Skeletal Rearrangement of Furanoeremophilane-6β,10β-diol into Farfugin A, Farfugin B, and 6-[(4*R*)-Chloropentyl]-3,5-dimethylbenzofuran[1]

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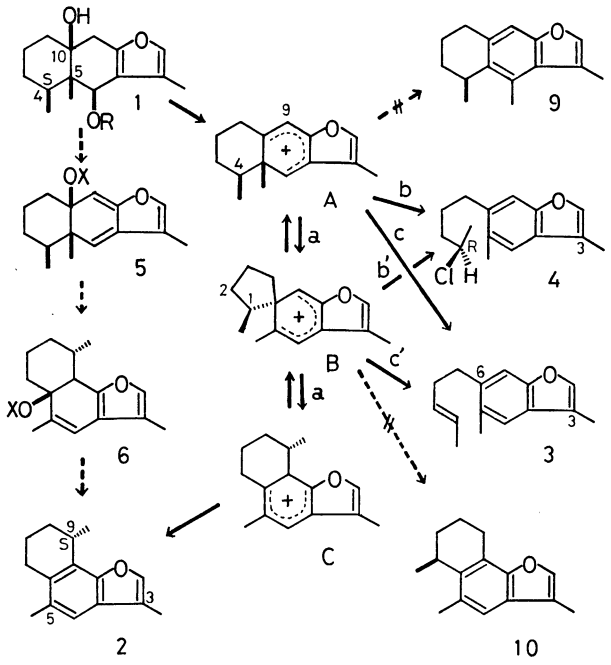
Treatment of furanoeremophilane-6β,10β-diol (**1**; R=H) with phosphoryl chloride in pyridine at 110 °C gave farfugin A (**2**; yield: 23%), farfugin B (**3**; y: 34%), and 6-[(4*R*)-4-chloropentyl]-3,5-dimethylbenzofuran (**4**; y: 15%). A mechanism of formation of these three compounds (**2**, **3**, and **4**) is discussed.

Furanoeremophilane-6β,10β-diol (**1**; R=H)[2] is a sesquiterpene of eremophilane-type isolated from *Ligularia japonica* Less., while farfugin A (**2**)[3] and farfugin B (**3**)[3] are benzofuran derivatives contained in *Farfugium japonicum* (L.) Kitam. In connection with a structure investigation of **1** (R=H), we found that farfugin A, farfugin B, and another benzofuran (**4**) were formed on dehydration of **1** (R=H) with phosphoryl chloride. In the present paper we wish to report the mechanism of these skeletal rearrangements.

The diol (**1**; R=H) was treated with phosphoryl chloride in pyridine at 110 °C under nitrogen to give three benzofuran derivatives (**2**, **3**, and **4**). The two products, **2** (yield: 23%), mp 78—79 °C, $[\alpha]_D$+32° (EtOH), and **3** (y: 34%), an oil, proved to be identical with farfugin A (**2**) and farfugin B (**3**), respectively. The molecular formula $C_{15}H_{19}OCl$ of the third product (**4**; y: 15%), an oil, $[\alpha]_D$−20° (EtOH), was determined by elemental analysis and mass spectrometry. The UV spectrum of **4** is superimposable with that of **3**; this suggests the presence of a benzofuran moiety in **4** similar to that in **3**. The IR spectrum of **4** indicates the presence of a C–Cl group (795 cm^{-1}) and the absence of a *trans* –CH=CH– system. The PMR spectrum of **4** shows a doublet (J=7.5 Hz) at δ 1.50 due to a secondary methyl (CH_3–CHCl–) and a multiplet at δ 4.0 due to a proton on the chlorine-bearing carbon (CH_3–CHCl–), while a multiplet at δ 5.45[3b] due to a *trans* olefin system (–CH=CH–) observed for **3** is absent. The other PMR spectral data of **3** are closely related to those of **4**. The observation shown above led to the structure **4** for the third product. The absolute configuration at the chlorine-substituted carbon in **4** (with negative sign of $[\alpha]_D$) was deduced to be (*R*) by application of Brewster rule.[4]

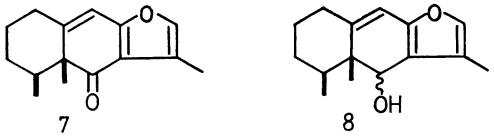
A similar treatment of 10β-hydroxy-6β-methoxyfuranoeremophilane (**1**; R=CH_3)[2] and 6β-acetoxy-10β-hydroxyfuranoeremophilane (**1**; R=Ac)[2] yielded also the three benzofuran derivatives (**2**, **3**, and **4**) (detected by TLC). When **1** (R=H) was treated with trace of hydrochloric acid in acetone at room temperature, the formation of these compounds (**2**, **3**, and **4**) was observed by TLC examination along with tarry products.

The fact that both **2** and **4** are optically active is of interest in view of the mechanism of these skeletal rearrangements. The absolute configuration at $C_{(4)}$ of the diol (**1**; R=H) and the absolute stereochemistry at $C_{(9)}$ of farfugin A (**2**) have recently been reported to be both (*S*).[2b,5] The configuration of the migrating center was thus shown to be retained before and after the transformation. The formation of **2** from **1** would be explained by two successive 1,2-alkyl shifts involving a spiro intermediate (**B**),[6] or by a 1,5-sigmatropic shift[7] *via* **5** and **6** (X=$POCl_2$ or other phosphate esters) (Scheme 1).



Scheme 1.

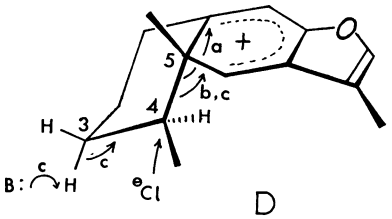
Reduction of furanoeremophil-9-en-6-one (**7**)[2b] with lithium aluminium hydride gave the corresponding alcohol (**8**), which was treated with phosphoryl chloride under the same conditions described for **1** (R=H). The three benzofuran derivatives (**2**, **3**, and **4**) were fairly obtained in a similar ratio to that observed for the rearrangement products of **1** (R=H). This fact strongly suggests that these three benzofurans are formed from an intermediate cyclohexadienyl cation (**A**),[8] which could be produced from **8** by elimination of a hydroxyl (or its equivalents). The pathway through the cation **A** would thus be favorable rather than the route involving 1,5-sigmatropic shift.



The presence of two stage 1,2-alkyl shifts through a spiro intermediate in the dienone-phenol rearrangement of a cyclohexadienyl cation has elegantly been demonstrated.[9,10] In an acid-catalyzed dienone-phenol rear-

rangement the medium affects the products.[11,12] A preferential migration, especially favored under the anhydrous conditions, of the more highly substituted carbon atom in the rearrangement was demonstrated.[9-12]

The mechanism of the rearrangement of **1** into **2**, **3**, and **4** could therefore be well rationalized as follows. The elimination of hydroxyls (or their equivalents) from **1** would give rise to the cyclohexadienyl cation **A** (depicted as **D**), which would then suffer rearrangements to form the three benzofuran derivatives (**2**, **3**, and **4**). (a) A migration of $C_{(4)}$–$C_{(5)}$ bond in **A** gives a spiro intermediate (**B**)[9-11] which would be further rearranged into another cation (**C**). An elimination of a proton from **C** affords farfugin A (**2**) whose configuration at $C_{(9)}$ is (*S*) (pathway a). Two processes could account for the formation of both **4** and **3**. (b and/or b') A S_N2 type substitution by Cl^- is effected at the secondary methyl carbon of **A** (path b) and/or of **B** (path b') with concomitant aromatization of ring B. These pathway would give the (4*R*)-4-chloropentyl side chain in **4**. (c and/or c') An abstraction of $C_{(3\alpha)}$–H from **A** with aromatization of ring B would lead to a formation of the *trans*-3-pentenyl side chain[3b] in farfugin B (**3**) (path c). An alternative route involving an elimination of $C_{(2)}$–H from **B** accompanied with aromatization could produce a mixture of isomers with the *cis* and *trans* side chains. The *cis*-isomer would then isomerize under the reaction conditions to give **3** (path c'). A choice between the two routes (between b and b', and between c and c') for each formation of **4** and **3**, remained undecided (*cf.* **D** and Scheme 1).



D

In the rearrangement of the diol (**1**; R=H), benzofuran derivatives such as **9**[13] and **10** might be expected to be produced form **A** and **B**, respectively. This was, however, contrary to the observation. This evidence could be interpreted by the preferential migration (or bond-scission) of the more highly substituted carbon atom[9-12] ($C_{(4)}$ of **A**, or $C_{(1)}$ of **B**), whose rearrangement would be especially pronounced in anhydrous conditions ($POCl_3$–pyridine), to afford **2** (**3**, and **4**).

In conclusion, the conversion of **1** into **2**, **3**, and **4** can be best explained by an intermediacy of the cyclohexadienyl cation **A** as in the case of dienone-phenol rearrangement.[14]

Experimental

IR spectra were measured using a Hitachi EPI-G2 spcetrometer. Optical rotation was measured on a JASCO DIL-SL polarimeter. Mass spectra were taken on a Hitachi RMU-6-Tokugata mass spectrometer with a direct inlet system operating at 70 eV. PMR spectra were measured using a JEOL PS-100 (100 MHz). Thin layer chromatography (TLC) was carried out on Kieselgel PF_{254} (E. Merck, Darmstadt). For column chromatography Wakogel 200 (Wako Pure Chemical Co.) was used. All mps were determined on a hot block and reported uncorrected.

Treatment of Furanoermophilane-6β,10β-diol (**1** : *R*=*H*) *with Phosphoryl Chloride.* To a solution of the diol (**1** : R=H; 67 mg)[2] in pyridine (2 ml), phosphoryl chloride (0.2 ml) was added dropwise with stirring, and the mixture was heated under nitrogen at 110 °C (bath temperature) for 1 h. The cooled reaction mixture was poured into a mixture of ice and water and extracted with ether. The organic layer was washed with 2 M hydrochloric acid and then with water, dried over anhydrous sodium sulfate, and evaporated to give a residue, which was chromatographed on a column of silica gel. Elution with petroleum ether gave farfugin A (**2**; 13 mg; y: 23%) and farfugin B (**3**; 19 mg; y: 34%) successively. These compounds (**2** and **3**) proved to be identical (by IR, UV, PMR, TLC, and mass spectrometry) with natural farfugin A[3b] and farfugin B[3b] respectively. Further elution with the same solvent yielded 6-[(4*R*)-4-chloropentyl]-3,5-dimethylbenzofuran (**4**; 10 mg; y: 15%), an oil, $[\alpha]_D$ −20° (*c* 1.0, EtOH); IR (liquid) 1630, 1580, 1132, 1090, and 795 cm^{-1}; UV (EtOH) λ_{max} 252 nm (ε 10600), 258 (sh), 276 (sh), 282 (3400), 285 (3300), and 292 (3800); PMR ($CDCl_3$) δ 1.50 (3H, d, J=7.5 Hz; $\underline{CH_3}$–CHCl–), 2.19 (3H, d, J=1.2 Hz; $C_{(3)}$–CH_3), 2.40 (3H, s; $C_{(5)}$–CH_3), *ca.* 4.0 (1H, m; CH_3–$\underline{CH}$Cl–), *ca.* 7.2—7.3 (3H, $C_{(2)}$–H, $C_{(4)}$–H, and $C_{(7)}$–H), and *ca.* 2.5—3.0 [6H, -$(CH_2)_3$-]; mass spectrum *m/e* 252 and 250 (M^+; in an intensity ratio of *ca.* 1 : 3) and 159 (base peak). Found: C, 71.70; H, 7.58; Cl, 14.42%. Calcd for $C_{15}H_{19}OCl$: C, 71.84; H, 7.64; Cl, 14.14%. Other benzofuran derivatives such as **9** and **10** were not obtained.

Gas chromatographic examination before effecting the column chromatographic separation showed that the ratio of these products (**2**, **3**, and **4**) was 1.0 : 1.5 : 0.4 based on the integrated area of the peak for each product [column: Diasolid H-523, 5(mm)×1.5(m); column temperature: 170 °C; detection: FID; carrier gas: N_2, 66 ml/min; instrument: Shimadzu GC-4A PF].

Treatment of 10β-Hydroxy-6β-methoxyfuranoeremophilane (**1** : *R*=*CH_3*) *and 6β-Acetoxy-10β-hydroxyfuranoeremophilane* (**1** : *R*=*Ac*) *with Phosphoryl Chloride.* A methoxy alcohol (**1**; R=CH_3; 5 mg)[2] or an acetoxy alcohol (**1**; R=Ac; 5 mg)[2] was treated with phosphoryl chloride (0.05 ml) in pyridine (0.5 ml) at 110 °C for 1 h. In each case the reaction mixture gave, after the work-up described above, a residue which was shown to be a mixture of the three benzofuran derivatives (**2**, **3**, and **4**) by TLC examination.

Acid-Catalyzed Rearrangement of the Diol (**1**; *R*=*H*). To a solution of the diol (**1**; R=H; 5 mg)[2] in dry acetone (0.5 ml) was added a drop of concentrated hydrochloric acid at room temperature. The reaction mixture was treated as usual to give a residue, which was examined by TLC to show the formation of the three benzofurans (**2**, **3**, and **4**) and of tarry products formed probably by degradation of the furan ring.

Reduction of Furanoeremophil-9-en-6-one (**7**) *with Lithium Aluminium Hydride and Successive Treatment with Phosphoryl Chloride.* Lithium aluminium hydride (100 mg) was added to a solution of the ketone (**7**; 40 mg)[2b] in ether (10 ml), and the mixture was stirred under nitrogen at room temperature for 1 h. The excess of lithium aluminium hydride was decomposed with water, and the mixture was extracted with ether. The ethereal layer was washed with water and brine, and then dried over anhydrous sodium sulfate. On

removal of the solvent, an unstable oily alcohol (**8**; ν_{OH} 3500 cm^{-1}; one spot on TLC) was obtained, which without further characterization was dissolved in pyridine (0.5 ml). After addition of phosphoryl chloride (0.1 ml), the resulting mixture was heated under nitrogen at 110 °C for 1 h. The reaction mixture was treated as usual to give a residue, which was subjected to separation by preparative TLC to afford the three benzofurans (**2**, **3**, and **4**). The ratio of these products (**2**, **3**, and **4**) was determined to be 1.0 : 1.3 : 0.3 by gas chromatography (under the same conditions mentioned above) before effecting the TLC separation.

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