (III), m.p. 179-81°, $[\alpha]_D$ +80°($CHCl_3$), $C_{30}H_{48}O$ (M^+, m/e 424), ν_{max}^{nujol} 1710 cm^{-1} (six-membered ketone), λ_{max}^{EtOH} 280 mμ (log ε,1.92) clearly demonstrating the secondary nature of the OH group. III gives positive Zimmermann test[5] thus indicating the site of the secondary OH group at the usual C-3 position of the triterpene skeleton in I. Sodium borohydride reduction of III produced the parent alcohol I confirming the equatorial orientation of the C-3 hydroxyl group.

The triterpene alcohol I (as well as compounds II and III) gives a distinct yellow colour with tetranitromethane showing the presence of unsaturation. The ethylenic linkage present is very hindered and stable since I and II are resistant to catalytic hydrogenation (PtO_2, AcOH) and are recovered unchanged after such treatment. Thus assuming that I is mono-olefinic, from its molecular

formula and functionality (only one OH group) it is apparent that it must be pentacyclic. The absence of any olefinic proton in the PMR spectra of I, II and III demonstrates the tetrasubstituted nature of the double bond. This is also supported by the absence of any C-H out-of-plane bending band in the region[6] 990-800 cm^{-1}. Furthermore, the molecular rotation difference (+182°) between the ketone (+339°) and the alcohol (+157°) is strikingly similar to that for Δ^{8}-triterpenoids[7,8] and hence the ethylenic linkage is expected to be at 8-9 position.

TABLE 1

IMPORTANT PEAKS IN THE MASS SPECTRA OF ISOBAUERENOL AND RELATED TRITERPENOIDS

Compounds		% base peak (approximate)									
		M^+	M^+-CH_3	a(M^+-167)	b(M^+-179)	c(M^+-206)	d	e	f		
	m/e	424	409	257	245	218	205	135	119		
Ketone III (=isobauerenone)		43	17	40	100	-	57	26	14		
Bauerenone (VI)*		13	11	17	100	10	22	13	18		
Multiflorenone(VII)*		7	7	33	36	100	53	12	14		
Isomultiflorenone(IV)*		18	7	60	46	11	100	16	18		
Arborenone*		60	90	100	22	-	-	18	36		
	m/e	426	411	259	247	220	"	"	"	241** a-H_2O	229** b-H_2O
Isobauerenol(I) (natural)		100	34	53	85	-	58	34	40	19	38
Isobauerenol (synthetic)		68	25	24	100	-	20	22	25	9	35
Isomultiflorenol(V)		89	40	87	39	-	100	52	52	33	37
	m/e	468	453	301	289	262	"	"	"	" a-AcOH	" b-AcOH
Isobauerenyl acetate(II)		77	27	49	100	-	93	37	50	32	69

*The characteristic peaks (m/e values) of these compounds and their approximate relative intensities have been taken from the published[9] mass spectra.

**The metastable peaks corresponding to a-H_2O, b-H_2O, a-AcOH and b-AcOH appear, as expected, at m/e 224.3, 212.2, 193.0 and 181.4 respectively.

The nature of the carbon skeleton of I as well as the location of the tetrasubstituted double bond was revealed by the general appearance of the mass spectrometric[10] fragmentation patterns of I, II and III (Table 1). II and III exhibit base peaks at m/e 289 and 245 respectively, attributable to the fragment b, characteristic[9] of pentacyclic triterpenes of bauerene series [Cf. bauerenone[9] (VI)]. The significant ion fragments of I, II and III and some related isomeric compounds[9] are recorded in Table 1. Although the fragmentation mode also resembles that of multiflorene system [Cf. multiflorenone[9] (VII) and isomultiflorenone[9] (IV)], the most significant difference is that in the latter case the fragment b is of rather reduced intensity. Again, the peak at m/e 205 assigned to fragment ion d appears in IV as the most abundant peak whereas in I, II and III it is still significant (relative intensity 58, 93 and 57% respectively) although in VI it becomes less intense (22%).

Fragment c which appears as the base peak at m/e 218 in VII and is of very little intensity in VI (10%) and IV (11%) is virtually absent in III. This fragment is also absent in I and II (no peaks at m/e 220 and 262 respectively). Fragment a which shows up as the most abundant peak in arborenone[10,11] having $\Delta^{9(11)}$ bond is more abundant in III (40%) than in VI (17%) just as it is more intense in IV (60%) than in VII (33%). The other significant peaks appearing at m/e 135 and 119 in all the spectra (Table 1) may be assigned to fragment ions e and f arising from ring D probably from the precursor ion d by allylic cleavage, and hydrogen migration or proton elimination as is necessary.

The mass spectral data in conjunction with other evidences stated above suggest that the triterpene alcohol I should be identical with isobauerenol (=bauera-8-en-3β-ol), a product obtained[7] from bauerenyl acetate (IX) by acid isomerisation followed by hydrolysis. II and III should, therefore, be isobauerenyl acetate and isobauerenone respectively. For direct comparison, isobauerenyl acetate (m.p. 223-25°), isobauerenol* (m.p. 166-67°) and isobauerenone* (m.p. 179-80°) were prepared from authentic bauerenyl acetate[2]. Although compounds I and II, even after repeated chromatography and crystallisations, were found to melt at temperatures 4-8° lower than the corresponding synthetic substances (m.p.'s noted simultaneously in a sulphuric acid bath), compound III showed same m.p. as authentic isobauerenone (m.m.p. undepressed). However, the IR spectra of I, II and III and the corresponding authentic substances are almost superimposable and the rotations are also consistent.

The important mass spectral fragments of the authentic samples of isobauerenol (I) and isomultiflorenol[8] (V) have also been recorded in Table 1 for comparison. It may be noted that natural isobauerenol shows the molecular ion peak (m/e 426) as the base peak and fragment b has 85% relative intensity, whereas, in authentic isobauerenol the former is of much less intensity (68%) and the latter appears as the base peak. The relative intensities of the fragments a and d also vary considerably. This discrepancy may be due to different degree of purity of the compounds which is very important in high resolution mass spectrometry.

Unlike bauerenyl acetate (IX), isobauerenyl acetate (II) upon heating with SeO_2 and AcOH (95%) on steam-bath for an hour or even under more drastic condition (reflux in oil-bath, 6 hr.) did not produce the expected bauera-7,9(11)-dienyl 3β-acetate (X) and was recovered unchanged. This reflects the inert nature of the 8-9 tetrasubstituted double bond and is reminiscent of the similar behaviour exhibited by $\Delta^{9(11)}$ pentacyclic triterpenes like arborenyl[11] and fernenyl[12] acetates.

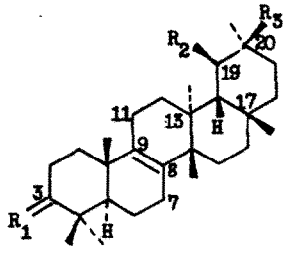
Based on exhaustive kinetic studies a reasonable mechanism for SeO_2 oxidation of ketones in AcOH (70%) has already been reported[13], but no completely satisfactory mechanism of SeO_2 oxidation of olefins is known as yet. However, examination of Dreiding models of isobauerenyl and bauerenyl acetates

*The melting points of these compounds were not reported earlier.

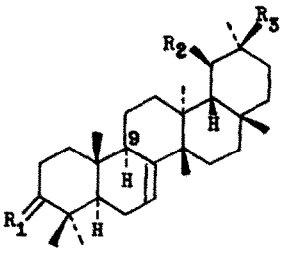
and analyses of the intermediate Se-complexes[13,14] expected to be formed provide a reasonable explanation for such remarkable difference in their reactivity towards SeO_2. In bauerenyl acetate (VIIIa, R= Ac), the instability associated with rigid boat conformation of ring C is enhanced by a strong flagpole-bowsprit interaction between C_{13}-Me and C_9-H. Now, in absence of kinetic evidence it may be postulated by analogy[13] that the electrophilic attack of $H\overset{+}{S}eO_2$ or $H_3\overset{+}{S}eO_3$ on the vinylic C_7 atom with simultaneous or subsequent nucleophilic attack on the allylic C_9-H leads to the formation of an unstable Se^{IV}-complex (XI) having rings B and C in half-chair form. The electrophile (as also the nucleophile) approaches from the less hindered α-side to occupy the energetically favourable quasi-axial position sustaining less $A^{(1,2)}$ strain[15]. Thus the internal strain present in bauerenyl acetate is relieved partly in this intermediate (XI) and completely in the heteroannular diene (X) formed, as shown. Activation energies of both the processes are thus expected to be low making the overall reaction a facile one. On the contrary, isobauerenyl acetate (Ia, R = Ac) with rings B and C in half-chair form is much more stable (it remains unchanged even after heating with 7% H_2SO_4 in AcOH on steam-bath for 0.5 hr.) than bauerenyl acetate. Moreover, in this case, formation of a Se-complex by similar electrophilic attack on C_8 or C_9, and nucleophilic attack on C_{11}-H or C_7-H is impossible due to the fact that in such a complex ring B or C respectively will have to assume high-energy rigid boat conformation with the bulky -SeO(OH) grouping at a hindered flagpole position. Consequently, diene formation does not take place even under more drastic condition.

The conformations of the other rings of bauerenol and multiflorenol systems have also been settled for the first time from careful examinations of Dreiding models. Although ring A is free to assume boat form the associated extra strain will be enhanced by a strong bowsprit-flagpole interaction between C_{10}-Me and C_3-OH. Contrary to recent report[16] chair conformation is, therefore, preferred in the ground state for both the systems. In bauerenol (VIIIa, R = H) or isobauerenol (Ia, R = H) system ring D might prefer chair form but ring E must exist in a boat (or skew-boat) conformation with C_{17}-Me and C_{20}-β-H at the bow and stern positions since a direct steric interference between α-methyl groups at C_{13} and C_{20}, in addition to 1,3 diaxial interaction between C_{17} and C_{19} methyls makes it improbable for ring E to attain chair conformation as in XII. Multiflorenol or isomultiflorenol with the same conformations of rings A, B and C as VIIIa or Ia will have both rings D and E preferably in the boat form, as shown in XIII, to avoid strong bowsprit-flagpole interaction between C_{17}-Me and C_{20}-β-Me groups appearing, in case, rings D and E assume chair and boat conformations respectively as in Ia.

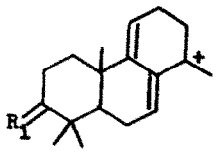
The dienyl acetate (X) could, however, be prepared in the following way[17]. Perbenzoic acid treatment of the acetate (II) in chloroform afforded an amorphous epoxide (single spot in TLC), which without further purification was treated (room temp., 24 hr.) with 10% AcOH containing 1% H_2SO_4 (v/v)



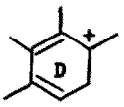
I. R_1=H(OH,β), R_2=CH_3, R_3=H
II. R_1=H(OAc,β), R_2=CH_3, R_3=H
III. R_1=O, R_2=CH_3, R_3=H
IV. R_1=O, R_2=H, R_3=CH_3
V. R_1=H(OH,β), R_2=H, R_3=CH_3



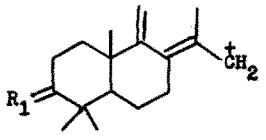
VI. R_1=O, R_2=CH_3, R_3=H
VII. R_1=O, R_2=H, R_3=CH_3
VIII. R_1=H(OH,β), R_2=CH_3, R_3=H
IX. R_1=H(OAc,β), R_2=CH_3, R_3=H



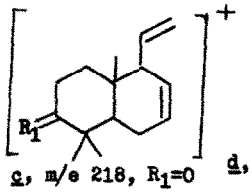
a, m/e 257, R_1=O
m/e 259, R_1=H(OH,β)
m/e 301, R_1=H(OAc,β)



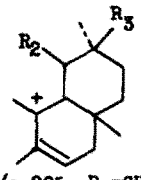
g, m/e 135



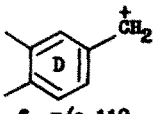
b, m/e 245, R_1=O
m/e 247, R_1=H(OH,β)
m/e 289, R_1=H(OAc,β)



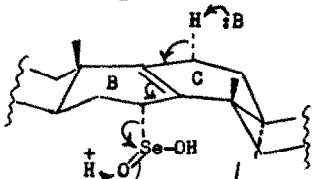
c, m/e 218, R_1=O



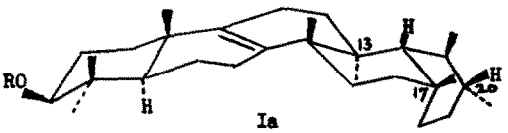
d, m/e 205, R_2=CH_3, R_3=H
m/e 205, R_2=H, R_3=CH_3



f, m/e 119



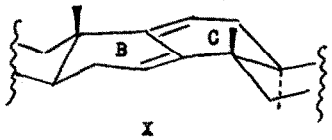
XI



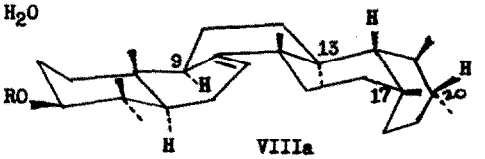
Ia

$2Se^{II}(OH)_2$

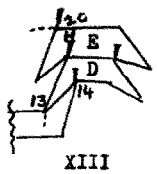
$Se + H_2SeO_3 + H_2O$



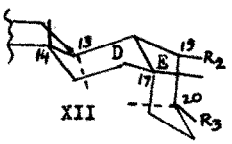
X



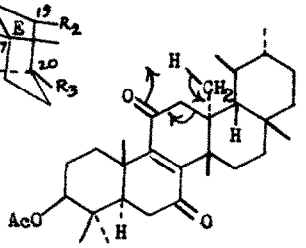
VIIIa



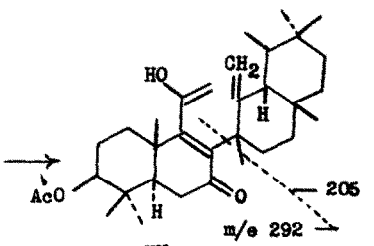
XIII



XII



XIV



XV

to give X in low yield (10%), m.p. 256°, identified with an authentic sample[7] by direct comparison (TLC, m.m.p., IR and UV), λ_{max}^{EtOH} 231 mμ (log ε, 4.23), 240 (4.25) and shoulder at 247 (4.06).

Heating the acetate (II) with chromic acid-acetic acid on steam-bath for 3 hr. afforded bauera-8-en-7,9-dione 3β-acetate (XIV), m.p. 254-56° (M^+, m/e 496, 100%), λ_{max}^{EtOH} 272 mμ (log ε, 3.82) by direct comparison (m.m.p., IR and TLC) with an authentic sample prepared[7] from bauerenyl acetate. The other significant peaks appeared at m/e 481 (M^+-Me, 28%), 292 (41%) and 205 (18%) - the genesis of the latter two being depicted as XIV → XV.

Recently, Row and Rao[16] reported that the action of PCl_5-petroleum ether on isobauerenol produced a dichloro adduct, melting at 170-72°, whereas, earlier, Lahey and Leeding[7] obtained a hydrocarbon, $C_{30}H_{48}$, the normal retropinacolinic rearrangement product. However, by repeated chromatography of the crude product (showing one major and two minor spots) of this reaction we could only isolate the major product as a gummy substance which could not be induced to solidify as yet. Work on the characterisation of this product as well as study of other reactions are currently in progress.

To our knowledge, this constitutes the isolation of a pentacyclic triterpene with a tetrasubstituted double bond at 8-9 position for the first time from nature.

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