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THE CONSTITUTION OF NOOTKATONE, NOOTKATENE AND VALENCENE

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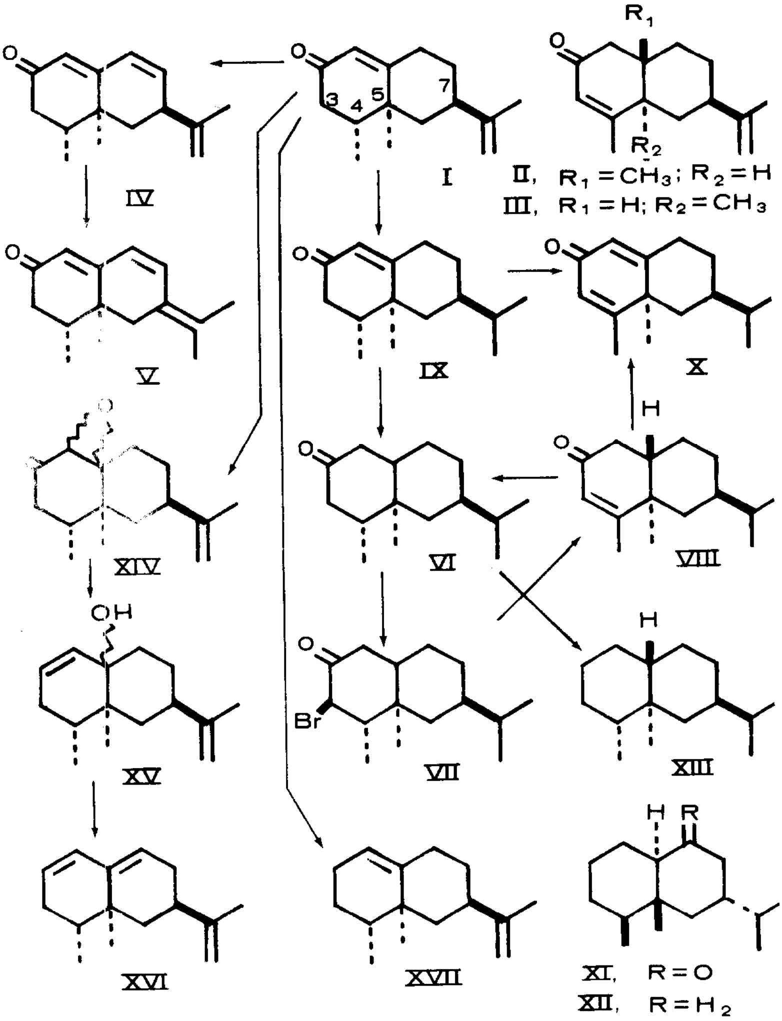
Nootkatone is a mildly pungent sesquiterpene ketone valued for its contribution to the distinctive flavor of grapefruit (Citrus paradisi), especially in the essential oil expressed from the peel (1). Originally, nootkatone was characterized (2) as a heartwood constituent of Alaskan yellow cedar (Chamaecyparis nootkatensis) and formulated as either II or III. We now report evidence that I represents the constitution of nootkatone, $\nu_{max}^{CCl_4}$ 1672, 1620, 1415, 895 cm^{-1}; λ_{max}^{EtOH} 237 mμ (ε 17X10^3).

The methyl doublet in the 60 mc. n.m.r. spectrum [δ 0.9 (3H,d, J = 6 c.p.s.), 1.1 (3H,s), 1.7 (3H,t, J ~ 1 c.p.s.), 2.1 (4H, broad), 4.7 (2H,d, J ~ 1 c.p.s.), 5.6 (1H, broad)] excludes structures II and III because they lack part structure, $CH_3-\overset{|}{\underset{|}{C}}H$. Structure I without stereochemistry specified is the only octalone consistent with the spectra of nootkatone and the selenium dehydrogenations (3) of Erdtman and Hirose (2). Support for this view came from the oxidation of nootkatone (I) with chloranil in hot acetic acid to afford dehydronootkatone (IV) λ_{max}^{EtOH} 281 mμ (ε 23X10^3), which readily isomerized in ethanolic KOH to isodehydronootkatone (V), λ_{max}^{EtOH} 347 mμ (ε 24X10^3) (4). The saturated methylene adjacent to the carbonyl (5) (ν max 1415 cm^{-1}) remained unaffected. The n.m.r. spectrum of IV resembles that of I with added peaks for two vinyl protons centered at δ 6.1 and 6.2 and split in a manner consistent with structure IV. When IV was isomerized to V the signals of these two protons became a distinct pair


I
3
4
5
7
II, R₁ = CH₃; R₂ = H
III, R₁ = H; R₂ = CH₃
R₁
R₂
IV
V
IX
X
H
VI
VIII
XIV
OH
XV
XVI
Br
VII
H
XIII
XVII
H R
XI, R = O
XII, R = H₂

of AB doublets centered at δ 5.8 and 6.4 (J = 10 c.p.s.) and the terminal methylene peak at δ 4.8 was replaced by a second vinyl methyl peak at δ 1.8.

The positions of the two annular methyls were confirmed by brominating tetrahydronootkatone (VI) in acetic acid to VII, m.p. 80-81°C, followed by dehydrobromination in refluxing collidine. The product, VIII, λ_{max}^{EtOH} 238 mμ (ε 13X10^3) was a dihydronootkatone isomeric with IX, λ_{max}^{EtOH} 238 mμ (ε 17X10^3) a hydrogenation product of I. Both VIII and IX could be reduced to VI or oxidized with dichlorodicyanoquinone to dienone X, λ_{max}^{EtOH} 244 mμ (ε 17X10^3), so it was apparent that both octalones had the same skeleton but that the conjugated double bond of VIII was on the side of the carbonyl opposite to that of IX. The chemical shift (6) of the vinyl proton quartet (δ 5.6, J ~ 2 c.p.s.) of VIII placed the vinyl methyl (δ 1.9, d, J ~ 2 c.p.s.) β to the carbonyl. The tertiary methyl, (ca. δ 1) evident in all these compounds, is required at the C-5 position to block tautomerization of X to a phenol.

The optical rotatory dispersion curves of nootkatone (I) and tetrahydronootkatone (VI) showed positive Cotton effects very similar to those of cholest-4-en-3-one (7) and cholestanone (8), respectively. Furthermore, when a drop of HCL was added to the methanol solution of VI, the amplitude of the curve diminished markedly, suggesting that the C-4 methyl was equatorial (9). This was supported by the coupling constant of the H-3 doublet (δ 5.3, J = 11 c.p.s.) of VII which required axial orientation (10) of the H-3 and H-4 protons and hence equatorial orientation of the C-4 methyl and the C-3 bromine (11).

The evidence discussed so far limits the structural possibilities of nootkatone to either I or its epimer having reversed configuration at C-7. The stereochemistry of this epimeric pair is analogous to the eremophilone series (12), although the absolute configurations are opposite (13). Comparisons were made between saturated hydrocarbons derived from both series by modified Wolff-Kishner reduction (14). Ketone XI (15), kindly provided by Prof. Zalkow, afforded a hydrocarbon (XII) with infrared spectrum and opposite optical rotation identical to that of (+) - nootkatane (XIII), $[\alpha]_D$ + 22°, obtained from I via VI. This enantiomeric correlation confirmed the constitution of nootkatone as I.

Prof. R. B. Bates and Dr. S. K. Paknikar generously pointed out (16) that the sesquiterpene triene, nootkatene (17), a congener of I, probably shared the same carbon skeleton. Correlation began with nootkatone oxide (XIV) m.p. 47-48°C, formed from I by reaction with alkaline hydrogen peroxide (18). When treated with hydrazine-ethanol-acetic acid reagent (19), XIV reacted smoothly to form the hydroxydiene (XV). Exposure to hot $POCl_3$-pyridine readily dehydrated XV to a triene XVI, identical to natural nootkatene in optical rotation and infrared and ultraviolet spectra.

Wolff-Kishner reduction (14) of nootkatone (I) to valencene, a major sesquiterpene of orange juice and peel oil (20) and Alaskan yellow cedar, has been confirmed. Formulation of valencene as XVII is consistent with its infrared and n.m.r. spectra and its reconversion (21) to nootkatone (I) with t-butyl chromate. Nootkatone (I), nootkatene (XVI) and valencene (XVII) represent a new and biogenetically interesting series of sesquiterpenes which, like eremophilone are exceptions to the isoprene rule, but not to β orientation of the isopropylene.

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