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ELECTROPHILE INDUCED CYCLIZATION OF FARNESOL

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The cyclization of farnesol with BF_3 etherate in dichloromethane solution afforded α-cedrene, 2-epi-α-cedrene and five new hydrocarbons of muurolane type together with isomeric bisabolenes, α-curcumene and δ-selinene. The structure determination of the new compounds and the formation mechanism of cyclized products are presented.

Chemically induced cyclization of farnesol or nerolidol have long been noticed in view of biogenesis of sesquiterpenoids, and have been carried out by several generations of chemists[1]. However, because of the complexities of the composition of the products, only a few compounds were identified such as isomeric farnesenes and bisabolenes , α-curcumene and bisabolol. In this communication, we wish to report the structure determination of several, especially polycyclic, compounds obtained from farnesol by cyclization with BF_3 etherate as electrophilic reagent, and their probable formation mechanisms.

To a dichloromethane solution of synthetic farnesol (1:1 mixture of cis, trans- and trans, trans-isomers) was added BF_3 etherate in the same solvent dropwise at 0°, and the mixture was stirred for an hour at room temperature. The volatile fraction (ca. 60% yield) was separated from non-volatile polymers by steam distillation of the reaction products. This fraction was analysed using column chromatography on silica gel impregnated with silver nitrate and preparative gas chromatography.

The following five new cadalene type compounds (3)~(7) were identified together with the known hydrocarbons, α-cedrene (1), 2-epi-α-cedrene (2), δ-selinene (8), α-,β-, and γ-bisabolene and α-curcumene. All these compounds are represented by the structures with relative stereochemistry only.

2-Epi-α-cedrene (2) : This compound showed the identical nmr spectrum with that of 2-epi-α-cedrene reported by Demole et al.[2], and finally identified by comparing its i.r. spectrum with that of the authentic sample obtained by Tomita et al. from β-isobiotol.[3]

Muurola-4,11-diene (3) : m/e 204 (M^+), 119 (100%); ν_{max} 3075, 1640, 1380 and 890 cm^{-1}; δ_{ppm} 0.91 (3H, d, J=6.0Hz), 1.58, 1.65 (each 3H, br s), 4.64 (2H, br s), and 5.25 (1H, m). On hydrogenation (PtO_2/AcOH), it afforded two tetrahydro derivatives one of

which was identical with muurolane obtained from γ-muurolene (9) by hydrogenation. The dihydro derivative obtained by selective reduction ($Rh(PPh_3)_3$/benzene) was identical with dihydro-γ-muurolene. From these results and the spectral data, the structure of this hydrocarbon was shown to be (3) except for the stereochemistry at C-10.

Muurola-3,11-diene (4) : m/e 204 (M^+, 16%), 119 (100%); ν_{max} 3070, 1640, 1380, 890 and 795cm^{-1}; δ_{ppm} 0.88 (3H, d, J=6.0Hz), 1.59 (6H, br s), 4.61 (2H, br s) and 5.25 (1H, m). This hydrocarbon was concluded to be a position isomer of the trisubstituted double bond of (3), because the two tetrahydro derivatives of (4) were identical with those from (3), respectively, and, further, the dihydro derivative differed from dihydro-γ-muurolene.

Muurola-4,7(11)-diene (5) : m/e 204 (M^+, 61%), 161 (100%); ν_{max} 1660, 1375, 1130, 1000, 840 and 805cm^{-1}; δ_{ppm} 0.87 (3H, d, J=4.5Hz), 1.65 (9H, br s), 3.29 (1H, br) and 4.90 (1H, br s). This compound afforded a tetrahydro derivative on hydrogenation (PtO_2/AcOH) as a sole product which was identical with an amorphane, one of the reduction products of α-amorphene (10). From this fact and the spectral data, especially the presence of the signal of a proton on a carbon atom located between two double bonds (1H at 3.29ppm), this hydrocarbon was represented by the structure (5) except for the stereochemistry at C-10.

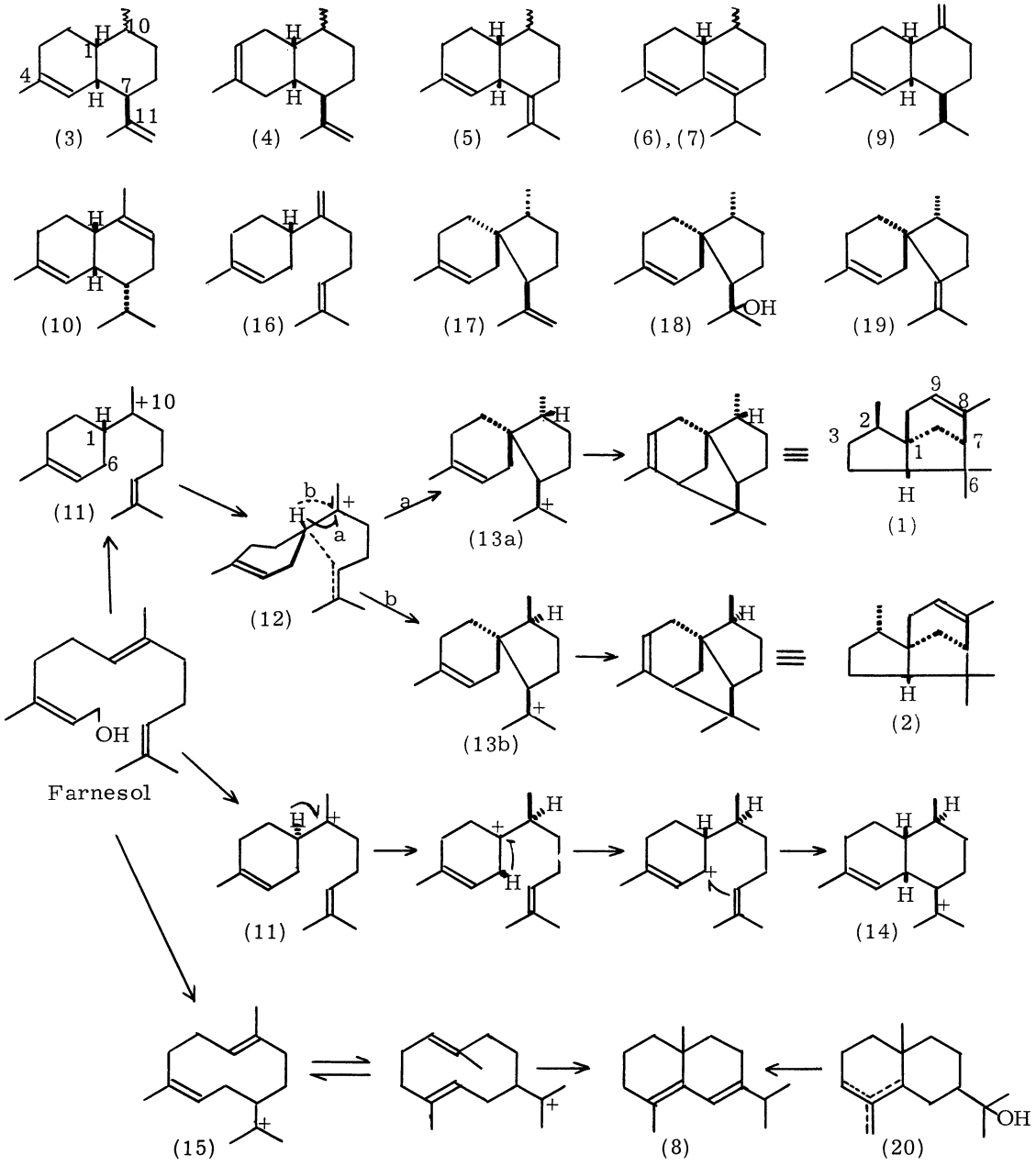
10-α or β-H muurola-4,6-diene (6) : m/e 204 (M^+), 161 (100%); λ_{max} 242.5 (ε, 18,600) and 248.5nm (ε, 18,800); δ_{ppm} 0.94 (9H, d, J=6.0Hz), 1.71 (3H, br s), 2.95 (1H, q, J=6.0Hz) and 6.10 (1H, br s).

10-β or α-H muurola-4,6-diene (7) : m/e 204 (M^+), 161 (100%); λ_{max} 243.0 (ε, 19,100) and 248.5nm (ε, 19,600); δ_{ppm} 0.78 (3H, d, J=6.6Hz), 0.94 (6H, d, J=7.0Hz), 1.72 (3H, br s), 2.95 (1H, q, J=7.0Hz) and 6.10 (1H, br s).

The hydrocarbon (6), containing a heteroannular conjugation system in the molecule, afforded the same amorphane on hydrogenation (PtO_2/AcOH). The structure of this compounds was concluded to be (6) on the basis of this carbon skeleton and the spectral data. The compound (7) showing the closely resembled UV and nmr and indistinguishable mass spectra, should be an isomer of (6) epimeric at C-10.

Formation mechanisms : It has been assumed that the proton induced cyclization of farnesol or nerolidol initiates to form bisabolenium ion (11) which can lose a proton to yield α-, β-, and γ-bisabolene.[1f] We confirmed this assumption by ensuring the gross identities of the compositions of cyclization products from farnesol and from synthetic α-bisabolol under the same conditions. It is the first time that α-cedrene and epi-α-cedrene were isolated from the cyclization products of farnesol. The genetical course of α-cedrene via the acorene type ion (13a) has already been proved; for example, (-)-α-acoradiene (17) and (-)-α-acorenol (18)[4] or α-alaskene[5] (γ-acoradiene[6]) (19) afforded (-)-α-cedrene (1) in excellent yield on treatment with acid. Furthermore, the stereochemical relationship between (+)-β-bisabolene (16) and these polycyclic compounds was well established by the coexistences of (16) and (19) in the leaf oil of Chamaecyparis

nootkatensis Sudw.[5,7] and of (1), (17) and (18) in the wood of Juniperus rigida Sieb. et Zucc.[4,6,8] Accordingly, it is also suggested that the pathway from bisabolenium ion (11) to α-cedrene in this reaction proceeded through the intermediate state (12) and acorenium ion (13a). When these steps are assumed to proceed in a concerted mechanism initiated by migration of the proton at C-1 to C-10, both of the two routes a) and b) are permitted leading to α-cedrene and epi-α-cedrene, respectively. This scheme well explains the formation of these epimeric cedrenes in a comparable ratio. The acoradienes expected from the intermediate ions (13a and 13b) could not be isolated because of their instabilities under the condition employed.



If the formation of cadalenic compounds proceeds concertedly via repeated 1,2-H shifts, the ion (14) should have cis ring junction and the stereochemistry of C-10 will be decided by the configuration of the proton at C-1. On the contrary, if the cadalenium ion is formed from the ion (11) via 1,3-H shift followed by cyclization, the product is supposed to be a mixture of cis and trans ring junction compounds. At this stage of our experiments, it is impossible to decide which of these two mechanisms is operating. However, the failure to detect the compounds with trans ring fusion in the products suggests the predominance of the cyclization via repeated 1,2-H shifts. Another question, the formation mechanism of (6) and (7), epimeric at C-10, is also to be solved.

Any way, the cadalene type compounds produced from the bisabolenium ion (11) retain sp^2 center at the isopropyl group. A few cadalenic compounds carrying sp^2 center at the isopropyl group have been found in nature, such as sesquibenihene[9], articulol[10] and articulone[10], and they are possibly formed via the scheme mentioned above. Usual cadalenic compounds are reasonably explained as the rearrangement products of germacrenium ion and carry sp^2 center at C-10.

It is very interesting that we could detect δ-selinene (8) among the products. The explanation for this may readily be done via the germacrenium ion (15). Other selinenes expected from this ion will isomerize to δ-selinene as evidenced by the fact that a mixture of α-, β-, and γ-eudesmols (20) afforded δ-selinene as the main product on treatment with BF_3 etherate. However, further study is needed to declare with some certainty that a portion of farnesol cyclized to cyclodecadienyl ion in an intermediate stage.

References

1), (a) F.W.Semmler and K.E.Spornitz, Chem.Ber., 46, 4025 (1913); (b) L.Ruzicka, Helv.Chim.Acta, 6, 492 (1923); (c) E.H.Farmer and D.A.Sutton, J.Chem.Soc., 116 (1942); (d) L.Ruzicka and E.Capato, Helv.Chim.Acta, 8, 259 (1925); (e) Y-R. Naves, ibid., 49, 1029 (1966); (f) C.D.Gutsche, J.R.Maycock and C.T.Chang, Tetrahedron, 24, 859 (1968).

2), E.Demole, P.Enggist and Mlle.C.Borer, Helv.Chim.Acta, 54, 1845 (1971).

3), B.Tomita, Y.Hirose and T.Nakatsuka, Mokuzai Gakkaishi, 15, 47 (1969). The authors are indebted to Dr.B.Tomita, Tokyo Univ., for comparison of the i.r. spectra.

4), B.Tomita and Y.Hirose, Tetrahedron Lett., 143 (1970).

5), N.H.Andersen and D.D.Syrdal, ibid., 2277 (1970).

6), B.Tomita, T.Isono and Y.Hirose, ibid., 1371 (1970).

7), N.H.Andersen, Phytochemistry, 9, 1325 (1970).

8), (a) B.Tomita and Y.Hirose, Abstracts of TEAC, p 143 (1968); (b) B.Tomita, Y. Hirose and T.Nakatsuka, ibid., p 65 (1970).

9), K.Kafuku and N.Ichikawa, J.Chem.Soc.Japan, 54, 1011 (1933).

10), F.M.Couchman, A.R.Pinder and N.H.Bromham, Tetrahedron, 20, 2037 (1964).

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