TERPENES - XVII

STRUCTURE OF CALARENE AND STEREOCHEMISTRY OF ARISTOLONE

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GAS chromatographic analysis of a Chinese Spikenard oil (Nardostachys jatamansi (Roxb.) DC., Valerianaceae) revealed the presence of at least six hydrocarbon constituents. The structures of the two major components are discussed in this communication. One of these (18 per cent) has $[\alpha]_D^{CHCl_3}$ -137° and its NMR spectrum (all in carbon tetrachloride) exhibited four methyl singlets at 8.42, 8.90, 8.98, 9.13 and a one proton multiplet at 9.25 τ with no olefinic protons. This hydrocarbon was identical in every respect with a synthetic sample of β-maaliene (1), $[\alpha]_D^{CHCl_3}$ -135°. [2]

The major constituent (65 per cent) $C_{15}H_{24}$ had m.w. 204 (mass spec.); b.p. 45-47° (0.1-0.08 mm); n_D^{26} 1.5029; $[\alpha]_D^{EtOH}$ +58°; λ^{EtOH} 200, 210 (ε 9560, 5480); NMR signals at 4.75 (1H broad), 9.03 (methyl doublet J6 cs), 8.92, 8.98, 9.02 (3 methyl singlets) and 9.40 τ (2 cyclopropane proton multiplet). Its I.R. spectrum was superimposable[3] on that of calarene, $[\alpha]_D^{liq.}$ +18° isolated from sweet flag (Acorus calamus L.).[4] Catalytic reduction gave a saturated dihydro derivative (6), $[\alpha]_D^{CHCl_3}$ -53° identified as calarane[4] by comparison of I.R. spectra. Treatment with formic acid (100°, 5 hr)

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[2] R.B. Bates, G. Büchi, T. Matsuura and R.R. Shaffer, J. Amer. Chem. Soc. 82, 2327 (1960).

[3] We are indebted to Drs. M. Stoll and A.F. Thomas, Firmenich and Cie, Geneva, for this information.

[4] F. Sorm, M. Holub, V. Sykora, J. Mleziva, M. Streibl, J. Pliva, B. Schneider and V. Herout, Coll. Czech. Chem. Comm. 18, 512 (1953).

produced an isomer, $[\alpha]_D^{CHCl_3}$ -220°, which was spectroscopically (NMR, I.R. and U.V.) and vapor chromatographically identical with diene 4 available by formic acid catalysed dehydration of maaliol.[5] These results taken in conjunction with biogenetic consideration suggested expressions 5 or its $\Delta^{9,10}$-isomer for calarene. Of these 5 is correct and all transformations are formulated accordingly. The conversion of 5 to 4 involves Wagner-Meerwein rearrangement and subsequent cleavage of a cyclopropane bond. Earlier experience[5] suggested that isomerization of 6 should be initiated by proton addition to the other, less hindered cyclopropane bond and when subjected to formic acid (100°, 30 hr) an isomer m.w. 206 (mass spec.), $[\alpha]_D^{CHCl_3}$ -45° was formed. It was identified as 3 by spectral data; λ^{EtOH} 200, 210 (ε 11400, 7450); NMR resonance at 8.72 (methyl singlet), three methyl doublets at 8.83 (J4 cs), 9.14 (J6 cs), 9.25 τ (J6 cs) with no olefinic hydrogen and by dehydrogenation to 1,8-dimethylnaphthalene m.p. 63° (mixture melting point, I.R. and U.V. comparisons).

The angular methyl group in calarene (5) must be α-oriented and if we assume β-orientation of the cyclopropane ring preferred addition to the double bond is from the α-side, β-approach being hindered by C_{12}. Hydroboration-oxidation[6] afforded the axial alcohol (7) m.p. 125-126° $[\alpha]_D^{CHCl_3}$ -57°, $v_{max}^{CCl_4}$ 1007 cm^{-1} (1240, 1225 cm^{-1} for the corresponding acetate).[7] Scale models show that calarane (6) and its derivatives can exist in only one double chair conformation and consequently the hydroxyl group in 7 is located at C_1 rather than at C_9 where it would have to be equatorially oriented. Oxidation of 7 with chromic acid afforded the cis-ketone (8), m.p. 34°, $[\alpha]_D^{CHCl_3}$ +31° which in agreement with the octant rule[8] had a

[5] G. Büchi, M. Schach v. Wittenau and D.M. White, <u>J. Amer. Chem. Soc.</u> <u>81</u>, 1968(1959).

[6] H.C. Brown and G. Zweifel, <u>J. Amer. Soc.</u> <u>81</u>, 247 (1959).

[7] E.A. Braude and E.S. Waight, <u>Progress in Stereochemistry</u> (Edited by W. Klyne) Vol. I, p. 166. Butterworths, London (1954).

[8] W. Moffitt, R.B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, <u>J. Amer. Chem. Soc.</u> <u>83</u>, 4013 (1961).

strongly positive Cotton effect curve. Reduction of this ketone (8) with
lithium aluminum hydride produced (7) (70 per cent) and the equatorial
alcohol (9) (30 per cent) m.p. 154-155°, $[\alpha]_D^{CHCl_3}$ -6°, $\nu_{max}^{CCl_4}$ 1030 cm^{-1}
while treatment with alkali caused essentially quantitative conversion to
the more stable trans-ketone (11), m.p. 124-125°, $[\alpha]_D^{CHCl_3}$ +60° with a
weakly negative Cotton effect curve.[8] Both 8 and 11 on exposure to formic
acid (100°, 5-10 hr) or trifluoroacetic acid (20°; 2 hr) yielded the same
unsaturated ketone (10); m.p. 102-103°; $[\alpha]_D^{CHCl_3}$ -31°; $\nu_{max}^{CCl_4}$ 3100, 1705,
1640, 890 cm^{-1}; NMR signals at 5.12 (2H, broad), 8.15 (methyl singlet),
9.19 (methyl doublet J6 cs), 9.25 τ (methyl singlet). It became of im-
portance to ascertain the mode of ring fusion in 10 and this was accomplished
as follows. Catalytic reduction furnished 13; m.p. 96-97°; $[\alpha]_D^{CHCl_3}$ -8°;
NMR signals at 9.25 (methyl singlet), 8.92, 9.02, 9.13 (three methyl doublets
all with J7 cs)τ, which was converted to the thioketal, m.p. 98° and the
latter desulfurized to the saturated hydrocarbon 14. An alternate synthesis
of 14 involved Wolff-Kishner reduction of 11 to a tricyclic hydrocarbon (12)
$[\alpha]_D^{CHCl_3}$ -6° (different from 6 !), followed by isomerization to 15 ($\nu_{max}^{CCl_4}$
3050, 1640, 890 cm^{-1}) with anhydrous hydrogen chloride (0°, 3 hr). Cata-
lytic reduction gave 14, identical spectroscopically and vapor chromato-
graphically with a sample synthesised from 10. Incidentally, exposure of
the trans-hydrocarbon (12) to formic acid under vigorous conditions (100°,
12 hr) yielded 3 identified by I.R., NMR and VPC comparisons. These corre-
lations proved trans-fusion in 10 and 13. Consequently, isomer 10 with an
axial isopropenyl substituent is favored at equilibrium over the unknown
cis-isomer (16) with severe "1,3-diaxial" interaction. A precisely identi-
cal situation would destabilize the trans-ketone with β-methyl configuration

[9] A. Lardon and T. Reichstein, Helv. Chim. Acta 28, 1420 (1945).

[10] Cf. Solvolyses of neomenthyl tosylate, S. Winstein, B.K. Morse, E. Grun-
wald, H.W. Jones, J. Corse, D. Trifan and H. Marshall, J. Amer. Chem. Soc.
74, 1127 (1952) and of 2-methylcyclohexyl tosylates, W. Hückel and H.D.
Sauerland, Liebigs Ann. 592, 190 (1955).

at C_4 but the corresponding cis-isomer is expected to be of comparable stability because it suffers from nonbonded interactions between C_{15}, C_7 and C_9. The exclusive presence of 10 at equilibrium indicated α-methyl configuration at C_4.

To complete the argument we had to establish the configuration at C_7. Calarene (5) was treated with N-bromoacetamide[9] and the resulting crude diaxial bromohydrin (17) reduced with Raney-nickel to the tertiary alcohol (18); m.p. 82-83°; $[\alpha]_D^{CHCl_3}$ +96°. Dehydration with thionyl chloride in excess pyridine gave only a nonconjugated diene (no U.V. absorption); $[\alpha]_D^{CHCl_3}$ +149° which was identified as 21 by its I.R. spectrum (3150, 1650, 900 cm^{-1}), proton resonance at 4.77 (1H doublet, J4 cs), 5.20, 5.31 (1H each, broad), 8.24 (1 methyl with fine splitting), 8.85 (methyl singlet), 8.85 τ (methyl doublet, J7.5 cs) and quantitative isomerization to 4 with formic acid or boron trifluoride in benzene solution. Dehydration of epi-maaliol (22)[5] under identical conditions produced the unrearranged olefins 1 (80 per cent) and 19 (20 per cent). When 22 was submitted to the action of thionyl chloride in ether solution (0°, 2 hr) and the resulting halogen containing crude product treated with hot collidine a mixture of 1 (25 per cent), 4 (23 per cent) and a third substance (52 per cent), $[\alpha]_D^{CHCl_3}$ +138° was forthcoming. An infrared spectrum of the latter was superimposable on that of 21 but the high field section of an NMR spectrum indicated the presence of approximately 10 per cent of an impurity (presumably 19 ?) which could not be removed by gas chromatography. Similar treatment of maaliol (C_4 epimer of 22) gave only unrearranged olefins. β-Maaliene (1) is not an intermediate in either transformation because (a) it was not affected by thionyl chloride in pyridine and (b) isomerized to a new diene (20) (55 per cent) by consecutive treatments with anhydrous hydrogen chloride in ether (0°, 2 hr) and with collidine. The structure of 20 rests on spectral data; $v_{max}^{CCl_4}$ 3150, 1640, 900 cm^{-1}; NMR signals at 4.83
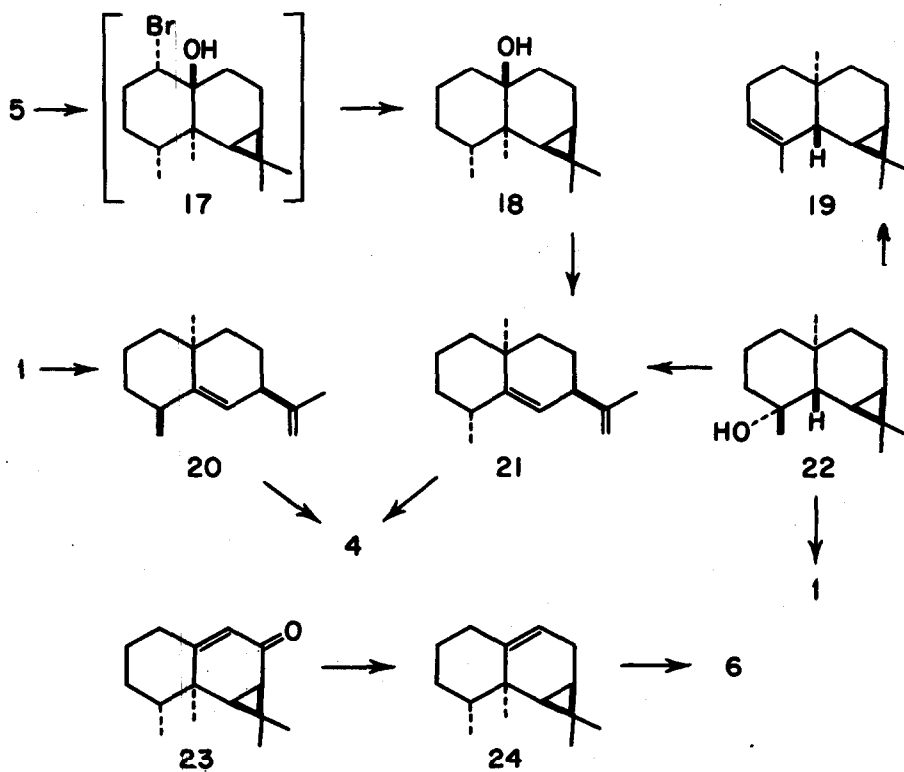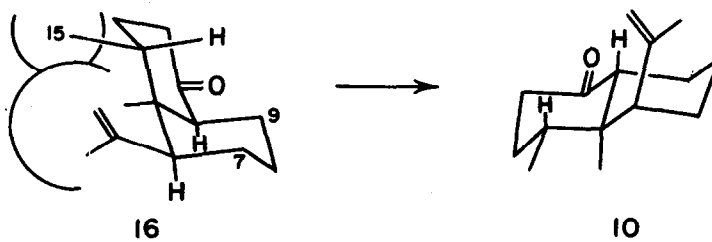
(1H doublet, J4 cs), 5.22, 5.34 (1H each, broad), 8.27, 8.95 (methyl

singlets), 9.02 τ (methyl doublet J7 cs) and acid catalysed isomerization

to 4. In agreement with the configuration assigned the two methyl groups

symmetrically disposed in relation to the cyclic double bond in 21 have

identical chemical shift. The results can be rationalized if dehydration

of both 18 and 22 proceed through the same cyclopropyl-carbinyl cation by

methyl and hydride shifts[10] respectively. The epimeric diene (20) origi-

nated from an epimeric carbonium ion and both rate and thermodynamically

controlled protonation demand β-methyl configuration at C_4.

While we were investigating the configuration of calarene (5) structure

23 (without stereochemistry) was proposed for aristolone, a constituent of

Aristolochia debilis Sieb et Zucc.[11] A correlation of the two natural pro-

ducts has now been achieved and formula 23 expresses the relative and abso-

lute configuration of aristolone. In complete agreement with 23 an NMR

spectrum of a sample of aristolone, kindly provided by Dr. Furukawa, had

peaks at 4.27 (1H doublet, J1 cs), 8.26 (1H quartet J8 and 1 cs),[12] 8.62

(1H doublet J8 cs), 9.07 (methyl doublet J6 cs), 8.72, 8.79 (3 methyl

singlets) τ. Raney nickel desulfurization of aristolone thioketal, m.p.

$56°$ yielded 24; $[\alpha]_D^{CDCl_3}$ $-93°$; NMR resonance at 4.90 (1H, broad), 9.07

(methyl doublet J6 cs), 8.91, 8.93, 8.97 (3 methyl singlets), 9.38 (2H

multiplet) prepared previously by Wolff-Kishner reduction of 23.[11] It

was different from calarene (5) but catalytic reduction furnished a satu-

rated hydrocarbon $[\alpha]_D^{CHCl_3}$ $-48°$ whose identity with 6 was ascertained by

comparisons of retention times in gas chromatograms and infrared spectra.

[11] S. Furukawa and N. Soma, J. Pharm. Soc. Japan 81, 559 (1961); S. Furukawa,
K. Oyamada and N. Soma, Ibid. 81, 565 (1961); S. Furukawa, Ibid. 81, 570
(1961).

[12] Similar transannular coupling was observed with 4,5-β-epoxycholest-1-en-
3-one, E.M. Burgess, J. Org. Chem. 27, 1433 (1962).