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TERPENOID CHEMISTRY IX. THE CADINENES

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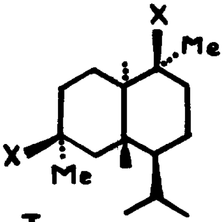
A recent publication[2] clarifying the actual structure of the so-called 'ϵ-cadinene', and describing a new ϵ-cadinene, demonstrates the difficulties involved in the separation and characterization of cadinene isomers.

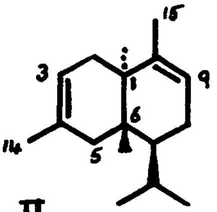
While the stereochemistry[3] and absolute configuration[4] of the cadinene dihydrohalides (I,X=Cl,Br or I) have been determined, the separation of the cadinene isomers and their characterization must be regarded in general as unsolved problems[5,6].

Treatment of the hydrochloride with basic reagents leads to a mixture of isomeric hydrocarbons, the main component of which has been assumed to be β-cadinene (cadina-3,9-diene, II) since Campbell and Soffer[7] obtained a 3% yield of 2,7-dimethylcadalene (III) from the dehydrogenation products of the methyl magnesium iodide-treated epoxides obtained from the regenerated cadinene. Later, a distillation fraction of high optical rotation (-251°) isolated from regenerated cadinene by Herout <u>et al</u>[4], was stated without proof to be "very pure β-cadinene"[4,6].

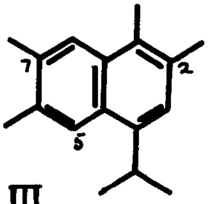
Inspection of the structures of the nine isomeric hydrocarbons derivable from I by simple dehydrohalogenation, suggests that the predominance of III in the dehydrogenation products may stem largely from the greater steric accessibility of the diepoxide of II to the Grignard reagent (cf. the unreactivity of δ-cadinene [cadina-4,10(1)-diene] diepoxide[8,9]).



I



II



III

In 1959 we had developed a useful microtechnique involving dehydrogenation of epoxides[9], which enabled us to determine the presence of 3,4 or 4,5 or 9,10 double bonds in cadinenes and which is of obvious value in the muurolene[2] series. We then attempted the separation of the cadinenes by efficient fractional distillation but were unable to obtain pure substances although some fractions were apparently gas-chromatographically homogeneous. Since the use of silver nitrate impregnated adsorption columns may well circumvent the limitations previously imposed by lack of homogeneity of the distillation fractions and since the β-cadinene structure is still incorrectly assigned in the literature to the sesquiterpene of high optical rotation (-251°), we now briefly report on earlier findings.

Dehydrogenations of micro-amounts (2-10mg) of cadinene diepoxides were carried out by heating with palladised charcoal at 265° for one hour, the whole reaction mixture being then steam distilled for one hour under an oil trap containing 10ml of isooctane. Quantitative transfer of the resulting cadalene and hydroxy-cadalenes to the isooctane was observed. The ultraviolet absorption spectrum of the isooctane solution was measured and compared with those of cadalene[9] and 2-[10], 5-[9], and 7[10]-hydroxycadalenes. Extraction with aqueous sodium hydroxide removes only 2- and 7-hydroxycadalenes from this solution, thus assisting the identification of the naphthols which have characteristic

Cadinene prepared from the dihydrochloride (m.p. 117.5°-118.5°, $[\alpha]_D^{20}$-37° in $CHCl_3$) with sodium acetate in glacial acetic acid compared well (n_D^{25}1.5022, d_4^{25} 0.9221, $[\alpha]_D^{23}$ - 112.3° [hom.]) with previous preparations[4,7]. Gas chromatography on Apiezon M showed the presence of at least five components. This material was fractionally distilled at 10 mm. pressure and a reflux ratio of 100 through a two metre Podbielniak Heligrid still. Ninety per cent of the distillate had $b.p._{10}$ 130-135° and n_D^{25} 1.5045-1.5075. A graph of rotation versus density[11] of the twenty-seven fractions indicated the presence of at least seven components, two of which were dextrorotatory. The highest boiling fraction had physical properties (n_D^{25} 1.5051, d_4^{25} 0.9194, $[\alpha]_D^{25}$- 254.9° [hom.]) in good agreement with previous samples of the highly laevorotatory component[4].

This fraction was treated with an excess of monoperphthalic acid and the product chromatographed on neutral alumina (Woelm, Grade II) to yield four main bands. Band 1 (eluted with hexane) was an oil whose analysis indicated a 2:1 mixture of mono- and di-epoxides. Band 2 (hexane) was a crystalline solid (A), m.p. 52-53° (from ethanol), $[\alpha]_D^{22}$ - 114°(C, 0.86 in $CHCl_3$) (Found : C, 76.3; H, 10.2. $C_{15}H_{24}O_2$ requires C, 76.3; H, 10.2%). Band 3 (benzene : hexane, 1:1) and band 4 (benzene) were combined and recrystallised from ethanol to yield another diepoxide (B), m.p. 117°, $[\alpha]_D^{24}$ - 122° (C, 2.01 in $CHCl_3$) (Found : C, 75.85; H, 10.3. $C_{15}H_{24}O_2$ requires C, 76.3; H, 10.2%). The two diepoxides (A) and (B) were obtained in 14% and 30% yield respectively. The infrared spectra of both diepoxides showed no carbonyl, hydroxyl or ethylenic functions. Both were dehydrogenated and the ultraviolet spectra of the steam-volatile products examined.

Diepoxide (A) yielded cadalene and all three hydroxycadalenes. Despite its sharp melting point and its apparent homogeneity on rechromatography, it appears to be a mixture. Dehydrogenation of band 1 gave essentially the same result. Diepoxide A could be obtained only from fractions of high rotation ($> 220^\circ$). Conclusive proof that the highly laevorotatory hydrocarbon fraction was not homogeneous follows from its partial resolution into two components by gas chromatography on a stationary phase comprising 10% Apiezon M and 15% of silver stearate. The dehydrogenation pattern of the diepoxide (A) is consistent with its being a mixture of diepoxides from II and the hitherto uncharacterised cadina-4,9-diene (α-cadinene). The dehydrogenation pattern however does not exclude the possibility of the presence of exocyclic or tetrasubstituted epoxides, although the crystalline nature of the diepoxide makes this unlikely.

Diepoxide (B) which could be obtained also from fractions of much lower rotation, gave a mixture of cadalene, 2-hydroxycadalene and 7-hydroxycadalene. Extraction of the isooctane solution with alkali left a cadalene spectrum. Acidification of the alkaline extract yielded material with the ultraviolet spectrum of a mixture of 2- and 7-hydroxycadalenes. The parent hydrocarbon is thus cadina-3,9-diene (β-cadinene) and the diepoxide, m.p. 117° is the first characteristic derivative of this sesquiterpene to be obtained. The isolation of a homogeneous epoxide offers a potential method for obtaining a pure hydrocarbon through reactions developed for this purpose by Cornforth <u>et al</u>[12].

Examination of other fractions from the distillation underlined the complexity of the mixture and the fact that the methods of separation were inadequate. Thus, a fraction, homogeneous by gas chromatography and with a retention time identical with cadina-4,10(1)-diene (δ-cadinene), failed to yield the diepoxide[8] characteristic of that olefin. Again, while a nitrosochloride, m.p. 93-94° of "cadinene" has been reported[13], we have isolated three nitrosochlorides, m.ps. 114-116° (dec.), 120-121° and 107.5-108.5° (dec.) from fractions of specific rotations -65.2°, -127.3° and -236° respectively.

With the exception of cadina-4,10(1)-diene (δ-cadinene)[8,9] and cadina-4(14),10(15)-diene(ϵ-cadinene)[2] the many reports of the isolation of particular cadinenes must be viewed with great reserve. The cadinene dihydrohalides can arise from structures other than the nine cadinenes (e.g. copaene[14]), and the isolation of these derivatives cannot even be taken as conclusive evidence for a trans ring fusion in the parent hydrocarbon[2,14].

Structural assignments based on physical and spectral properties are of little value in the sesquiterpene field unless accompanied by unequivocal proof of homogeneity. It can be safely stated that no conclusive evidence exists concerning the structure of the highly laevorotatory component of regenerated cadinene.

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