Tetrahedron Letters No.16, pp. 1913-1918, 1968. Pergamon Press. Printed in Great Britain.

SESQUITERPENOIDS FROM THE WOOD OF *CEDRELA TOONA* ROXB; PARTIAL SYNTHESIS OF T-MUUROLOL, T-CADINOL AND CUBENOL; STRUCTURES OF δ -CADINENE AND δ -CADINOL

B.A. Nagasampagi, L. Yankov[*] and Sukh Dev
National Chemical Laboratory, Poona 8 (India)

(Received in UK 5 January 1968)

IN view of two publications on the new sesquiterpenes from the wood of *Taiwania cryptomerioides* Hayata[1] and from the essential oil of cubeb[2], we would like to record our results on the structure of new sesquiterpene alcohols from the timber of *Cedrela toona* Roxb., as our alcohols appear to be identical with these. We have also effected partial synthesis of two of these from δ -cadinene. The latter correlation has a bearing on the recently proposed structures for δ-cadinene[3] and δ -cadinol[4,5]. This work is in continuation of our earlier investigations[6,7] on the constituents of *Cedrela toona*.

The sesquiterpene portion[8] (0.15 - 0.2%, based on dry trunk wood) of the wood extractives, separated by solvent segregation and column chromatography (Al_2O_3), contains at least 14 components, comprising essentially of hydrocarbons [75%; (-)-copaene[+] farnesene[+], (-)-alloaromadendrene, (+)- δ -cadinene[+], (-)-calamenene, (+)-α-calacorene, cadalene and unidentified] and alcohols (25%), the latter contain, besides (-)-δ-cadinol and (-)-ledol, atleast three new alcohols (Alcohol-I, Alcohol-II, Alcohol-III), the subject matter of the present communication.

Alcohol-III (T-muurolol)

Alcohol-III (R_{dye}[**] =1.00), m.p. 78.5-80, $[\alpha]_D^{30}$ -89°($CHCl_3$), analyses for $C_{15}H_{26}O$ and shows in its IR spectrum (Nujol) bands assignable to: OH (3330,1160 cm^{-1}) and $-\underset{|}{C}=CH-$(1670, 840 cm^{-1}). Its PMR spectrum[10] displays signals for: $CH_3-\underset{|}{\overset{|}{C}}-O$ (3H, singlet, 69 c/s), $C\underline{H_3}-\underset{|}{C}=C$ (3H, somewhat broad singlet, 98 c/s, W_H = 4 c/s) and $-\underset{|}{C}\underline{H}=\underset{|}{C}-$ (1H, broad doublet centred at 333 c/s, J=5 c/s); a set of four sharp singlets (6H, located between 47-57 c/s) occurring in the spectrum, is best assigned to an isopropyl group (pair of two doublets, centred at 50 and 53.5 c/s, each with J = 7 c/s, with

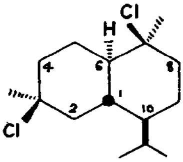
---

[*] Scientists Exchange Fellow, 1966-67; present address: Department of Organic Chemistry, Institute of Chemical Technology, Sofia, Bulgaria.

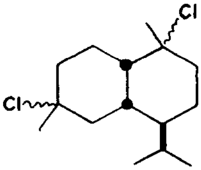
[+] Major components; the relative proportions of the various components vary widely with the source of the wood.

[**] Silica gel-G layers (0.3 mm); solvent: 20% acetone in n-hexane; solvent front: 10 cms; temp.: 25°; reference dye[9]: Sudan-III. Under these conditions δ -cadinol has R_{dye} = 0.66.

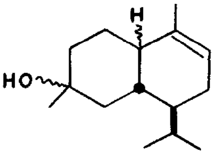
restricted rotation[11] leading to non-equivalence. These spectral characteristics, considered along with the structures of other sesquiterpene components present in the wood, suggested that this mono-olefinic, tertiary alcohol may be cadalenic. This was confirmed, when treatment of alcohol-III in dry ether with hydrogen chloride gave a mixture of (-)-cadinene dihydrochloride (I) and muurolene dihydrochloride (II)[12].



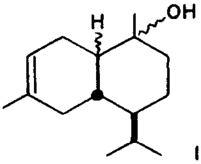
I



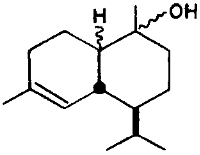
II



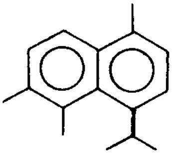
III



IV



V

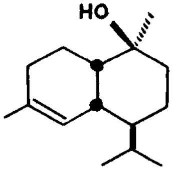


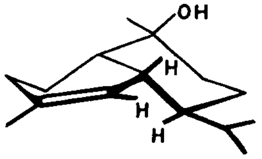
VI

This transformation, taken along with the fact that the olefinic linkage in alcohol-III is trisubstituted, leads to three basic possible formulations III, IV and V for the alcohol. That the olefinic linkage in this alcohol is located at C_2-C_3 (as in V) was established as follows: the alcohol was hydroborated and the product directly oxidised with chromic acid[13]; the resulting keto alcohol was treated with excess CH_3Li in ether and the crude product dehydrogenated with sulphur to give 5-methylcadalene (VI) identified by comparison with an authentic sample[14].

The above work establishes the structure of alcohol-III as V, in which the stereochemistry at C_6 and C_7 must be defined. An examination of molecular models of both trans- and cis- fused V showed that only when the rings are cis-fused (C_{10}-isopropyl equatorial) significant coupling between the C_1-H and the olefinic proton at C_2, as actually observed for alcohol-III, can occur[15]. Thus, alcohol-III must be a muurolene derivative (i.e. cis-fusion of rings) and its behaviour towards HCl gas, as described earlier, is also in accord with this as it has been stated[4] that only muurolenes and muurolols (and not cadinenes and cadinols) give muurolene dihydrochloride (and cadinene dihydrochloride) under these conditions. The only unsettled point remaining is the configuration of the hydroxyl at C_7. This could be deduced, as in VII (≡ VIII) and the evidence is discussed below under the title 'Partial synthesis'. Since, the absolute stereochemistry of (-)-cadinene dihydrochloride is well-established as I, VII should also represent the absolute stereochemistry of (-)-alcohol-III.

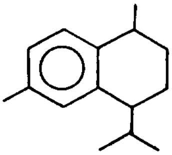
The same structure has been recently assigned[1] to T-muurolol, a sesquiterpene from *Taiwania cryptomerioides*, the various properties of which fully agree with those of alcohol-III.

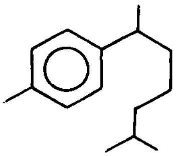

VII

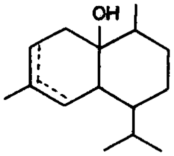

VIII

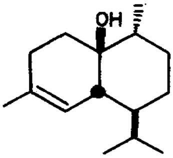
Alcohol-II (epi-Cubenol)

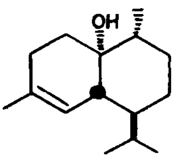
Alcohol-II (R_{dye}= 1.34), b.p. 170-180°(bath)/2.5 mm, n_D^{30} 1.4998, $[\alpha]_D^{30}$ -100.6° ($CHCl_3$), also analyses for $C_{15}H_{26}O$ and is a mono-olefinic tertiary alcohol: OH(IR, smear: 3480, 1030 cm^{-1}; PMR: no signal for $\underline{H}\overset{|}{C}$-OH), $-\underset{|}{C}$=CH- (IR: 1665, 856 cm^{-1}; PMR: 1H, broad doublet centred at 324 c/s, J = 5 c/s). The PMR spectrum further shows a 3H, somewhat broad singlet at 100 c/s, assigned to $C\underline{H}_3$-$\underset{|}{C}$=CH- and, a set of five sharp singlets (total 9H) considered as arising due to $C\underline{H}_3$-CH (52, 58 c/s) and an isopropyl group (pair of doublets centred at 48 and 52 c/s respectively, each with J=6.8 c/s)[11]. From these data, alcohol-II was considered, like alcohol-III, cadalenic. Full support for this was forthcoming from the results of its dehydration with Al_2O_3 (pyridine treated)[16] at 225-230° (2 hr) when three products were obtained. Two of these could be isolated and identified (IR, PMR) as calamenene (IX) and 2-methyl-6-(p-tolyl)-heptane (X), while the third product, during isolation (preparative layer chromatography) and distillation, changed into calamenene and is thus considered to be a dihydrocalamenene. It was clear from these results and biogenetic considerations that alcohol-II should be XI*. In view of the publication of the work of Ohta and Hirose[2]


IX


X

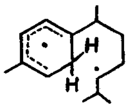

XI


XII


XIII

---

*The formation of X from XI is readily rationalised in terms of (a):


(a)

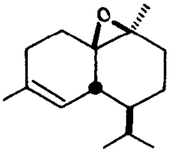
on the structure of epi-cubenol (XII), further work has been discontinued as it was clear from the reported data on epi-cubenol that alcohol-II must be identical with this.

Alcohol-I (Cubenol)

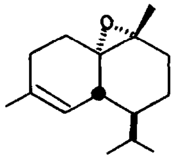
Alcohol-I (R_{dye}=1.55) b.p. 170-180°(bath)/2.5 mm, n_D^{30} 1.4988, $[\alpha]_D^{30}$-30.6° ($CHCl_3$), analyses for $C_{15}H_{26}O$ and, like the other two alcohols, is also a bicyclic, mono-olefinic tertiary alcohol: OH (IR, smear: 3500, 984 cm^{-1}; PMR: no signal for $\underline{H}\overset{|}{C}-OH$), $-\underset{|}{C}=CH-$ (IR: 1665, 872, 840 cm^{-1}; PMR: 1H, broad singlet at 320 c/s), $C\underline{H}_3-\underset{|}{C}=CH$ (PMR: 3H, somewhat broad singlet at 102 c/s), $C\underline{H}_3-CH$ (PMR: 3H, doublet centred at 59 c/s, J=5 c/s), and $C\underline{H}_3-\underset{CH_3}{\underset{|}{C}H}-$ (PMR: 6H, two doublets centred at 44.5 and 56.5 c/s, each with J=7 c/s). It was clear from the nature of the methyl signals that alcohol-I is closely related to alcohol-II. When alcohol-I was exposed to HCl gas in dry ether (-)-cadinene dihydrochloride (I) was isolated and identified. Thus, it became clear that alcohol-I may also have the structure XI, the two alcohols differing from each other, either in the position of the olefinic linkage or, in stereochemistry at C_6/C_7. Cubenol (XIII), recently described by Ohta and Hirose[2] is evidently ($[\alpha]_D$ and spectral data) identical with our alcohol-I. The structure proposed by these authors is fully supported by its partial synthesis, reported below.

Partial Synthesis

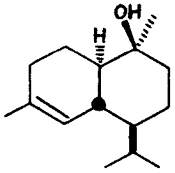
When during the course of the above investigations, the most probable structures had become apparent, work on the reductive cleavage of epoxides, XIV and XV, was initiated, as the resulting tertiary alcohols were expected to provide decisive evidence either for or against some of the structural conclusions drawn earlier. Treatment of (+)-δ-cadinene (XIX) with a C_6H_6 solution of perbenzoic acid gave a mixture (TLC, GLC) of products, from which the major (GLC) component could be separated by chromatography (Al_2O_3/II) and characterised (PMR) as essentially XIV containing some XV*. This, on reduction with Li-EtNH$_2$[17] gave two major and one minor alcohol, which were separated by chromatography.



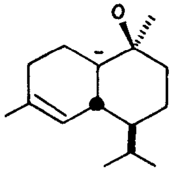
XIV



XV



XVI



XVII

---

* A distinction between XIV and XV is possible from the coupling between the C_1 and C_2 protons, as these protons make an almost 90° dihedral angle in XV, as against $\lesssim$ 40° in XIV.

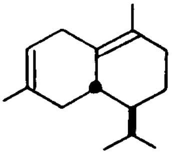
The major product ($[\alpha]_D$-2.4°), as might have been anticipated from the diaxial cleavage[17] of XIV, has been found to be XVI: PMR: $C\underline{H}_3$-$\underset{CH_3}{C}$H- (6H, a pair of overlapping doublets centred at 48 and 55 c/s, each with J=7 c/s), $C\underline{H}_3$-$\overset{|}{\underset{|}{C}}$-OH (3H, singlet, 70 c/s), $C\underline{H}_3$-C=CH- (3H, broad singlet, 98.5 c/s, W_H=4 c/s), -$\underset{|}{C}$=C$\underline{H}$- (1H, broad singlet, 330 c/s, W_H= 5.5 c/s). This structure has been recently assigned to T-cadinol, a sesquiterpene from <u>Taiwana cryptomerioides</u>[1]. The PMR data of our compound closely agree with that reported for T-cadinol and thus, the present synthetic transformation provides additional support for their structure.

The next major product was found to be identical with our alcohol-III. Since, we have shown earlier that alcohol-III is a muurolol, this could arise only by the <u>cis</u>-protonation[18] of the intermediate XVII from XIV[+] to give VII.

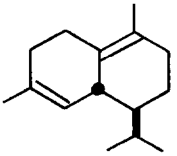
The minor alcohol was identified (PMR) as the alcohol-I (cubenol) and arises from the preferred diaxial opening of the α-oxide (XV). Thus, the structure of cubenol (alcohol-I) now receives synthetic support.

Structure of (+)-δ-cadinene

It has been recently put forward[3] that δ-cadinene is XVIII, rather than XIX. Since, in T-muurolol (alcohol-III, VII), the position of the trisubstituted olefinic linkage has been secured by its transformation into 5-methylcadalene(VI) both by us



XVIII



XIX

and another group[1] independently and, since we have also transformed (+)-δ-cadinene[*] into T-muurolol by a sequence of reactions which should leave the olefinic linkage in δ-cadinene oxide undisturbed[**], it is clear that δ-cadinene should be XIX. Its PMR spectrum is also in better agreement with XIX (-$\underset{|}{C}$=C$\underline{H}$-, 1H, <u>broad singlet</u> at 324 c/s, W_H = 4.5 c/s). The evidence presented by Vlahov <u>et al.</u>[3] in favour of XVIII is not binding, but this will not be discussed any further here.

Structure of (-)-δ-cadinol

Recently, the so far accepted structure (XX)[20] for δ-cadinol has been questioned by two different groups of workers[4,5], who have proposed structures XXI[4] and

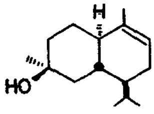
---

[+] The possibility of XV, being the progenitor of alcohol-III, was discounted, as XV was present in the starting oxide mixture to a small extent only and a muurolol could arise from this only by the unfavourable equatorial cleavage of the oxide ring. Also see under δ-cadinol.

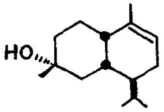
[*] δ-Cadinene used was isolated from <u>Cedrela toona</u> and was duly identified by its physical characteristics and the IR spectrum[19].

[**] In a separate experiment it was shown that δ-cadinene is recovered unchanged after exposure to Li-$EtNH_2$.

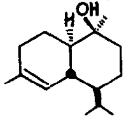
XXII[5] for (-)-δ-cadinol [≡ (-)-torreyol[4] ≡ cedrelanol[5]]. Westfelt[4] has provided excellent evidence that this alcohol has the two rings cis-locked (as in XXI), whereas



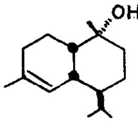
XX



XXI



XXII



XXIII

Smolders[5] has adduced sound evidence that the olefinic linkage is located at C$_2$-C$_3$ (as in XXII). However, in each case, the evidence pertaining to the rest of the structure is not binding*. From these considerations, two possible structures (VII and XXIII epimeric at C$_7$ emerge for δ-cadinol. Since, VII has already been assigned to alcohol-III (T-muurolol), (-)-δ-cadinol must have the absolute stereostructure XXIII. This structure is in accord with all the known reactions of δ-cadinol, and a discussion of these is reserved for a detailed publication, later.

Acknowledgement - The authors are grateful to Dr.L.Westfelt for a sample of muurolene dihydrochloride.

---

* Moreover, structure XXII has been assigned to T-cadinol[1] which has also received synthetic support (present work), hence δ-cadinol cannot be XXII.

REFERENCES

1 Y.S.Cheng, Y.H.Kuo and Y.T.Lin, Chem. Comm. 565 (1967).

2 Y.Ohta and Y. Hirose, Tetrahedron Letters 2073 (1967).

3 R.Vlahov,M.Holub and V.Herout, Coll.Czech.Chem.Comm. 32,822 (1967).

4 L. Westfelt, Acta Chem. Scand. 20, 2893 (1966).

5 R.R.Smolders, Can. J. Chem. 45, 889 (1967).

6 V.H.Kapadia,B.A.Nagasampagi,V.G.Naik and Sukh Dev, Tetrahedron 21,607 (1965).

7 B.A.Nagasampagi,L.Yankov and Sukh Dev, Tetrahedron Letters 189 (1967).

8 P.P.Pillai and B.S.Rao, J.Soc.Chem.Ind. 50,220T(1931); P de Mayo,R.E.Williams, G.Buchi and S.H.Feairheller, Tetrahedron 21, 619 (1965).

9 A.S.Gupta and Sukh Dev, J. Chromatog. 12, 189 (1963).

10 All PMR spectra were taken in CCl$_4$, unless stated otherwise, on a Varian A-60 spectrometer; the signals are recorded in c/s from tetramethylsilane as zero.

11 The isopropyl group protons in δ-cadinene, calamenene, α-calacorene and δ-cadinol occur as a pair of doublets. Also see: G.M.Whitesides,D.Holtz and J.D.Roberts, J.Am.Chem.Soc. 86, 2628 (1964).

12 L. Westfelt, Acta Chem. Scand. 20, 2852 (1966).

13 H.C.Brown and C.P.Garg, J.Am.Chem.Soc. 83, 2951 (1961).

14 B.A.Nagasampagi, Sukh Dev, C.Rai and K.L.Murthy, Tetrahedron 22, 1949 (1966).

15 M.Karplus, J.Chem.Phys.30,11(1959); M.Karplus,J.Am.Chem.Soc.85, 2870 (1963).

16 E. von Rudloff, Can.J. Chem. 39, 1860 (1961).

17 A.S.Hallsworth and H.B.Henbest, J.Chem.Soc. 4604 (1957).

18 This has bearing on the mechanism of cleavage of epoxides with Li-EtNH$_2$ and is under further study.

19 J.Pliva, M.Horak, V.Herout and F.Sorm, Terpenspektren p.54, Akademie-Verlag, Berlin (1960).

20 W.G.Dauben,B.Winstein,P.Lim and B.Anderson, Tetrahedron 15, 217 (1961).