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INTERACTION OF 6,7-EPOXYGERANYL ACETATE AND OF 10,11-EPOXY-(E,E)-FARNESYL ACETATE WITH FLUOROSULFONIC ACID

N. D. Ungur, N. P. Popa, and P. F. Vlad

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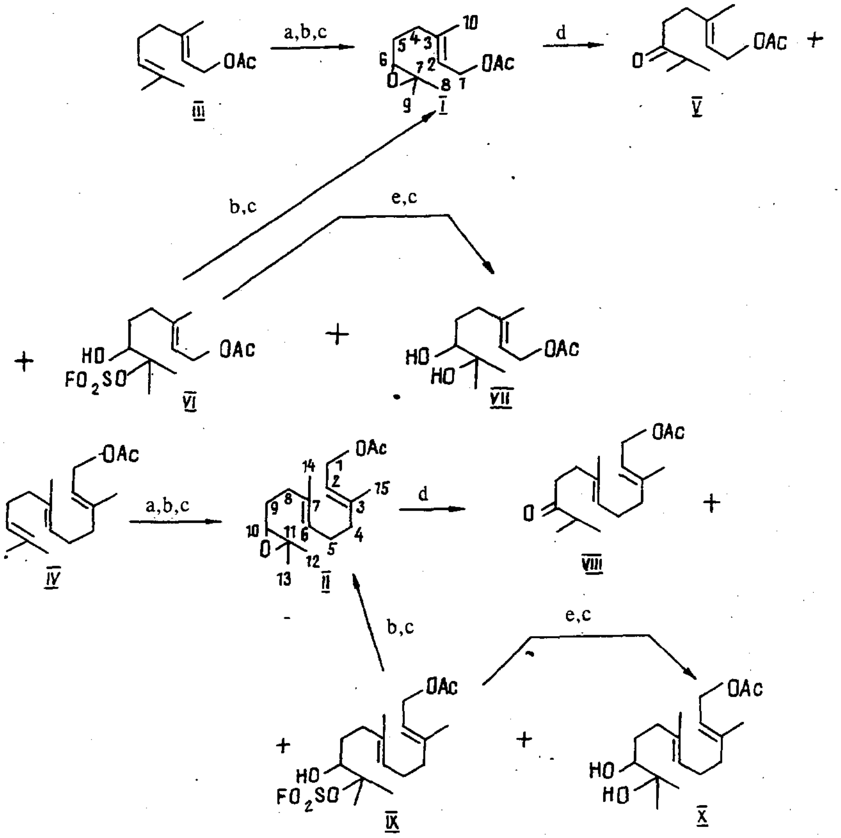
The interaction of 6,7-epoxygeranyl acetate and of 10,11-epoxy-(E,E)-farnesyl acetate with fluorosulfonic acid forms isomerization products and products of the opening of the epoxide rings.

Van Tamelen et al. [1-3] have shown that by the cyclization of epoxyterpenoids with a terminal epoxy group it is possible to perform a biomimetic synthesis of hydroxylated cyclic terpenoids. However, as a rule, the cyclization of such epoxyterpenoids under the action of the usual protonic acids and Lewis acids takes place structurally nonselectively, with the formation of complex mixtures of products from which the desired compounds have been isolated with difficulty in low yield.

We have previously [4-7] achieved good results in the superacid cyclization of terpenols and their acetates. In view of this, it appeared of interest to investigate the behavior of epoxyterpenoids in a superacid medium. In the present communication we give the results obtained on the reaction of 6,7-epoxygeraniol (I) and of 10,11-epoxy-(E,E)-farnesol (II) with fluorosulfonic acid. The epoxy acetates (I) and (II) were synthesized by the method of [8] from geranyl and (E,E)-farnesyl acetates (III) and (IV), respectively.



a) N-bromosuccimide-THF; b) K_2CO_3 — CH_3OH; c) $(CH_3CO)_2O$ — C_5H_5N; d) FSO_3H — $iC_3H_7NO_2$,— 80°C; e) $LiAlH_4$— $(C_2H_5O)_2O$.

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On the interaction of 6,7-epoxygeranyl acetate (I) with FSO_3H in 2-nitropropane or methylene chloride, the main reaction product was 1-acetoxy-3,7-dimethyloct-2-en-6-one (V) (yield 60-65%). In addition to this, small amounts of 1-acetoxy-7-fluorosulfonyloxyoct-2-en-6-ol (VI) (11-12.5%) and the product of its saponification — 1-acetoxy-3,7-dimethyloct-2-ene-6,7-diol (VII) (~9%) — were formed. Compound (V) is mentioned in the literature [9] but its characteristics are not given. We identified it from the results of elementary and spectral (IR, PMR) analyses. The structures of compounds (VI) and (VII) were shown on the basis of spectral (IR, PMR) characteristics, elementary analysis, and chemical transformations. The IR spectrum of the hydroxydiester (VI) contained the bands of hydroxy, acetoxy, and sulfonyloxy groups, and its PMR spectrum the signals of two methyl groups at carbinol atoms and one at a double bond, and of one carbinol proton and one vinyl proton. When the hydroxydiester (VI) was saponified with potash in methanol and the reaction product was acetylated with acetic anhydride in pyridine, the initial 6,7-epoxygeranyl acetate (I) was obtained. The reaction of the hydroxydiester (VI) with lithium tetrahydroaluminate followed by the selective acetylation of the reduction product led to the dihydroxyacetate (VII).

Under the conditions given above for the epoxyacetate (I), 10,11-epoxy-(E,E)-farnesyl acetate (I) reacted with fluorosulfonic acid analogously. The reaction product contained compounds (VIII-X), which were separated by column chromatography on silica gel. The structures of substances (VIII-X) followed from the results of spectral analyses (see the Experimental part), their comparison with the spectral characteristics of compounds (VI) and (VII), and the results of elementary analysis. On alkaline saponification and acetylation, the hydroxydiester (IX) gave the initial epoxyfarnesyl acetate (II), and on reduction with lithium tetrahydroaluminate and acetylation it gave the acetoxydiol (X).

Thus, on the interaction of the epoxyacetates (I) and (II) with the superacid, the main direction of the reaction is the isomerization of the epoxide group to give a keto group, with the formation of the ketoacetates (V) and (VIII) and also the opening of the epoxide ring, leading to the hydroxysulfonates (VI) and (IX), which, apparently, in the working up process undergo partial saponification, giving the dihydroxyacetates (VII) and (X). In contrast to the reactions of the epoxyacetates (I) [9] and (II) [3] with protonic or Lewis acids, on their interaction with the superacid no formation of carbocyclization products was detected even under those conditions in which partial opening of the epoxide ring took place, which may, in principle, proceed through intermediates having a carbocationic nature. It is difficult to give an unambiguous explanation of this fact. It might be assumed that it is a consequence of the appearance of dicationic intermediates in the superacid medium [10]. However, while such an explanation may be suitable for the reaction of 6,7-epoxygeranyl acetate (I), the protonation of which should lead to a 1,8-dication with a relatively close position of the positively charged centers, repulsion between which may give preference to such a conformation of the molecule as cannot undergo cyclization, this explanation is not suitable for the case of epoxyfarnesyl acetate (II), on the protonation of the molecule of which the positively charged atoms will be remote from one another.

Apparently, the main reason for the absence of carbocyclization during the reactions of the epoxyacetates (I) and (II) with the superacid consists in the fact that under the influence of the superacid the predominant process is the concerted isomerization of the epoxide group into a ketone group [11]. The absence of carbocyclization products under those conditions in which, together with the ketoacetates (V) and (VIII), the hydroxydiesters (VI) and (IX) are also obtained can be explained either by the assumption that in this case the opening of the epoxide ring takes place by a S_N2 mechanism or by the assumption that the prereaction conformation of the substrate differs from that (chair-like) which is necessary for the formation of carboxyclic systems.

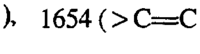
EXPERIMENTAL

PMR spectra were recorded on Bruker AC-80 and Tesla-BS-467 (60 MHz) instruments in $CDCl_3$ with TMS as internal standard. The signals are given on the δ scale. IR spectra were recorded on a Specord 74 IR instrument in CCl_4. The purity of the initial substances was checked and the reaction products were analyzed by GLC, TLC, and NMR spectroscopy. GLC analysis was performed on a Chrom-5 instrument with a 3 × 1500 mm glass column containing as stationary phase 5% of SE-30 on Chromaton N-AW-DMCS, with a flame-ionization detector, the carrier gas being helium at 45 ml/min.

The reaction products were separated by column chromatography on SiO_2 (L 40/100 μ and L 100/160 μ). Silica gel LS 5/40 μ was used for TLC.

Solutions of the substances in organic solvents were dried with anhydrous sodium sulfate.

Synthesis of 6,7-Epoxygeranyl Acetate (I). With stirring, 11.7 g of N-bromosuccinimide was added to a solution of 15 g of geranyl acetate (III) in 235 ml of tetrahydrofuran and 80 ml of H_2O cooled to 0°C. The mixture was stirred at the same temperature for 1.5 h and was then heated to room temperature. The bulk (~ 180 ml) of the solvent was distilled off in vacuum, and the residue was extracted with ether. The ethereal extract was washed with water, with saturated $NaHCO_3$ solution, and with water again, and was dried and the solvent was distilled off. The residue (20.5 g) was dissolved in 250 ml of ethanol, and 19 g of K_2CO_3 was added. The mixture was stirred at room temperature for 36 h, the solid matter was filtered off, and the solvent was distilled off in vacuum. The residue (10 g) was dissolved in 80 ml of pyridine, and 9 ml of acetic anhydride was added. The solution was left at room temperature for 18 h. The solvent was distilled off in vacuum, and the residue was diluted with water (80 ml) and was extracted three times with ether. The ethereal extract was washed with 10% H_2SO_4 solution, water, saturated $NaHCO_3$ solution, and water again, and was dried, and the solvent was distilled off. The residue (12 g) was chromatographed on a column containing 100 g of SiO_2.

Petroleum ether-ethyl acetate (97:3) eluted from the column 5.8 g of 6,7-epoxygeranyl acetate (I), a colorless viscous liquid. IR spectrum (cm^{-1}): 1220, 1725 ($OCOCH_3$), 865, 1020  $(>\underset{O}{C-C}<H)$, 1654 ($>C{=}C<H$). PMR spectrum (CCl_4, ppm): 1.17 (s, 3H) and 1.19 (s, 3H) ($2CH_3$ at C7), 1.72 (br.s, 3H, CH_3 at C3), 1.92 (s, 3H, $OCOCH_3$), 4.47 (d, J = 7.5 Hz, 2H, CH_2-O), 5.33 (m, 1H, $>C{=}C<H$). Calculated %: C 67.61; H 9.40. $C_{12}H_{20}O_3$. Found %: C 67.89; H 9.50.

Then a mixture of the same solvents in ratio of 4:1 eluted from the column 2.4 g of a mixture of polar substances, which was not investigated.

Interaction of 6,7-Epoxygeranyl Acetate (I) with Fluorosulfonic Acid in 2-Nitropropane. With stirring, a solution of 172 mg of 6,7-epoxygeranyl acetate (I) in 2 ml of 2-nitropropane cooled to −78 to −80)°C was added to a solution of 80 mg of FSO_3H in 1 ml of 2-nitropropane cooled to the same temperature. The mixture was stirred at this temperature for 40 min, and then 2 ml of a 1:1 solution of Et_3N in hexane was added. The solution was diluted with 5 ml of H_2O and extracted with ether. The extract was worked up in the usual way, giving 168 mg of a reaction product, which was chromatographed on a column containing 6 g of SiO_2.

Petroleum ether−ethyl acetate (97:3) eluted 112 mg (65%) of the ketoaldehyde (V), a colorless viscous liquid. IR spectrum (cm^{-1}): 1220, 1730 ($OCOCH_3$), 1700 ($>C{=}O$), 855, 1657 ($>C{=}C<H$). PMR spectrum (ppm): 1.14 (d, J = 7 Hz, 6H, $2CH_3$ at C7) 1.72 (s, 3H, CH_3 at C3), 2.01 (s, 3H, $OCOCH_3$), 4.57 (d, J = 7 Hz, 2H, $-CH_2-O$), 5.32 (m, 1H, $>C{=}C<H$) Calculated %: C 67.98; H 9.69. $C_{12}H_{20}O_3$. Found %: C 67.89; H 9.50.

Then a mixture of same solvents in a ratio of 9:1 eluted 28 mg (11%) of the acetoxyfluorosulfonate (VI), a colorless viscous liquid. IR spectrum (cm^{-1}): 1220, 1725 ($OCOCH_3$), 1010, 3445, (OH group), 1335 (FSO_2). PMR spectrum (CCl_4, ppm): 1.21 (s, 3H) and 1.24 (s, 3H) ($2CH_3$ at C7), 1.71 (s, 3H, CH_3 at C3), 1.98 (s, 3H, $OCOCH_3$), 3.96 (m, 1H, $>CHOH$), 4.48 (d, J = 7 Hz, 2H, $-CH_2-O$), 5.33 (m, 1H, $>C{=}C<H$). Calculated %: C 46.38; H 6.64. $C_{12}H_{21}FSO_6$. Found %: C 46.14; H 6.78.

A mixture of the same solvents in a ratio of 5:1 eluted from the column 18 mg (9.6%) of the triol monoacetate (VII) (a colorless viscous liquid, IR spectrum (cm^{-1}): 1220, 1730 ($OCOCH_3$), 1050, 1130, 3453, 3610 (OH groups), 1665 ($>C{=}C<H$). PMR spectrum (ppm): 1.19 (s, 6H, $2CH_3$ at C7), 1.70 (s, 3H, CH_3 at C3), 2.05 (s, 3H, $OCOCH_3$), 4.57 (m, 2H, CH_2-O), 5.32 (m, 1H, $>C{=}C<H$). Calculated %: C 62.73; H 9.88. $C_{12}H_{22}O_4$. Found %: C 62.58; H 9.63.

Interaction of the Epoxyacetate (I) with Fluorosulfonic Acid in Methylene Chloride. A solution of 115 mg of epoxide (I) in 1 ml of CH_2Cl_2 cooled to -78 to −80°C was added with stirring to a solution of 27 mg of FSO_3H in 1.5 ml of CH_2Cl_2 cooled to the same temperature. The mixture was stirred at this temperature for 15 min and was then worked up as described above. The reaction product (106 mg) was chromatographed on a column containing 2 g of SiO_2. Petroleum ether−ethyl acetate (19:1) eluted 69.4 mg (60%) of the ketoacetate (V), identical in its chromatographic and spectral characteristics with the sample the production of which was described above.

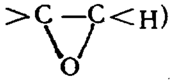
Then a mixture of the same solvents in a ratio of 9:1 eluted 21 mg (12.4%) of compound (VI), and a 4:1 mixture eluted 11.5 mg 9.2% of the triol monoacaetate (VII).

Conversion of the Acetoxyfluorosulfonate (VI) into the Epoxyacetate (I). A solution of 80 mg of the acetoxyfluorosulfonate (VI) in 1.5 ml of CH_3OH was treated with 75 mg of K_2CO_3 and the mixture was stirred at room temperature for 20 h. The resulting solution was diluted with water (5 ml) and extracted with ether, and the extract was washed with water to neutrality and dried, and the solvent was distilled off. The residue (42 mg) was dissolved in 2 ml of dry pyridine, and 0.02 ml of acetic anhydride was added, after which the mixture was left at the ordinary temperature for 12 h and was worked up in the usual way. The reaction product (51 mg) was chromatographed on a column containing 0.8 g of SiO_2. Petroleum ether−ethyl acetate (19:1) eluted 41 mg of 6,7-epoxygeranyl acetate (I), identical in its chromatographic and spectral characteristics with an authentic sample.

Conversion of the Acetoxyfluorosulfonate (VI) into the Triol Monoacetate (VII). A solution of 65 mg of the acetoxyfluorosulfonate (VI) in 4 ml of absolute ether was treated with 35 mg of $LiAlH_4$, and the mixture was boiled under reflux for 1 h. The excess of $LiAlH_4$ was decomposed with ethyl acetate, and the mixture was acidified with 10% H_2SO_4 and was extracted three times with ether. The ethereal extract was washed with water, with saturated $NaHCO_3$ solution, and with water again and was dried, and the solvent was distilled off. The residue (36.3 mg) was dissolved in 2 ml of dry pyridine, and 0.02 ml of acetic anhydride was added.

The resulting solution was left at room temperature for 8 h and was then diluted with water (5 ml) and extracted with ether. The extract was washed with 10% H_2SO_4 solution, with water, with saturated $NaHCO_3$ solution, and with water again, and was dried, and the solvent was distilled off. The residue (43.2 mg) was chromatographed on a column containing 1 g of SiO_2. Petroleum ether–ethyl acetate (9:1) eluted 5.6 mg of a mixture of feebly polar substances, which were not investigated. Then a mixture of the same solvents in a ratio of 4:1 eluted 34 mg of the triol monoacetate (VI), identical with a sample the production of which has been described above.

Synthesis of 10,11-Epoxy-(E,E)-Farnesyl Acetate (II). With stirring, 1.63 g of N-bromosuccinimide was added to a solution of 2.2 g of (E,E)-farnesyl acetate in 40 ml of tetrahydrofuran and 13 ml of H_2O cooled to 0°C. The mixture was stirred at the same temperature for 0.5 h and was then warmed to room temperature over 1 h. It was worked up as described above. The reaction product (2.1 g) was dissolved in 55 ml of methanol, and 2.1 g of K_2CO_3 was added to the resulting solution. The mixture was stirred at room temperature for 20 h, the solid matter was filtered off, and the solvent was distilled off in vacuum. The residue (1.7 g) was dissolved in 20 ml of pyridine, 2.5 ml of acetic anhydride was added, and the mixture was left at room temperature for 18 h. It was worked up in the usual way, and the reaction product (1.2 g) was chromatographed on a column containing 15 g of SiO_2.

Petroleum ether–ethyl acetate (97:3) eluted from the column 0.78 g of 10,11-epoxy-(E,E)-farnesyl acetate (II), a colorless viscous liquid. IR spectrum (cm^{-1}); 1225, 1725 ($OCOCH_3$), 1020 ( $>\underset{O}{C-C}<H$). 865, 1667 ($>C{=}C<H$). PMR spectrum (ppm): 1.18 (s, 3H), 1.23 (s, 3H), ($2CH_3$ at C11), 1.60 (s, 3H, CH_3 at C7), 1.70 (s, 3H, CH_3 at C3), 1.97 (s, 3H, $OCOCH_3$), 3.93 (m, 1H, 10-H), 4.46 (d, J = 7 Hz, 2H, $-CH_2-O$), 5.15 (m, 1H, $>C{=}C<H$), 5.30 (m, 1H, $>C{=}C<H$). Calculated %: C 72.66; H 10.12. $C_{17}H_{28}O_3$. Found %: C 72.82; H 10.06.

Then a mixture of the same solvents in a ratio of 3:1 eluted from the column 0.21 g of a mixture of polar substances, which was not investigated.

Interaction of 10,11-Epoxy-(E,E)-Farnesyl Acetate (II) with Fluorosulfonic Acid. With stirring, a solution of 110 g of 10,11-epoxy-(E,E)-farnesyl acetate (II) in 3 ml of 2-nitropropane cooled to −78 to −80°C was added to a solution of 190 mg of FSO_3H in 4 ml of nitropropane cooled to the same temperature. The resulting solution was stirred at this temperature for 40 min, and was then worked up in the usual way, and the reaction product (106 mg) was chromatographed on a column containing 5 g of SiO_2. Petroleum ether–ethyl acetate (97:3) eluted 44 mg (39.6%) of the ketoacetate (VIII), a colorless viscous liquid. IR spectrum (cm^{-1}): 1230, 1735 ($OCOCH_3$), 1710 ($>C{=}O$), 865, 1637 ($>C{=}C<H$). PMR spectrum (ppm): 1.10 (d, J = 7 Hz, 6H, $2CH_3$ at C11), 1.63 (s, 3H, CH_3 at C7), 1.70 (s, 3H, CH_3 at C3), 2.05 (s, 3H, ($OCOCH_3$), 4.59 (d, J = 7 Hz, 2H, $-CH_2-O$), 5.16 (m, 1H, $>C{=}C<H$), 5.35 (m, 1H, $>C{=}C<H$). Calculated %: C 72.84; H 10.12. $C_{17}H_{28}O_3$. Found %: C 72.82; H 10.06.

Then a mixture of the same solvents in a ratio of 9:1 eluted 36 mg (23.9%) of the acetoxyfluorosulfonate (IX), a colorless viscous liquid. IR spectrum, cm^{-1}: 1215, 1720 ($OCOCH_3$), 1350 (OSO_2F), 3475, 3600 (OH groups), 1655 ($>C{=}C<H$). PMR spectrum (ppm): 1.26 (s, 6H, $2CH_3$ at C11), 1.61 (s, 3H, CH_3 at C7), 1.70 (s, 3H, CH_3 at C3), 2.05 (s, 3H, ($OCOCH_3$), 3.68 (t, J = 6 Hz, 1H, 10-H), 4.59 (d, J = 7 Hz, 2H, $-CH_2-O$), 5.13 (m, 1H, $>C{=}C<H$), 5.36 (m, 1H, $>C{=}C<H$). Calculated %: C 53.81; H 7.69. $C_{17}H_{29}FSO_6$. Found %: C 53.67; H 7.68.

A mixture of the same solvents in a ratio of 5:1 eluted from the column 23 mg (19.5%) of the triol monoacetate (X), a colorless viscous liquid. IR spectrum (cm^{-1}); 1228, 1725 ($OCOCH_3$), 1068, 1115, 3453, 3610 (OH groups). PMR spectrum (ppm): 1.17 (s, 3H) and 1.20 (s, 3H) ($2CH_3$ at C11), 1.60 (s, 3H, CH_3 at C7), 1.68 (s, 3H, CH_3 at C_3), 2.04 (s, 3H, $OCOCH_3$), 3.54 (m, 1H, 10-H), 4.57 (m, J = 6.5 Hz, 2H, $-CH_2-O$), 5.14 (m, 1H, $>C{=}C<H$), 5.34 (m, 1H, $>C{=}C<H$). Calculated %: C 68.28; H 10.18. $C_{17}H_{30}O_4$. Found %: C 68.42; H 10.13.

Conversion of the Acetoxyfluorosulfonatae (IX) into the Epoxyacetate (II). By the method described above, 60 mg of the acetoxyfluorosulfonate (IX) yielded 36 mg of epoxyfarnesyl acetate (II), identical in its chromatographic characteristics with an authentic sample.

Conversion of the Acetoxyfluorosulfonate (IX) into the Triol Monoacetate (X). In the way described above, 70 mg of the acetoxyfluorosulfonate (IX) yielded 32 mg of the triol monoacetate (X), identical in its chromatographic characteristics with an authentic sample.

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