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EPOXIDATION OF ALANTOLACTONE AND ISOALANTOLACTONE

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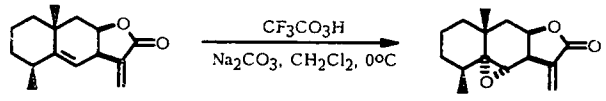
Alantolactone and isoalantolactone have been epoxidized with peracetic, m-chloroperbenzoic, and trifluoroperacetic acids. The structure of 4(15)-α-epoxyisoalactone has been established by an x-ray structural investigation.

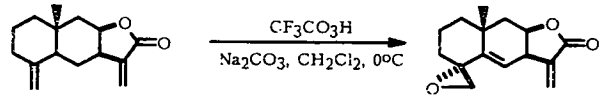
Alantolactone (**1**) and isoalantolactone (**2**) are sesquiterpenes widely distributed in Nature that exhibit a broad spectrum of biological activity. The antiulcer drug Alanton, consisting of a mixture of the alantolactones, is known in industry.

We have carried out the epoxidation of these lactones, using various epoxidizing agents — *m*-chloroperbenzoic acid (MCPBA), peracetic acid, and trifluoroperacetic acid (TFPAA). Under the conditions of the reaction with TFPAA at 0°C, epoxidation took place instantaneously, while in the cases of peracetic acid and of MCPBA the reaction took place considerably more slowly. Furthermore, according to TLC, in epoxidation with TFPAA only trace amounts of by-products were formed; i.e., the reaction was stereospecific. The yields of (**3**) and (**4**) amounted to 80 and 75%, respectively.

The stereochemistry of epoxide (**3**) was established by a comparative analysis of the PMR spectrum with literature information [2]. Table 1 gives the chemical shifts and coupling constants of epoxides (**3**) and (**4**). The use of a spectrometer with a frequency of 200 MHz also permitted an assignment of the signals of the H-9 and H-9′ protons. In the spectrum of (**3**) and that of (**4**) the signals of these protons appeared in the form of an individual doublet of doublets. For example, for epoxyisoalantolactone the H-9 and H-9′ signals at 2.15 and 1.45 ppm were split because of their interaction with one another and with the lactone proton, H-8. The coupling constants of these protons (15 Hz for (**3**) and 15.5 Hz for (**4**)) agree with the handbook values of the geminal constants for the protons of the cyclohexane fragment [3].



(**1**) (**3**)



(**2**) (**4**)

The α-orientation of the oxygen atom in (**4**) may be proposed on the basis of the following facts. In the first place, according to [4], after the epoxidation of telekin and isotelekin with perbenzoic acid, the α-epoxides are formed as the main products, the β-epoxides being formed in minor amounts. In the second place, the chemical shift of the angular methyl group at C-10 in (**4**) amounts to 0.95 ppm, which is comparable with the corresponding value of 0.97 ppm for 4(15)-α-epoxyisotelekin. In the case of 4(15)-β-epoxyisotelekin the signal of the angular methyl group is shifted downfield to 1.08 ppm through the descreening influence of the oxygen atom of the 4(15)-β-epoxide ring [4].

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TABLE 1. Details of the PMR Spectra of Compounds (3) and (4), 200 MHz, δ, $CDCl_3$

Compound	H-6	H-7	H-8	H-9 H-9′	H-13 H-13′	H-14	H-15 (H-15′)
(3)	2.88 (1H,d) J=2.5 Hz	3.63 (1H,dddd) J_1=9.0 Hz $J_2=J_3$=2.5 Hz J_4=3 Hz	4.66 (1H,ddd) J_1=9.0Hz J_2=4.5Hz J_3=2.0Hz	1.85 (1H, dd) J_1=15Hz J_2=4.5Hz 1.55 (1H, dd) J_1=15 Hz J_2=2.0Hz	6.38 (1H, d) J=3Hz 5.75 (1H, d) J=2.5Hz	1.10 (3H,s)	1.03 (3H, d) J=7.5Hz
(4)		2.86 (1H,m)	4.48 (1H,ddd) $J_1=J_2$=5Hz J_3=1.5 Hz	2.15 (1H, dd) J_1=15.5 Hz J_2=1.5 Hz 1.45 (1H, dd) J_1=15.5 Hz J_2=5 Hz	6.07 (1H, d) J=1.5Hz 5.51 (1H, d) J=1.0Hz	0.95 (3H,s)	2.63 (1H, dd) J_1=4.5Hz J_2=2.0Hz 2.50 (1H, d) J=4.5Hz

TABLE 2. Bond Lengths in Structure (4)

Bond	Å	Bond	Å
O1–C8	1.469(4)	C5–C6	1.521(4)
O1–C12	1.367(4)	C5–C10	1.551(4)
O2–C12	1.197(4)	C6–C7	1.544(5)
O3–C4	1.452(4)	C7–C8	1.536(5)
O3–C15	1.446(5)	C7–C11	1.494(5)
C1–C2	1.530(6)	C8–C9	1.508(5)
C1–C10	1.537(5)	C9–C10	1.542(4)
C2–C3	1.531(6)	C10–C14	1.533(5)
C3–C4	1.500(5)	C11–C12	1.483(5)
C4–C5	1.522(4)	C11–C13	1.321(5)
C4–C15	1.461(5)		

For a complete study of the stereochemistry of (4) we made an x-ray structural investigation. The general form of the (4) molecule is shown in Fig. 1. The bond lengths (Table 2) and valence angles (Table 3) are close to the usual values [5], with the exception of the angles C7C8C9 (117.2(3)°), C8C9C10 (116.8(3)°), and C8C7C11 (100.7(3)°). The distortion of these valence angles is obviously a consequence of the steric stresses arising because of the *cis*-linkage of rings *B* and *C* (torsional angle H7C7C8H8 −40(3)°), as shown previously [6]. The linkage of rings *A* and *B* is *trans* (torsional angle H5C5C10C14 − 179(2)°). The conformation of the six-membered ring *A* is close to an ideal chair (maximum value of the asymmetry parameter $\Delta C_2^{1,2}$=2.7°, $\bar{\varphi}$=56.0°; the torsional angles are given in Table 4. The conformation of ring *B* is a highly distorted chair: the torsional angles vary within the interval 60.8° ≤ | φ | ≤ 37.7° (Table 4). Of all the possible symmetry elements in ring *B* only the plane passing through the C5 and C8 atoms is retained (ΔC_S^5 = 2.1°), while the maximum asymmetry parameter $\Delta C_2^{6,7}$ amounts to 15.9°. Such pronounced distortion of ring *B* is a consequence of 1,3-interaction between the C-14 methyl group and the axially oriented O1 atom of the β-*cis*-linked lactone ring (the C14···O1 distance is 2.214 Å). An analogous distortion of ring *B* is observed in other *trans,cis*-linear eudesmanolides — for example, pulchellin C [6], subcardatolide C [7], and ivalin bromoacetate [8]. The conformation of the γ-lactone ring is an almost ideal 7β,8α-half-chair (ΔC_2^{12} = 2.3°).

Thus, on the epoxidation both of alantolactone and of isoalantolactone using TFPAA, PAA, and MCPBA the α-epoxy derivatives of these lactones are formed predominantly, while the reaction with trifluoroacetic acid takes place faster than with the other reagents.

EXPERIMENTAL

Samples of the alantolactones had been isolated previously from *Inula helenium* [9]. The mixture of (1) and (2) was separated on Chemapol silica gel impregnated with 10% of $AgNO_3$. The concentration of a solution of H_2O_2 was increased

TABLE 3. Valence Angles in Structure (4)

Angle	Degrees	Angle	Degrees
C8O1C12	109.3(3)	O1C8C7	104.1(3)
C4O3C15	60.5(2)	O1C8C9	110.7(3)
C2C1C10	112.2(3)	C7C8C9	117.2(3)
C1C2C3	111.1(3)	C8C9C10	116.8(3)
C2C3C4	110.4(3)	C1C10C5	108.5(3)
O3C4C3	115.0(3)	C1C10C9	108.1(3)
O3C4C5	115.6(3)	C5C10C9	107.2(2)
C3C4C5	113.7(3)	C1C10C14	109.8(3)
O3C4C15	59.5(2)	C5C10C14	112.8(3)
C3C4C15	120.1(3)	C9C10C14	110.3(3)
C5C4C15	121.3(3)	C7C11C12	107.4(3)
C4C5C6	114.4(3)	C7C11C13	129.9(3)
C4C5C10	110.2(2)	C12C11C13	122.7(3)
C6C5C10	112.1(3)	O1C12O2	121.7(3)
C5C6C7	112.3(3)	O1C12C11	108.2(3)
C6C7C8	111.9(3)	O2C12C11	130.1(3)
C6C7C11	109.6(3)	O3C15C4	59.9(2)
C8C7C11	100.7(3)		

TABLE 4. Torsional Angles in the Rings of Structure (4)

Angle	Degrees	Angle	Degrees
C10C1C2C3	-56.7(4)	C7C8C9C10	40.5(4)
C1C2C3C4	53.6(4)	C8C9C10C5	-48.7(4)
C2C3C4C5	-55.1(4)	C6C5C10C9	58.8(3)
C3C4C5C10	57.0(4)	O1C8C7C11	-31.5(3)
C4C5C10C1	-56.3(3)	C7C8O1C12	27.8(3)
C5C10C1C2	57.3(4)	C8O1C12C11	-11.7(3)
C10C5C6C7	-60.8(4)	O1C11C7C8	-9.7(6)
C5C6C7C8	47.5(4)	C8C7C11C12	25.3(3)
C6C7C8C9	-37.7(4)		

TABLE 5. Coordinates of the Atoms ($\times 10^4$; for the H atoms, $\times 10^3$) of Structure (4)

Atom	X	Y	Z	Atom	X	Y	Z
O1	7220(2)	484(2)	1864(2)	H1b	397(4)	156(2)	481(3)
O2	7969(3)	-618(2)	518(2)	H2a	143(5)	181(3)	492(3)
O3	641(3)	1339(2)	1372(2)	H2b	175(4)	56(3)	445(2)
C1	3475(4)	1742(3)	4175(3)	H3a	-26(4)	140(3)	335(3)
C2	1805(5)	1393(4)	4305(3)	H3b	83(3)	249(2)	327(2)
C3	864(4)	1719(4)	3323(3)	H5	328(3)	245(2)	220(2)
C4	1585(3)	1271(3)	2324(3)	H6a	402(3)	44(2)	110(2)
C5	3246(4)	1615(3)	2181(2)	H6b	337(3)	145(2)	51(2)
C6	3959(4)	1241(3)	1133(3)	H7	548(4)	254(3)	76(2)
C7	5569(4)	1733(3)	963(3)	H8	740(3)	211(2)	188(3)
C8	6573(4)	1607(3)	1962(3)	H9a	645(4)	148(2)	362(3)
C9	5808(4)	1756(3)	3033(3)	H9b	576(4)	258(3)	313(3)
C10	4203(3)	1247(3)	3163(2)	H13a	589(4)	160(3)	-127(3)
C11	6432(4)	1031(3)	183(3)	H13b	599(4)	43(3)	-126(3)
C12	7311(4)	202(3)	807(3)	H14a	484(5)	-35(3)	266(3)
C13	6427(5)	1050(4)	-874(3)	H14b	342(4)	-37(3)	327(3)
C14	4313(4)	-20(3)	3269(3)	H14c	484(4)	-23(3)	389(3)
C15	985(4)	262(3)	1827(3)	H15a	15(4)	-6(3)	214(3)
H1	346(4)	264(3)	414(2)	H15b	159(4)	-24(3)	136(3)

by distilling off the water under vacuum until its volume had been reduced to one half of its original value [10]. Trifluoroperacetic acid was prepared by a handbook method [11]. PMR spectra were recorded on a Bruker WP-200SY instrument. IR spectra were taken on a UR-20 spectrophotometer (in KBr).

General Epoxidation Procedure. Epoxidation by peracetic acid and MCPBA was conducted by the standard procedure [12, 13]. A threefold excess of Na_2CO_3 was added to a stirred solution of the substance in CH_2Cl_2 at 0°C. Then a freshly prepared solution of CF_3CO_3H was added dropwise until the initial substance had disappeared (monitoring by TLC). The reaction mixture was treated with a dilute solution of $NaHCO_3$ and was then washed with water and with saturated NaCl solution, dried with Na_2SO_4, and evaporated in a rotary evaporator. The product was recrystallized from petroleum ether—ethyl acetate (1:1) or was additionally purified by column chromatography.

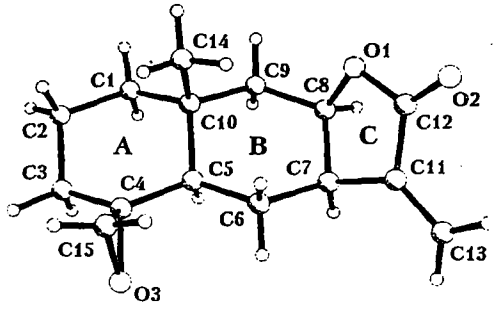

Fig. 1. Structure of the molecule of 4(15)-α-epoxyisoalantolactone (4).

5α,6α-Epoxyalantolactone (3) — white acicular crystals with mp 169-171°C. Yield 80%. IR spectrum (KBr, ν, cm^{-1}): 1750, 1740, 1260, 1140, 1040, 975, 925.

Elementary analysis. Found, %: C (72.86), H (8.18). Calculated, %: C (72.58), H (8.06).

4(15)α-Epoxyisoalantolactone (4) — white rhombic crystals with mp 136-138°C. Yield 75%. IR spectrum (KBr, ν, cm^{-1}) 1760, 1260, 1140, 960, 950.

Elementary analysis. Found, %: C (73.20), H (8.40). Calculated, %: C (72.58), H (8.06).

X-Ray Structural Experiment. The cell parameters and the intensities of 1809 reflections were measured at 20°C on a Siemens P3/PC automatic four-circle diffractometer (λMoK_α, graphite monochromator, $\theta/2\theta$ scanning, $2\theta \leq 60°C$). Crystals rhombic, a = 8.757(2), b = 12.025(2), c = 12.505(3) Å, V = 1316.8(5) $Å^3$, M = 248.3, d_{calc} = 1.252 g/cm^3, Z = 4 ($C_{15}H_{20}O_3$), sp.gr. $P2_12_12_1$.

In the calculations we used 1361 independent reflections with $I > 5\sigma$. The structure was interpreted by the direct method and was refined by full-matrix MLS in the anisotropic approximation for the nonhydrogen atoms and the isotropic approximation for the hydrogen atoms (all the atoms were revealed in a difference synthesis). The final discrepancy factors were R = 0.041 and R_w = 0.038. For the coordinates of the atoms and the temperature factors, see Table 5. All the calculations were performed on an IBM PC/AT computer by the Siemens SHEXTL software package (PC Version).

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