# The Transformations of Terpene Ketones by Oxygen. I. The Autoxidation of Fukinone

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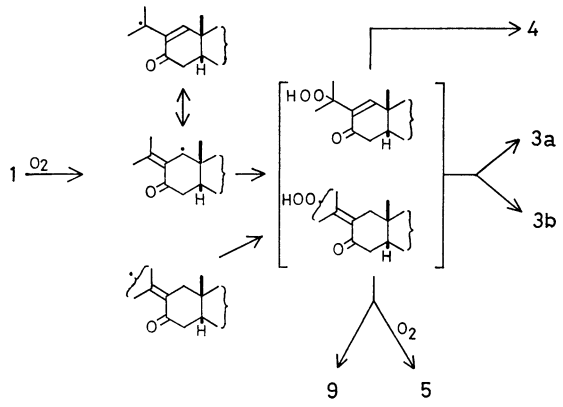
Fukinone, possessing a cisoid enone system, is susceptible to air oxidation. The oxidation products have been extensively examined and have been established as including diastereomeric epoxides, a hydroxy ketone (petasitolone), a lactol (8β-hydroxyeremophilenolide), and a peroxy hemiacetal. Also, the products were compared with those derived from the autoxidation of pulegone, a monoterpenic analogue of fukinone.

A fragrant oil, fukinone (**1**),[1] $C_{15}H_{24}O$, is rather sensitive to air. Even on storage, several polar spots appear on TLC. We have been interested in the autoxidation in connection with the biogenetic-type oxidation process. Furthermore, as little is known about the autoxidation of α,β-unsaturated ketones with an exo-cyclic double bond, we have studied the autoxidation of **1** in parallel with the base-catalyzed autoxidation.[2] Pulegone (**2**), with a similar enone system, has been widely studied;[3,4] hence, the autoxidation was reinvestigated in order to compare it with the products from **1**.

The autoxidation of the title compound, **1**, was achieved by heating it at 80—90 °C under a bubbling of air for 44 h. From the reaction mixture we isolated epoxides, $C_{15}H_{24}O_2$ (**3**), a hydroxy ketone, $C_{15}H_{22}O_2$ (**4**), and a lactol, $C_{15}H_{22}O_3$ (**5**) in 24.5, 3, and 3.5% yields respectively by column chromatography on silica gel.

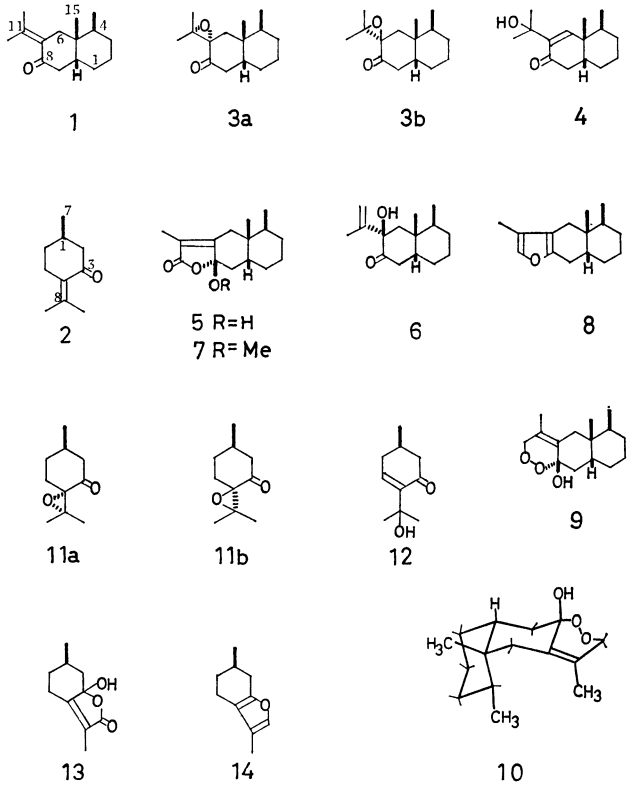
The epoxides, **3**, was shown by GLC analysis to be mixtures comprising approximately equal amounts of the diastereomers. **3** was separated into (**3a**) (mp 66—67 °C) and (**3b**) (mp 83—84 °C)[5] by repeated chromatogrphy on deactivated silica gel. Both the epoxides were identified by comparison with the authentic samples prepared by treating **1** with hydrogen peroxide in an alkaline solution.[6] The absolute configurations[5] previously proposed for fukinone epoxides, **3a** and **3b**, were finally settled by the X-ray analysis of the 7β-hydroxy-8-oxoeremophil-11(12)-ene (**6**)[7] prepared by the stereospecific cleavage of **3b** in the presence of *p*-toluenesufonic acid in dry benzene.[8]

The oily hydroxy ketone, **4**, was found to be identical with natural petasitolone[9] by a comparison of the IR and GLC.




Scheme 1.

The lactol, **5**,[10] showed a wide melting range (mp 180—200 °C), even after repeated recrystallizations. Therefore, **5** was transformed into the methoxylactone (**7**) by refluxing in methanol in the presence of a catalytic amount of hydrochloric acid, which was identical with 8β-methoxyeremophilenolide[10] prepared by the photosensitized oxygenation of furanoeremophilane (**8**)[11] in methanol. Accordingly the 8-hydroxyl and 8-methoxyl groups in both the lactones can be identified as β-configurations as in the **5** and **7** formulas.




In addition, **1** left in air for a long time afforded a peroxy hemiacetal (**9**) (mp 100—103 °C) besides **3**, **4**, and **5**. The structure for **9** was readily determined from the spectral and chemical properties. In the Dreiding-model inspection, the 8α- or 8β-substituents in the peroxy hemiacetal will force the *cis*-decalin system to adopt a nonsteroidal or a steroidal A/B *cis* chair/chair configuration respectively in a manner similar to that used in the case of eremophilenolides.[10,12] Therefore, on the basis of a similar relationship between the chemical shifts of 14- and 15-methyls, the peroxy hemiacetal was tentatively assigned to the stereoformula (**10**) bearing an 8β-hydroxyl group. The reduction

of **10** with triphenylphosphine gave furanoeremophilane (**8**), which occurs with **1** in the same plant,[11] implying a biosynthetic pathway to **8** from **1**. The hemiacetal, **9**, was itself rather stable in the crystalline state at room temperature, but it decomposed considerably in solution. The isolation of **9** suggests that the primary oxidation products of **1** are hydroperoxides; hence, the epoxides, **3a** and **3b**, the main products, are probably produced by the attack of the hydroperoxides on the alternate fukinone molecule.

The reinvestigation of the autoxidation of **2** was performed in a manner similar to that used for **1** and proved to afford products similar to those from **1**. Thus, the reaction mixture was separated to give epoxides (**11**), an oily hydroxy ketone (**12**), and a lactol (**13**) in 15, 6.4, and 28% yields respectively. The absolute configurations of α-epoxide (**11a**) (mp 57—58 °C) and β-epoxide (**11b**) (mp 53—54 °C) have previously been established.[13,14] The physical properties of **12** and **13** (mp 186—187 °C) were in good agreement with those of the photooxygenation product of **2**,[15] and of the autoxidation[4] or the photooxygenation[16] product of menthofuran (**14**) respectively.

From the above results, it seems that the autoxidation of **1** and **2** should proceed in the same manner, and that the autoxidation process of **1** is as depicted in Scheme 1.

## Experimental

All the melting and boiling points are uncorrected. The IR, UV, and mass spectra were taken with Hitachi EPI-G3, Shimadzu Spectronic 505, and Hitachi RMU-6 spectrophotometers respectively. The PMR spectra were recorded with a Hitachi R-20B (60 MHz) spectrometer, and the chemical shifts are reported in δ-values, with TMS as the internal reference. The optical rotations were measured with a Perkin-Elmer 141 polarimeter. The analytical and preparative GLC were performed with a Shimadzu GC-1C apparatus on a stainless steel column ($\phi$=3 mm). The TLC were run on silica gel (Merck Kieselgel G). The microanalyses were carried out in the analytical section of the Research Laboratory, Toyo Jozo Co., Ltd.

*Autoxidation of Fukinone (1).* Fukinone (**1**) (3.759 g) was oxidized without a solvent under the bubbling of air at 80—90 °C for 44 h. The resulting mixture (3.637 g) was chromatographed on silica gel (70 g). Elution with benzene afforded, successively, the recovered fukinone (**1**), a mixture of epoxides (**3a** and **3b**) (982 mg), a hydroxy ketone (**4**) (119 mg), and a lactol (**5**) (150 mg).

Each of the epoxides, (**3a**) and (**3b**), was obtained by repeated column chromatography on deactivated silica gel (Grade II), followed by recrystallization from light petroleum. Both epoxides, **3a** (mp 66—67 °C) and **3b** (mp 83—84 °C), were identical in all respects (IR, PMR, and mixed-melting-point determination) with authentic samples.[5]

The hydroxy ketone (**4**) was found to be identical with natural petasitolone[9] by a comparison of the IR and GLC results.

*Lactol (5)*:[10] Mp 180—200 °C, colorless prisms (from ethyl acetate), $[\alpha]_D^{23}$ +155° (*c*, 1.03, $CHCl_3$); IR($CHCl_3$): 3550, 3330, 1750, 1696, 1230 $cm^{-1}$; UV: $\lambda_{max}^{MeOH}$ 223 nm (ε, 25000); PMR ($CDCl_3$): 3.53 (s, OH), 1.77 (d, *J*=1.5 Hz, 12-Me), 1.02 (s, 15-Me), 0.77 (d, *J*=5.0 Hz, 14-Me).

Found: C, 72.15; H, 8.72%. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%.

*Methoxy Lactone (7).* A solution of the lactol (**5**) (86 mg) in methanol containing a catalytic amount of concentrated hydrochloric acid was refluxed for 2.5 h. The reaction mixture was then poured into water, and the deposited crystals (77 mg, 84%) were recrystallized from aqueous methanol; mp 99.5—100 °C as colorless needles; $[\alpha]_D^{23}$ +192° (*c*, 1.00, $CHCl_3$); MS: *m/e* 264 ($M^+$), *m/e* 236 (base peak); IR(KBr): 1760, 1695, 1180, 990 $cm^{-1}$; ($CCl_4$): 1763, 1700, 1177 $cm^{-1}$; UV: $\lambda_{max}^{MeOH}$ 223 nm (ε, 15000); PMR ($CCl_4$): 3.07 (s, OMe), 1.80 (d, *J*=1.5 Hz, 12-Me), 1.04 (s, 15-Me), 0.80 (d, *J*=6.0 Hz, 14-Me).

Found: C, 72.84; H, 9.07%. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15%. This compound was identical with the 8β-methoxyeremophilenolide (**7**) prepared from furanoeremophilane (**8**) by photosensitized oxygenation;[10] this was determined by a comparison of the IR, UV, and PMR, and by a mixed-melting-point determination.

*Isolation of Peroxy Hemiacetal (9).* Fikinone (**1**) (13.591 g) was left in air and in a dark place at room temperature for several months. The resulting oil was chromatographed on silica gel, and a polar part (with $R_f$ values less than 0.3; silica gel, benzene) was collected. The yellow viscous oil (3.164 g) was repeatedly chromatographed on silica gel, with benzene as the eluent, to give two fractions, one containing **3**, **4**, and **9**, and the other containing **4** and **5**. From each fraction, **5** and **9** were deposited as crystals in 131 mg and 107 mg yields respectively. **9** was recrystallized from light petroleum; mp 100—103 °C; long, colorless leaflets, $[\alpha]_D^{24}$ −46° (*c*, 0.98, $CHCl_3$); MS: *m/e* 252 ($M^+$), *m/e* 110 (base peak); IR ($CHCl_3$): 3555, 1055, 1048 $cm^{-1}$; PMR ($CDCl_3$): 4.74 and 3.99 (each dd, *J*=3.0 and 16 Hz, 12-$CH_2$), 2.90 (br s, OH), 1.67 (br s, 13-Me), 0.92 (s, 15-Me), 0.78 (d, *J*=6.0 Hz, 14-Me).

Found: C, 71.21; H, 9.46%. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59%.

*Reduction of Peroxy Hemiacetal (9) with Triphenylphosphine.* A solution of **9** (113 mg) and triphenylphosphine (229 mg) in benzene was refluxed for 8 h, and subsequently the solvent was evaporated *in vacuo*. The residue was extracted with light petroleum, and the extract (169 mg) was chromatographed on deactivated silica gel (Grade II, 5 g). Subsequent elution with light petroleum–ether (50:1) gave an oil (120 mg). Further purification by preparative TLC (silica gel; light petroleum–ether, 20:1) afforded furanoeremophilane (**8**) (16 mg, 17%), which was found to be identical with an authentic sample[11] by a comparison of the IR and GLC (SE-30, 2.6 m; column temperature, 155 °C; $H_2$-flow rate, 40 ml/min; retention time, 6.7 min).

*Autoxidation of Pulegone (2).* Pulegone (**2**) (1.330 g) was subjected to oxidation for 62 h in the same fashion as in the case of **1**. The resulting mixture (1.121 g) was chromatographed on silica gel (25 g) with benzene to give a mixture of epoxides (**11**) (222 mg) and a hydroxy ketone (**12**) (95 mg). Subsequent elution with benzene–ethyl acetate (50:1) gave a lactol (**13**) (44 mg).

A mixture of epoxides (**11**) was separated into two diastereomers, (**11a**) and (**11b**), by preparative GLC (PEG 20 M, 2.6 m; column temperature, 145 °C; $H_2$-flow rate, 45 ml/min; retention time; β-epoxide (**11b**): 12.4 min, α-epoxide (**11a**): 19.1 min). Both the epoxides, **11a** (mp 57—58 °C) and **11b** (mp 53—54 °C), were found to be identical with authentic samples[13] by a comparison of the IR, PMR, and GLC, and by a mixed-melting-point determination.

*Hydroxy Ketone (12)*:[15] Bp 130—140 °C (bath temperature)/15 mmHg, preparative GLC (PEG 20 M, 1.1 m; column temperature, 130 °C; $H_2$-flow rate, 72 ml/min; reten-

tion time, 6.8 min); IR(film): 3410, 1660 $cm^{-1}$; UV: $\lambda_{max}^{MeOH}$ 234 nm ($\varepsilon$, 7900); PMR($CCl_4$): 6.83 (m, 5-H), 3.73 (s, OH), 1.30 (s, 9- and 10-Me), 1.06 (d, $J$=4.0 Hz, 7-Me).

*Lactol (**13**)*:[4] Mp 186—188 °C, colorless prisms (from acetone); IR(KBr): 3325, 1735, 1693, 1195, 1120, 960 $cm^{-1}$; UV: $\lambda_{max}^{MeOH}$ 219 nm ($\varepsilon$, 16100); PMR (acetone-$d_6$): 2.95 (s, OH), 1.70 (d, $J$=1.0 Hz, Me-C=C), 0.93 (d, $J$=7.0 Hz, Me-CH). (Found: C, 65.75; H, 7.95%).

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## References

1) K. Naya, I. Takagi, Y. Kawaguchi, Y. Asada, Y. Hirose, and N. Shinoda, *Tetrahedron*, **24**, 5871 (1968).
2) The details will be presented in a subsequent paper.
3) N. Seragiotto, *Gazz. Chim. Ital.*, **47**, 150 (1917).
4) R. B. Woodward and R. H. Eastmann, *J. Am. Chem. Soc.*, **72**, 399 (1950).
5) K. Kobayashi, Y. Yamamoto, H. Miyanaga, and K. Naya, 23th National Meeting of the Chemical Society of Japan, Tokyo, April 1970, Abstr. No. 18337. The hydrate of **6b** showed a mp of 69.5—70.5 °C as colorless needles (from aqueous methanol).
6) K. Naya, M. Hayashi, I. Takagi, S. Nakamura, and M. Kobayashi, *Bull. Chem. Soc. Jpn.*, **45**, 3673 (1972).
7) The details of X-ray analysis will be published soon.
8) W. Reusch, D. F. Anderson, and C. K. Johnson, *J. Am. Chem. Soc.*, **90**, 4988 (1968).
9) K. Naya, F. Yoshimura, and I. Takagi, *Bull. Chem. Soc. Jpn.*, **44**, 3165 (1971).
10) K. Naya, N. Nogi, Y. Makiyama, H. Takashina, and T. Imagawa, *Bull. Chem. Soc. Jpn.*, **50**, 3002 (1977). Though the reason for the wide range remains unexplained, **10** should be identical with 8$\beta$-hydroxyeremophilenolide, mp 212—213 °C, $[\alpha]_D$ +157°.
11) K. Naya, M. Nakagawa, M. Hayashi, K. Tsuji, and M. Naito, *Tetrahedron Lett.*, **1971**, 296.
12) K. Naya, R. Kanazawa, and M. Sawada, *Bull. Chem. Soc. Jpn.*, **48**, 3220 (1975).
13) W. Reusch and C. K. Johnson, *J. Org. Chem.*, **28**, 2557 (1963).
14) G. W. K. Cavill and C. D. Hall, *Tetrahedron*, **23**, 1119 (1967).
15) K. H. Schulte-Elte, M. Gadola, and B. L. Müller, *Helv. Chim. Acta*, **54**, 1870 (1971).
16) C. S. Foote, M. T. Wuesthoff, S. Wexler, I. G. Burstain, R. Denny, G. O. Schenck, and K. H. Schulte-Elte, *Tetrahedron*, **23**, 2583 (1967).