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CONVERSION OF DIHYDROALANTOLACTONE TO EREMOPHILANE-TYPE DERIVATIVES: A BIOGENETIC-TYPE TRANSFORMATION

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An eudesmane-type intermediate(i) has been postulated to participate in the biogenesis of an eremophilane-type sesquiterpenoid(via cation (ii))[1]. The pathway from (i) to (ii) is said to involve the 1,2-shift of angular methyl group and such methyl migration has also been considered to occur during the biogenesis of various types of terpenoids and steroids[2]. On the other hand, a terminal epoxide function has been paid much attention as an initiating site in the biological formation of terpenoid skeleton[3]. In connection with the concept, several efforts have been made for the purpose of constructing the eremophilane or related carbon framework[4]. However, no work which effects the formation of an eremophilane skeleton directly from an eudesmanoid precursor has been documented.

As a continuation of our study on the biogenetic-type transformation leading to the natural terpenoid[5], we have conducted the conversion of an eudesmane derivative aiming at an eremophilane-type sesquiterpenoid. After several attempts, the object has been accomplished as described in this communication.

First, a benzoate[I] and γ-eudesmol[II] were treated under a variety of conditions. However, all the attempts did not bring about the desired result. Next, an epoxide[IV][4c,6] prepared from dihydroalantolactone[III][7] was chosen as a starting material. In this case, the rearrangement formally expected through a cation (iii) would primarily, for example, give rise to the substances of types (iv)~(xii)(without stereochemistry, R= H or CHO). Treatment of IV in HCOOH-acetone mixture at reflux for 2 hours followed by silica gel chromatography furnished three products A, B, and C, in the respective yields of 10%, 34%, and a few percent[8].

Product A, $C_{16}H_{22}O_4$, mp 114-116°, $[\alpha]_D^{18°}$ -0.7°($CHCl_3$), IR($CHCl_3$, cm^{-1}): 1768(γ-lactone),

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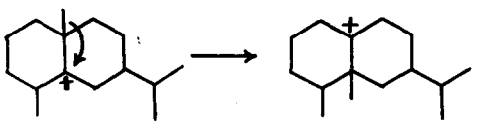
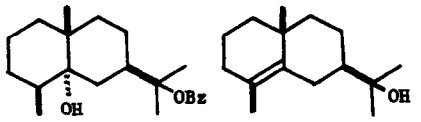
1715(formate), 1640(double bond); Mass: m/e 232(M^+-COOH, highest peak), 143(base peak); PMR($CDCl_3$, 100 MHz, τ): 1.94(1H, s, formyl), 4.49(1H, m, vinyl proton), 4.76(1H, d, J= 4 Hz, >CH-OCHO), 5.36(1H, d.t, J= 5 & 6, >CH-O-CO-), 8.64(3H, d, J= 7, secondary methyl), 9.04(3H, s, tertiary methyl), 9.18(3H, d, J= 6, secondary methyl), shows the absence of vinyl methyl, terminal methylene, and free hydroxyl and the presence of two secondary and one tertiary methyls as based on its physical properties. Therefore, it has been assumed that the product A possesses the type (iv) carbon framework and the assumption has been substantiated by the following decoupling experiment.

Thus, the irradiation at 4.49τ varies the signals centered at 7.26τ (2H + 1H, m) and 7.95 τ (2H, m), while the irradiations around 7.26τ result in the changes: a multiplet at 4.49τ (1H) to a clear triplet(J= 4), a doublet at 4.76τ (1H, J= 4) to a singlet, and a double triplet at 5.36τ (1H) to a singlet-like signal. On irradiation at 7.95τ, a multiplet at 4.49τ (1H) changes to a broad singlet($W_{\frac{1}{2}}$ = 4 Hz, due to long range coupling), whereas the irradiation at 5.36τ varies the signal pattern of a multiplet at 7.26τ (3H). It is noted that the irradiation at 4.76τ varies only the signal pattern at 7.26τ. Furthermore, the similar signal pattern as at 5.36τ (d.t) in product A is observed in the spectra of III, product B[VI], and product B acetate[VIII](vide infra). These observations along with the IR data have assured the retention of lactone ring, thus putting forward the partial structure(xiii) for the product A. Since two secondary methyl functions of IV have been considered to be preserved in the product A(8.64τ and 9.18τ), the plane structure(xiv) has become rational for the product A. In addition to mechanistic consideration(xv), the vicinal coupling constant(J= 4) between C_6-H and C_7-H and the change of a multiplet at 7.02τ (1H, C_{11}-αH) to a doublet($J_{7,11}$= 10) upon irradiation at 8.64τ (C_{11}-βCH_3) have finally settled the structure V for the product A.

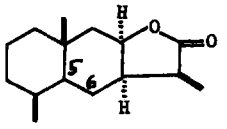
Product B, $C_{15}H_{22}O_3$, mp 113-114.5°, $[\alpha]_D^{28°}$-68.4°($CHCl_3$), IR($CHCl_3$, cm^{-1}): 3620, 3540(hydroxyl), 1766(γ-lactone); Mass: m/e 250(M^+), 158(base peak), exhibits the resembled physical properties to V except lacking the formate function. On K_2CO_3-MeOH hydrolysis V gave the product B while on acetylation the product B furnished a monoacetate[VII], $C_{17}H_{24}O_4$, glassy, $[\alpha]_D^{26°}$-16.3°($CHCl_3$); IR($CHCl_3$, cm^{-1}): 1767(γ-lactone), 1725(acetate), 1655(double bond); PMR ($CDCl_3$, 60 MHz, τ): 4.54(1H, m, C_1-H), 4.90(1H, d, J= 5, C_6-H), 5.30(1H, m, C_8-H), 7.96(3H, s, OAc), 8.69(3H, d, J= 7, C_{11}-CH_3), 9.05(3H, s, C_5-CH_3), 9.17(3H, d, J= 6, C_4-CH_3). These features are in accord with the structure VI for the product B.



(i) (ii)



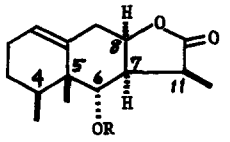
I II



III : Δ^5

IV : 5α,6α-epoxide

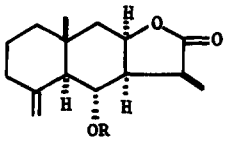
X : 5α-H, 6α-OH



V : R = CHO (product A)

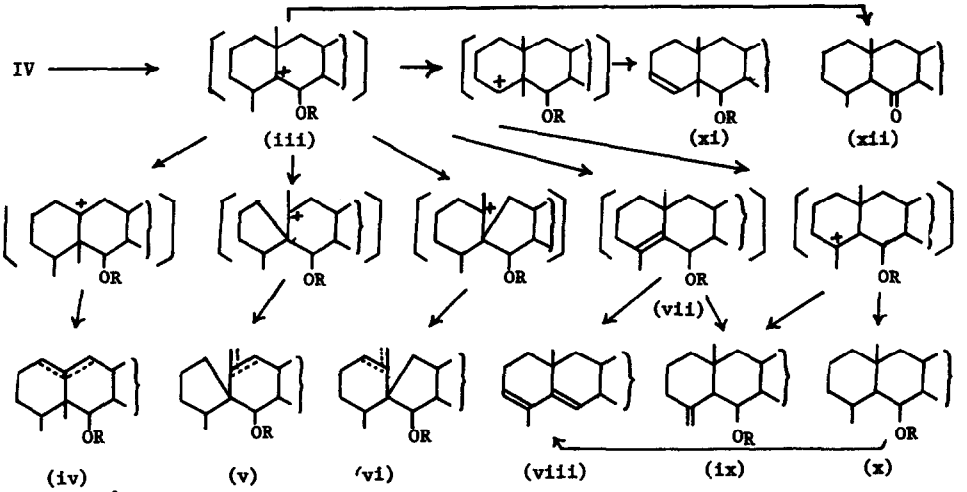
VI : R = H (product B)

VII : R = Ac



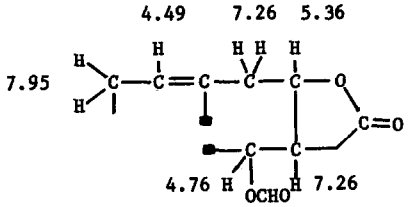
VIII : R = H (product C)

IX : R = Ac

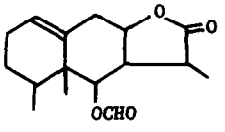


(iii) (xi) (xii)

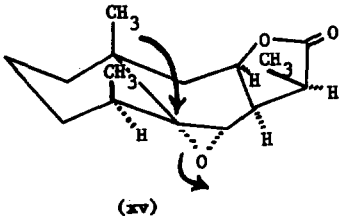
(iv) (v) (vi) (vii) (viii) (ix) (x)



(xiii)



(xiv)



(xv)

■ denotes a quaternary carbon atom

Product C, $C_{15}H_{22}O_3$, mp 131.5-133°, Mass: m/e 250(M^+), 147(base peak), has been assumed to be a compound of type (ix) on the basis of its physical properties: IR(KBr, cm^{-1}): 3480(hydroxyl), 1754(γ-lactone), 1638, 901(terminal methylene); PMR($CDCl_3$, 60 MHz, τ): 4.92, 5.32(1H each, br.s, terminal methylene), 5.43(1H, m, >CH-O-CO-), 6.14(1H, d.d, J= 11 & 9, >CH-OH), 7.14 (1H, quintet, J= 7.2, >CH-CH-CH_3), 8.58(3H, d, J= 7.2, secondary methyl), 9.15(3H, s, tertiary methyl). It gave a monoacetate[IX], $C_{17}H_{24}O_4$, mp 188-189°; IR($CHCl_3$, cm^{-1}): 1770(γ-lactone), 1728(acetate). Eventually, the product C has been assigned VIII[9] since it was catalytically hydrogenated to a dihydro derivative being identical with a compound[X] prepared from III via hydroboration.

The conversion of VI to a natural eremophilane derivative is in progress. It is interestingly pointed out that the present transformation would provide a new synthetic route to an eremophilane-type sesquiterpenoid via a precursory eudesmane system.

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References and Footnotes

1) a) R.Robinson,"The Structural Relations of Natural Products", Clarendon, Oxford, 1955, p. 12. b) J.B.Hendrickson, Tetrahedron, 7, 82(1959). c) W.Parker, J.S.Roberts, and R.Ramage, Quart. Rev., 21, 331(1967).

2) J.H.Richards and J.B.Hendrickson,"The Biosynthesis of Steroids, Terpenes, and Acetogenins", W.A.Benjamin, Inc., New York, 1964.

3) E.E.van Tamelen, Accounts of Chem. Res., 1,111(1968).

4) a) C.H.Heathcock and T.R.Kelly, Tetrahedron, 24, 3753(1968). b) G.Mehta, G.L.Chetty, U.R. Nayak, and S.Dev, Tetrahedron, 24, 3775(1968). c) P.Vita-Finzi, Y.Kashman, E.Glotter, and D.Lavie, Tetrahedron, 24, 5847(1968). d) H.Hikino, T.Kohama, and T.Takemoto, Tetrahedron, 25, 1037(1969). e) H.W.Whitelock,Jr. and A.H.Olson, J. Am. Chem. Soc., 92, 5383(1970). f) D.J.Dunham and R.G.Lawton, J. Am. Chem. Soc., 93, 2075(1971).

5) a) I.Kitagawa, K.Kitazawa, and I.Yosioka, Tetrahedron, 28, 907(1972). b) I.Kitagawa, K.Kitazawa, K.Aoyama, M.Asanuma, and I.Yosioka, Tetrahedron, 28, 923(1972).

6) Identified with an authentic sample kindly provided by Dr. D.Lavie of the Weizmann Institute of Science, Israel, to whom the authors' thanks are due.

7) A generous gift of Dr. K.Tanabe of Sankyo Co., Ltd. to whom the authors are grateful.

8) The yield of product C varies due to the subtle difference of reaction condition, however, the true reason is still obscure.

9) The C_{11}-βCH_3 configuration of VIII, IX, and X is provisionally based on the coupling constant(J= 7.2) between C_{11}-H and C_{11}-CH_3 of VIII.