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THE STRUCTURE OF DOLABRADIENE[1]

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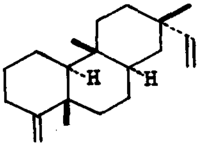
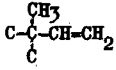
We wish to propose (1) for dolabradiene which is the first example of a new structural type of diterpene.

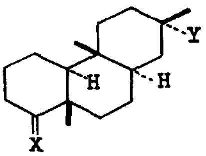


(1)

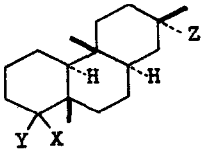
Dolabradiene (1), oil, $C_{20}H_{32}$,[2] b.p. 169°/7 mm.Hg, n_D^{20}1.5240, $[\alpha]_D^{25}$-70° (neat), molecular weight 272 (determined mass-spectrometrically), was isolated from an essential oil of the leaves of Thujopsis dolabrata Sieb. et Zucc. The infrared spectrum[3] of (1) (pure liquid) exhibited the absence of a geminal dimethyl group and the presence of $C=CH_2$ (1783, 890 cm^{-1}) and $-CH=CH_2$(1820, 988, 908 cm^{-1}), while the ultraviolet spectrum showed no conjugation between these double bonds. The sharp and intense peaks at 9.23, 9.08 and 8.97 in the n.m.r. spectrum[4] of (1) are attributed to three methyl groups bound on quarternary carbon atoms. Signals at a region of 4.06-5.30τ showed the presence of terminal vinyl group and the spectrum indicated that the vinyl grouping is attached to carbon bearing no protons.

The catalytic hydrogenation of (1) over Pd-C proceeded almost stepwise to give an oily dihydro compound (2), $C_{20}H_{34}$, infrared max. (liquid) 889 cm^{-1} ($\rangle C=CH_2$), signals at 9.24, 9.19, 8.96τ (3 protons each, sharp), and 9.07τ (triplet, J=4.2 cps, 3 protons), and an oily tetrahydro compound (14), $C_{20}H_{36}$. A comparison between n.m.r. spectra of (1) and (2) suggests the presence of  $C-\underset{C}{\overset{CH_3}{C}}-CH=CH_2$ in the dolabradiene molecule. Dehydrogenation of both (1) and (14) yielded 1,7-dimethylphenanthrene. Ozonolysis of (2) gave a norketone (3), m.p. 60-61°, $C_{19}H_{32}O$, (IR: $\rangle C=O$, 1705 cm^{-1}). On deuterium exchange reaction of (3) with NaOD in $EtOD-D_2O$, two atoms of deuterium were introduced, $M^+=278$.

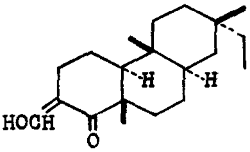
The reaction of (3) with isopropyl lithium furnished an alcohol (15), m.p. 111-111.5°, $C_{22}H_{40}O$ (IR: OH, 3340 cm^{-1}). (1) was ozonized to formaldehyde and a ketoaldehyde (4), m.p. 112.5-113°, $C_{18}H_{28}O_2$ (IR: $\rangle C=O$, 1703; -CHO, 2700, 1725 cm^{-1}). The latter was oxidized with permanganate to a keto-carboxylic acid (5), m.p. 210-212°, $C_{18}H_{28}O_3$ (IR: $\rangle C=O$, 1707; -COOH, 1697 cm^{-1}), and by sodium borohydride reduction (5) gave a hydroxycarboxylic acid (16), m.p. 196-198°, $C_{18}H_{30}O_3$ (IR: OH, 3400; -COOH, 1698 cm^{-1}). Dehydrogenation of both (15) and (16) with selenium gave 1,7-dimethyl-phenanthrene, while that of a desoxocarboxylic acid (6), m.p. 210-211.5°, $C_{18}H_{30}O_2$ (IR: -COOH, 1693 cm^{-1}), obtained by Huang-Minlon reduction of (5), resulted in the formation of



(2) $X = CH_2$, $Y = Et$
(3) $X = O$, $Y = Et$
(4) $X = O$, $Y = CHO$
(5) $X = O$, $Y = COOH$
(6) $X = H_2$, $Y = COOH$
(7) $X = H_2$, $Y = COOMe$
(8) $X = H_2$, $Y = CH_2OH$
(9) $X = H_2$, $Y = CH_2OTs$
(10) $X = H_2$, $Y = Me$
(11) $X = H_2$, $Y = NH_2$
(12) $X = H_2$, $Y = NMe_2$
(13) $X = H_2$, $Y = CHO$



(14) X = Me, Y = H, Z = Et
(15) X = i-Pr, Y = OH, Z = Et
(16) X = OH, Y = H, Z = COOH



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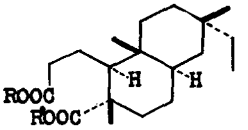
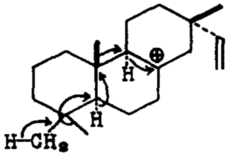


(18) R = R' = H
(19) R = Me, R' = H
(20) R = R' = Me
(21) R = H, R' = Me



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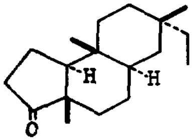

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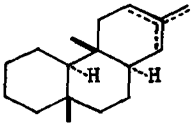

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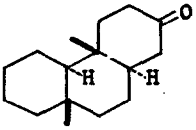

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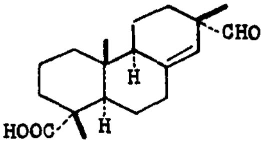

(26)

2-methylphenanthrene with loss of an angular methyl group.

Further proof for the methyl group at C_5 was obtained as follows. The hydroxymethylene ketone (17), m.p. 92-95°, $C_{20}H_{32}O_2$, derived from (3) was ozonized and followed by hydrogen peroxide oxidation to give a dicarboxylic acid (18), m.p. 217-219°, $C_{19}H_{32}O_4$ (IR: $>C=O$, 1703 cm^{-1}), a carboxyl group of which was sterically hindered, viz., (a) Fischer esterification gave a monomethyl ester (19), m.p. 83.5-84.5°, $C_{20}H_{34}O_4$ (IR: $>C=O$, 1738, 1693 cm^{-1} in CCl_4); (b) the dimethyl ester (20), oil, $C_{21}H_{36}O_4$ (IR: $>C=O$, 1738, 1724 cm^{-1}, liquid film) obtained by esterification of (18) with diazomethane on alkaline hydrolysis afforded an isomeric monomethyl ester (21), oil, $C_{20}H_{34}O_4$ (IR: $>C=O$, 1722, 1708 cm^{-1} in CCl_4, p-bromophenacyl ester, m.p. 76-77°).

Reduction with lithium aluminum hydride converted the methyl ester (7), m.p. 65-66°, $C_{19}H_{32}O_2$ (IR: ester, 1726 cm^{-1}), of (6) to an oily alcohol (8), $C_{18}H_{32}O$ (IR: OH, 3340 cm^{-1}, liquid film) and its tosylate (9), m.p. 78-78.5°, $C_{25}H_{38}O_3S$ was reduced with lithium aluminum hydride to a hydrocarbon (10), m.p. 43-44°, $C_{18}H_{32}$, which showed in the infrared spectrum geminal dimethyl groups at 1390 and 1367 cm^{-1}.

If dolabradiene does not possess the "wrong" configuration with respect to steroids, the configuration except C_{13} might be predicted to be (1), from the consideration of biogenetic route through an intermediate carbonium ion[5] (22) initiated from geranylgeraniol or an equivalent precursor, involved methyl and hydride migration.

Absolute Configuration

A/B Ring juncture The ORD curve ($[\alpha]_{315}$ +185°, $[\alpha]_{282}$ -610° in dioxane) of the norketone (3) was compared with that of D-homoandrostan-3β-ol-17α-one[6] but no reliable conclusion could be derived

The dicarboxylic acid (18) was treated with acetic anhydride and followed by pyrolysis to give a cyclopentanone derivative (23), b.p. 130-135°(bath temp.) /2 mm.Hg, $C_{18}H_{30}O$ (IR: >C=O, 1735 cm^{-1}, 2,4-DNP: $C_{24}H_{34}O_4N_4$, m.p. 203.5-204°), whose ORD curve ($[\alpha]_{318.5}$ +3000°, $[\alpha]_{272}$ -3650° in dioxane) showed a positive Cotton effect and was similar to that of androstan-17-one[7]. Therefore the A/B ring juncture is 5β-trans.

B/C Ring juncture: The amine (11), oil, b.p. 148-152° /4 mm.Hg, $C_{17}H_{31}N$(IR: $-NH_2$, 3360, 3280 cm^{-1}, benzamide derivative, m.p. 169-169.5°), obtained by Curtius rearrangement of the acid chloride of (6) was methylated with formalin and formic acid to a dimethylamine (12), oil, b.p. 150-155° (bath temp.) /2 mm.Hg, $C_{19}H_{35}N$ (picrate: m.p. 231°). Hofmann degradation of the methiodide, m.p. 232-235°, $C_{20}H_{38}NI$, of (12) afforded a mixture of olefins (24), oil, b.p. 100-110° (bath temp.) /2 mm.Hg, $C_{17}H_{28}$, (IR: 880, 787 cm^{-1}), ozonolysis of which yielded a ketone (25), m.p. 103-104°, $C_{16}H_{26}O$ (IR: 1710 cm^{-1}). The ORD curve showed a negative Cotton effect ($[\alpha]_{312}$-1532°, $[\alpha]_{270}$ +1320° in methanol), amplitude of which underwent a marked reduction upon addition of hydrochloric acid. Accordingly the ketone is antipodal with respect to a 3-keto steroid[6,8] This eliminates the possibility of the presence of an angular methyl group at C-8 and suggests that the B/C ring juncture is 9β-trans.

Configuration of C-13: The alcohol (8) was oxidized with chromium trioxide in pyridine to an aldehyde (13), m.p. 81-82°, $C_{18}H_{30}O$ (IR: -CHO, 2680, 1722 cm^{-1}). Since the ORD curve of (13) showed negative Cotton effect ($[\alpha]_{326}$ -338°, $[\alpha]_{292}$ +545° in methanol) and has the same sign as the aldehyde carboxylic acid[9] (26) obtained from sandaracopimaric acid, the vinyl group at C-13 probably is α-oriented.

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1. Paper was read at 5th Symposium on the Chemistry of Natural Products, Japan (October, 1961).
2. Satisfactory analyses have been obtained for all new compounds described in this paper.
3. Infrared spectra were taken as KBr pellet unless otherwise indicated.
4. Spectra were obtained in carbon tetrachloride with Varian DP-60 Spectrometer. The spectra were calibrated by audiofrequency sideband technique against internal tetramethylsilane standard.

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