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CYCLIZATION OF POLYENES XXX[1]
SYNTHESIS OF 2-HYDROXY- AND 1,2-DEHYDRO-7,8-OXIDO-NEPHTENOLS AND CEMBRENOL

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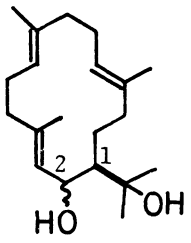
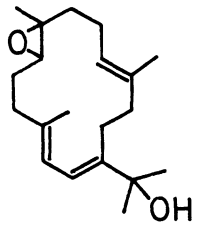
The naturally occurring cembrenoids (I, II, and III) were successfully synthesized, demonstrating unequivocally the assigned structure.

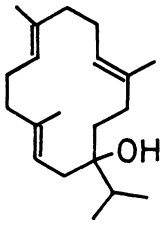
Recent papers concern with the isolation and structural elucidation of several kinds of oxygenated cembrenoids, in which 2-hydroxy- and 1,2-dehydro-7,8-oxido-nephtenols (I and II) and cembrenol (III) are the typical examples. In connection with our recent interest in the chemistry of cembrenoids, we have further continued the synthetic study and have achieved the derivation of these naturally occurring oxygenated cembrenoids starting from the easily prepared chloro ketone (IVa)[2].



I



II



III

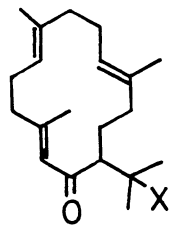
2-HYDROXYNEPHTENOL 2-Hydroxynephtenol (Ia or b) was isolated from a soft coral, the alcyonarian Litophyton viridis[3] and its structure was elaborated excepting the relative stereochemistry of two asymmetric carbons and of the geometry of the ring olefinic bonds. The all trans geometry of the double bonds was suggested by analogy with the other cembranes occurring in the same species and with the biogenetical precursor geranylgeraniol.

In order to determine the stereostructure, both cis (Ia, C_2-βOH) and trans (Ib, C_2- αOH) isomers[4] were derived from the chloro ketone (IVa) as follows. Treatment of IVa with AgOAc (1.5 mol eq.) in AcOH (60°C, 3 h) resulted in the formation of a mixture of keto acetate (IVb, 53 %) and isopropenyl ketone (V, 37 %), which was separated by SiO_2 column chromatography[5]. IVb(oil): PMR, δ 1.35 and 1.38 (each 3H, s, CMe_2OAc), 1.50 and 1.67 (each 3H, s, C=CMe x 2), 1.86 (s, OAc), 2.11 (s, COC=CMe), 3.40 (1H, dd, 11 and 2 Hz, $COCHCMe_2OAc$), 4.88 (m, C=CH x 2) and 5.89 ppm (1H, s, C=CHCO).

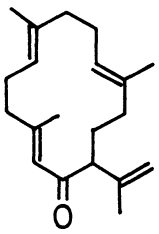
The keto acetate (IVb) was reduced with AlH_3 (3 mol eq.) in ether at -78°C, giving a hydroxy ketone (VI)(ca 1:1 stereoisomeric mixture concerning a secondary

methyl and -CMe_2OH groups)[6], cis (Ia) and trans (Ib) diols in 25, 57, and 18 % yields, respectively. The minor diol (Ib), thus obtained, was identical with natural 2-hydroxynephtenol in the PMR and mass spectra[7]. The stereochemistry of the newly formed secondary hydroxyl group of Ia and b was deduced on the basis of the coupling mode in the PMR spectra. Each coupling pattern of C_2-proton of Ia and b is quite similar with that of cis (VIIa) and trans (VIIb) mukulols, respectively. The stereochemistry of the mukulols was determined by physical evidence including X-ray analysis[8].

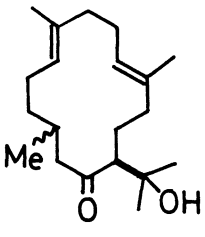
It has thus been clarified unambiguously the geometry of the ring olefinic bonds and also the relative stereochemistry concerning two asymmetric carbons in natural 2-hydroxynephtenol. Ib(mp 97°): PMR, δ 1.27 and 1.30 (each 3H, s, CMe_2OH), 1.56 and 1.58 (s, C=CMe x 2), 1.70 (s, C(OH)C=CMe), 3.53 (br. m, OH x 2), 4.52 (1H, t, 9 Hz, =CCH(OH)), 4.94 (2H, m, =CH x 2), and 5.27 ppm (1H, d, 9 Hz, =CHC(OH)). Ia(oil): PMR, δ 1.28 and 1.38 (each 3H, CMe_2OH), 1.60, 1.64 and 1.66 (each 3H, =CMe x 3), 2.70 (br. m, OH x 2), 4.96 (1H, d, 9 Hz, =CCH(OH)), 4.99 (m, =CH x 2), and 5.28 ppm (1H, d, 9 Hz, =CHC(OH)).



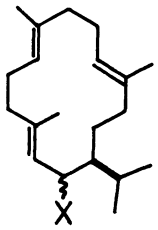
IVa X = Cl
IVb X = OAc



V



VI



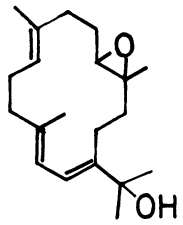
VIIa X = βOH
VIIb X = αOH

1,2-DEHYDRO-7,8-OXIDO-NEPHTENOL A sarcophyton species of soft corals has been recently reported to produce a cembrenoid, to which two possible structures (II and VIII) were equally suggested from spectroscopic evidence[9]. The final structure (II) was assigned for the cembrenoid by X-ray analysis. It seems, therefore, of interest to compare the spectroscopic data of two isomers by synthesizing both compounds.

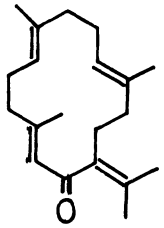
The cross conjugated ketone (IX), easily obtained from IVa[10], was oxidized with m-Cl-$C_6H_4CO_3H$ (ca 1.5 mol eq.) in CH_2Cl_2 at -18°C, affording a mixture of mono-oxides (X and XI) in 47 and 15 % yields accompanying the formation of bis-oxide (XII, 4 %)[11]. Since epoxide position of each mono-oxide could not be confirmed exactly at this stage[12], each isomer was converted to the hydroxy oxides (II and VIII) by the following manner. The major product (X) was reduced with $LiAlH_4$ (1.7 mol eq.) in ether at -78°C and the reaction mixture was passed through a SiO_2 column, affording two kinds of hydroxy oxides (VIII, 40 % and XIII[14], 8 %) and keto oxide (XIV, 26 %). The resultant hydroxy oxides (VIII and XIII) are the rearranged products derived from the corresponding 2-hydroxy derivative, which is labile to acids and rearranges easily when contacted with SiO_2. VIII (oil): PMR, δ 1.27 (s, C-O-CMe), 1.37 (6H, s, CMe_2-OH), 1.69 (s, =CMe), 1.76 (s, $(C=C)_2Me$), 2.93 (1H, dd, 9 and 3 Hz, C-O-CH), 5.30 (m, =CH), 5.84 and 6.28 ppm (each 1H, d, 11 Hz, C=CHC=CH-). X (mp 79-80°): PMR, δ 1.29 (s, C-O-CMe), 1.68 (=CMe), 1.81 and 1.88 (each 3H, COC=CMe_2), 2.05 (s, COC=CMe), 5.14 (m, =CH) and 6.02 ppm (COCH=C). XI (mp 69-70°): PMR, δ 1.31 (s, C-O-CMe),

1.58 (s, =CMe), 1.80 and 1.86 (each 3H, COC=CMe$_2$), 2.21 (COC=CMe), 5.07 (m, =CH), and 6.15 ppm (s, COCH=C). XII (mp 105-106°): PMR, δ1.26 and 1.33 (each 3H, C-O-CMe x 2), 1.82 and 1.88 (each 3H, COC=CMe$_2$), 2.21 (COC=CMe), and 6.19 ppm (COCH=C).

Similar treatment of the isomeric mono-oxide (XI) with $LiAlH_4$ under the same conditions converted XI to a mixture of hydroxy oxide (II) and keto oxide (XV)[15] in 23 and 31 % yields, respectively[16]. The PMR and IR in CCl_4 spectra of the hydroxy oxide (II), thus prepared, were identical with those of natural 1,2-dehydro-7,8-oxido-nephtenol[17]. II: PMR, δ 1.27 (s, C-O-CMe), 1.38 (6H, s, CMe$_2$OH), 1.65 (=CMe), 1.79 ((C=C)$_2$Me), 2.88 (1H, dd, 6 and 4 Hz, C-O-CH), 5.14 (m, =CH), 5.94 and 6.37 ppm (each 1H, d, 11 Hz, C=CHC=CH).



VIII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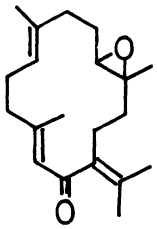
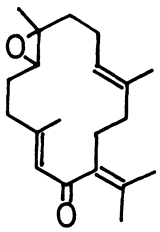
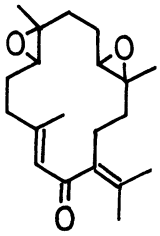
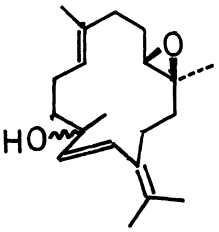
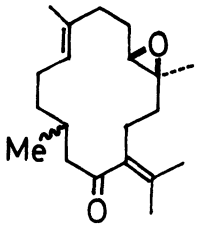

X


XI


XII



XIIIa βOH
XIIIb αOH



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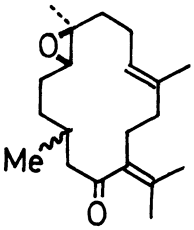
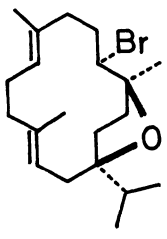


XV

CEMBRENOL Cembrenol (III) was isolated, together with incensole, from the resin of Boswellia carteri and its structure was proposed mainly on the basis of chemical degradation[18].

As reported previously[19], we have prepared five membered bromo ether (XVI) from dl-mukulol (VIIa) in 25 % overall yield. The bromo ether was transformed into the cembrenol (III) when XVI in 90 % aq EtOH was refluxed for 8 h in the presence of Zn (4 mol eq.) followed by purification with SiO_2 column chromatography. An alcoholic compound, obtained in 36 % yield, was identical with natural cembrenol (III) in the PMR and mass spectra[20]. The present result demonstrates the trans nature of the ring double bonds in natural cembrenol and at the same time the synthetic scheme seems applicable for the synthesis of albocerol[21], a sesterterpene alcohol having the similar structural feature.



XVI

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2. T. Kato, T. Kobayashi, and Y. Kitahara, Tetrahedron Lett., 3299 (1975).
3. B. Tursch, J. C. Braekman, and D. Daloze, Bull. Soc. Chim. Berg., 84, 767 (1975).
4. One enantiomer of the dl-forms is depicted. Numbering of the compounds described herein is based on that of nepht(h)enol.
5. All the SiO_2 chromatographyies were carried out using a mixed solvent of n-hexane: AcOEt in the ratio of 2:1~10:1.
6. The mixture (ca 1:1) was separated by repeated column chromatography although the relative stereochemistry of each isomer remains unsolved. VIa (oil): PMR, δ0.92 (d, 6 Hz, CHMe), 1.13 (6H, s, CMe_2OH), 1.59 (=CMe x 2), and 5.07 ppm (=CH x 2). VIb (oil): PMR, δ 0.88 (d, 6 Hz, CHMe), 1.13 and 1.16 (s, CMe_2OH), 1.55 and 1.62 (=CMe x 2), and 5.04 ppm (=CH x 2)
7. The copies of physical data of natural 2-hydroxynephtenol were kindly given by Dr. D. Daloze.
8. T. Kato, C. Kabuto, K. H. Kim, H. Takayanagi, T. Uyehara, and Y. Kitahara, Chemistry Lett., 827 (1977).
9. J. C. Coll, G. B. Hawes, N. Liyanage, W. Oberhansli, and R. J. Wells, Aust. J. Chem., 30, 1305 (1977).
10. see ref. 2.
11. Although cis and trans isomers are possible with respect to two epoxy rings, the exact stereochemistry of XII is uncertain.
12. Our preliminary study[13] on the conformation of cembrenoids suggests that 7,8-double bond is sterically more hindered than 11,12-double bond. Further study on the conformation is now in progress.
13. see ref. 8.
14. Two isomers (XIIIa and b) were separated by repeated column chromatography. XIIIa: PMR, δ 1.24 and 1.32 (each 3H, s, -O-CMe x 2), 1.75 (s, =CMe), 1.83 (s, $(C=C)_2Me_2$), 2.76 (1H, dd, 10 and 2 Hz, C-O-CH), 5.32 (m, =CH), 5.87 and 6.68(each 1H, d, 16 Hz). XIIIb: PMR,δ1.30 and 1.41 (each 3H, s, -O-CMe x 2), 1.73 (s, =CMe), 1.81 (6H, s, $(C=C)_2Me_2$), 2.83 (1H, dd, 10 and 2 Hz, C-O-CH), 5.39 (m, =CH), 5.96 and 6.64 ppm (each 1H, d, 17 Hz, CH=CH).
15. An infinite development on SiO_2 TLC revealed that each of the keto oxides (XIV and XV) was ca 1:1 stereoisomeric mixture although each isomer was not purified.
16. Although formation of the isomeric hydroxy oxide corresponding to XIII was observed on TLC, further separation was not carried out.
17. The authors are indebted to Drs B. F. Bowden and J. C. Coll for their generous gift of natural 1,2-dehydro-7,8-oxido-nepht(h)enol.
18. E. Klein and H. Obermann, Tetrahedron Lett., 349 (1978).
19. T. Kato, C. C. Yen, T. Uyehara, and Y. Kitahara, Chemistry Lett., 565 (1977).
20. The authors appreciate Dr. H. Obermann for his sending copies of physical data of natural cembrenol.
21. T. Kato, M. Suzuki, Y. Nakajima, K. Shimizu, and Y. Kitahara, Chemistry Lett., 705 (1977).

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