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SKELETAL REARRANGEMENT OF FURANOEREMOPHILANE-6β,10β-DIOL INTO FARFUGIN A AND FARFUGIN B

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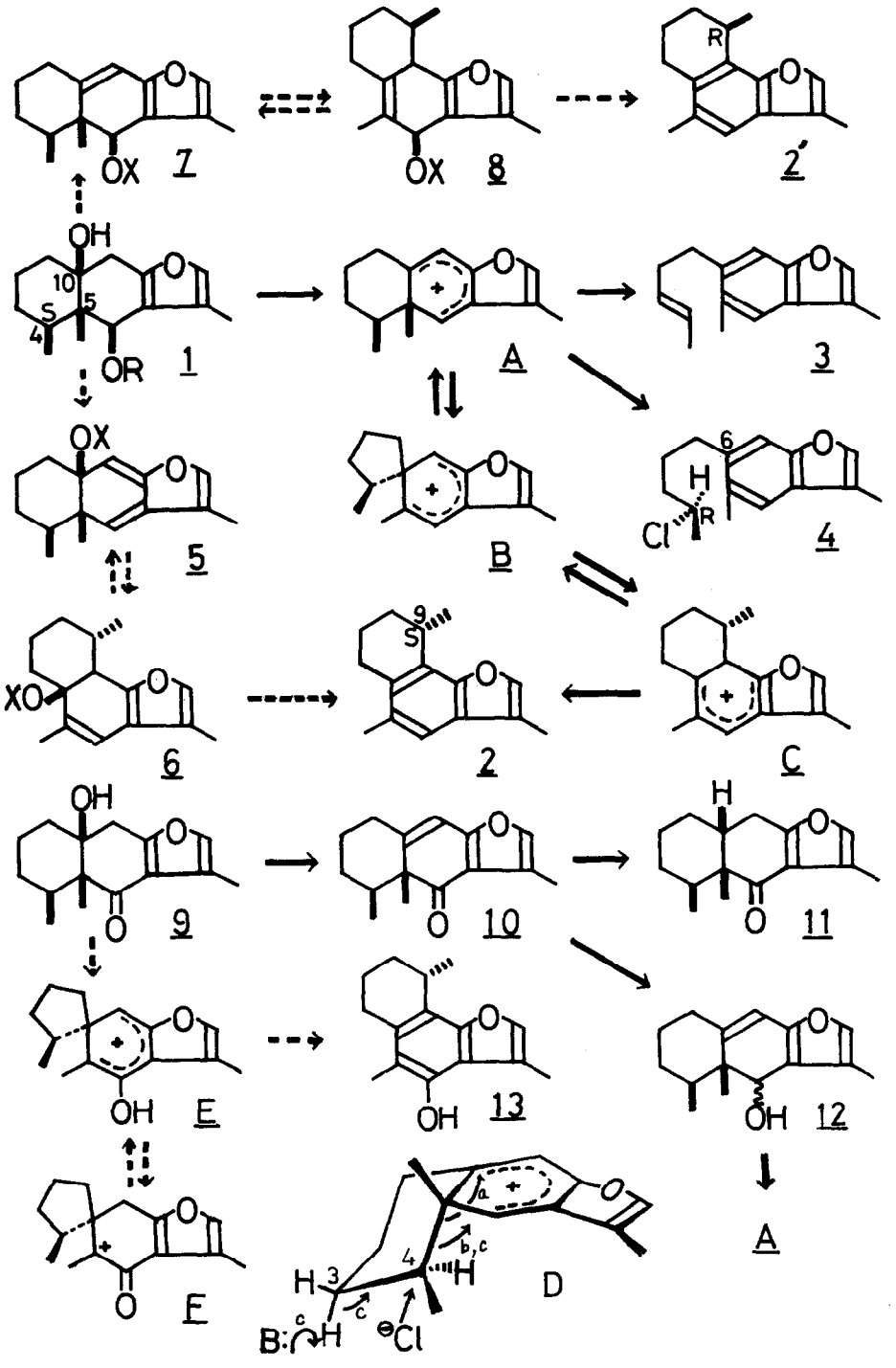
During the course of the structural investigation of furanoeremophilane-6β, 10β-diol (1, R = H),[1] we have found that 1 (R = H) is readily transformed into farfugin A (2)[2], farfugin B (3)[2] and another benzofuran (4) on dehydration with $POCl_3$. We wish to report here the mechanism of these skeletal rearrangements.

Treatment of 1 (R = H) [$C_{15}H_{22}O_3$, m.p. 122°, $[\alpha]_D$ + 58°(EtOH)] with $POCl_3$ in pyridine at 110° under N_2 gave rise to three benzofuran derivatives; 2 [$C_{15}H_{18}O$, m.p. 78 - 79°, $[\alpha]_D$ + 32°(EtOH); yield after isolation 23 %], 3 [$C_{15}H_{18}O$, an oil; y. 34 %] and 4 [y. 15 %], two of which were identified as farfugin A and B[2] by comparison of their spectral data. The third one, $C_{15}H_{19}OCl$, a colorless oil, $[\alpha]_D$ - 20°(EtOH), was found to be 6-(4-chloropentyl)-3,5-dimethylbenzofuran (4) on the basis of its spectral properties.[3] These products (2, 3 and 4) were also formed from 10β-hydroxy-6β-methoxyfuranoeremophilane (1, R = CH_3) and 10β-hydroxy-6β-acetoxyfuranoeremophilane (1, R = Ac) by the same treatment. Treatment of 1 (R = H) with trace of HCl in acetone at room temperature gave three benzofurans (2, 3 and 4) though in low yield (TLC).

The fact that both 2 and 4 are optically active is of interest in connection with the mechanism of these skeletal rearrangements. The migrating center at C-9 in 2 must be either (i) unchanged or (ii) inversed during the transformation of 1 into 2. In the former case (i), this rearrangement would be accounted for by two successive 1,2-alkyl shifts via a spiro intermediate (B)[4], or by a 1,5-sigmatropic shift[5] (via 5 and 6)?[6] In the latter case (ii), this transformation might involve a 1,3-sigmatropic shift[5] (route 1→7→8→2')[6].


OX 7
OX 8
R
2'
OH
10
5
4
OR 1
A
3
OX
5
B
6
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R
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4
XO
6
9
S
2
C
OH
O 9
O 10
H
O 11
OH E
OH 13
OH 12
A
O F
H 3
4
H
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D
B:
c
H
c
⊖Cl

The absolute configuration at C-9 in farfugin A (2) has been shown to be (S) as reported in the preceding paper,[7] while that at the chlorine-substituted carbon in 4 (with negative sign of $[\alpha]_D$) is deduced to be (R) by application of Brewster rule.[8] However, the absolute configuration at C-4 in the diol (1, R = H) was left undetermined.[1] Full evidence for this configuration was obtained by correlation of 1 (R = H) with ligularone (11)[9] as follows. The diol (1, R = H) was oxidized with CrO_3 in pyridine to give a hydroxyketone (9), m.p. 147.5 - 148°, $[\alpha]_D$ + 31°(EtOH), which on dehydration with $POCl_3$ in pyridine gave 10, m.p. 109 - 109.5°, $[\alpha]_D$ - 410°(EtOH). Hydrogenation of 10 over Pd-C in AcOEt afforded a dihydro derivative, $[\alpha]_D$ - 58°($CHCl_3$), which was found to be identical with ligularone (11)[9] in all respects. Therefore, the absolute configuration of the diol was established as depicted in 1 (R = H); i.e. it has (S)-configuration at C-4. The configuration of migrating center was thus demonstrated to be unchanged before and after rearrangement.

The absolute configuration of compounds in question (1, 2 and 4) being established, it is adequate to discuss the mechanistic aspects of this rearrangement (cf. D). The fact that the configuration at C-4 in 1 is retained in transformation of 1 into 2 shows the reaction pathway (i) must be followed during the rearrangement rather than the course (ii). Reduction of 10 with $LiAlH_4$ gave an alcohol (12), treatment of which under the same conditions described for 1 afforded fairly 2, 3 and 4. This fact supports strongly the pathway via a cyclohexadienyl cation (A)[10] (not the course involving 1,5-sigmatropic shift). Thus, the elimination of hydroxyls (or their equivalents) would give rise to the cyclohexadienyl cation (A). Fate of this cation (A) may be explained as follows. (a) Migration of C-4 - C-5 bond affords a spiro intermediate (B) which would be further transformed into another cation (C). Elimination of proton from C, being irreversible process, furnishes 2 in a fair yield. The preference of more highly substituted carbon atom in 1,2-shift is well documented.[11] (b) Nucleophilic substitution is effected at C-4 by Cl^- from less hindered side with concomitant aromatization of ring B. This process would lead to a formation of 4(R)-chloropentyl side chain in 4. (c) Abstraction of 3α-H with aromatization of ring B gives rise to trans-pentenyl side chain[2] in 3.[12]

Dehydration of 9 under the same conditions gave solely a normal product (10). No phenol (13), which might be formed by intermediacy of an unstable cation (E) (equivalent to cation F), was obtained.

In conclusion, transformation of 1 into 2, 3 and 4 can be best accounted for by intermediacy of the cyclohexadienyl cation A as in the case of dienone-phenol rearrangement.[13]

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3. MS: M^+ at m/e 252 and 250 with intensity ratio 1 : 3. Base peak at m/e 159. UV(EtOH): λ_{max} 252, 282 and 292 nm (ε 10600, 3400 and 3900). IR(nujol): 1630, 1580, 1130 and 1090 cm^{-1}. PMR($CDCl_3$; δ in ppm): 1.50 (d, J = 7.5 Hz; $C\underline{H}_3$-CHCl-), 2.19 (d, J = 1.5 Hz; $C_{(3)}$-$C\underline{H}_3$), 2.40 (s; $C_{(5)}$-$C\underline{H}_3$), ~4.0 (m; CH_3-$C\underline{H}$Cl-) and ~7.25 (m; $C_{(2)}$-H, $C_{(4)}$-H and $C_{(7)}$-H).
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5. R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie GmbH, Weinheim (1970).
6. X = -$POCl_2$, -POCl-, etc. for 5 and 6 ; X = -CH_3, -Ac, -$POCl_2$, -POCl-, etc. for 7 and 8.
7. M. Tada, Y. Moriyama, Y. Tanahashi and T. Takahashi, Tetrahedron Lett. 1972: the preceding paper.
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9. H. Ishii, T. Tozyo and H. Minato, Tetrahedron 21, 2605 (1965). Cf. L. Novotný, J. Jizba, V. Herout, F. Sorm, L. H. Zalkow, S. Hu and C. Djerassi, Tetrahedron 19, 1101 (1963).
10. e.g. V. P. Vitullo and N. Grossman, J. Amer. Chem. Soc. 94, 3844 (1972). Cf. refs. 4, 11 and 13, and a large number of reports on dienone-phenol rearrangement in steroids and terpenes.
11. e.g. R. B. Woodward, H. H. Inhoffen, H. O. Larson and K. Menzel, Ber. 86, 594 (1953); S. M. Bloom, J. Amer. Chem. Soc. 80, 6280 (1958).
12. Concerted mechanism involving elimination of 10- and 6-hydroxyls (or their equivalents) with concomitant rearrangements (a), (b) and (c) may also result in the same products. However, this would be less plausible by consideration of the formation of 2, 3, and 4 from 12, as described above.
13. The presence of two stage 1,2-alkyl shifts in the dienone-phenol rearrangement of a cyclohexadienyl cation was elegantly shown by Woodward et al. [R. B. Woodward, in "Perspectives in Organic Chemistry", p. 155, ed. by A. Todd, Interscience, New York (1956)]