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REARRANGEMENT OF ACYLOXYOXIRANES: A REVISED STRUCTURE FOR THE OXIDATION PRODUCT OF 5α-ANDROST-16-ENE-3α,17-DIOL 3-BENZOATE 17-ACETATE[1]

Gottumukkala V. Subbaraju[2], Zofia Urbanczyk-Lipkowska[3], Sardar N. Newaz, Maghar S. Manhas and Ajay K. Bose*

Department of Chemistry and Chemical Engineering, Stevens Institute of Technology, Hoboken, NJ 07030

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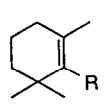
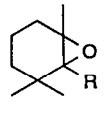
Abstract--During the oxidation of conjugated enones to α-acyloxyoxiranes by m-chloroperbenzoic acid, the preferred sequence is epoxidation followed by Baeyer-Villiger oxidation. Rearrangement of acyloxyoxiranes to α-acyloxyketones, in situ, was observed. The α-ketoacetate structure assigned previously to the m-CPBA oxidation product of 5α-androst-16-ene-3α,17-diol 3-benzoate 17-acetate, has been revised to an acyloxyoxirane structure based on spectroscopic and X-ray diffraction data.

Peracid oxidation of unsaturated ketones and aldehydes can generate a variety of end products by a combination of epoxidation, Baeyer-Villiger oxidation and facile molecular rearrangement of initial oxidation products.[4,5] Some of these reactions are sensitive to steric factors and are therefore affected by the nature of the enone system, for example, the size and conformation of the ring which contains part of the conjugated enone group and the nature of the peracid used for the oxidation.

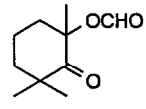
Recently, we[6] have studied the relative importance of some of these factors in the course of peracid oxidation of β-cyclocitral (1) and found that oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) produced an intermediate **2a** that underwent Baeyer-Villiger Oxidation to **3a** which in turn was rearranged to **3b**. The same end products **3a**, and **3b**, were also obtained by peracetic acid oxidation of **1** but *via* the intermediate **2b**.



1 R = CHO
2b R = OCHO



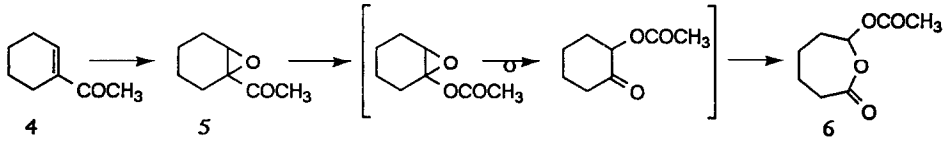
2a R = CHO
3a R = OCHO



3b

We have now investigated the oxidation of 1-acetyl-1-cyclohexene (**4**) with *m*-CPBA. Two products were isolated and characterized as 1,2-epoxy-1-acetylcyclohexane (**5**)[7] and 7- acetyloxy-2-oxepanone (**6**)[8] based on spectroscopic data. However, when 3 moles of *m*-CPBA were used for this oxidation, **6** was obtained as the sole product of this reaction (Scheme I). Formation of **6** from **4** involves sequential epoxidation, Baeyer-Villiger oxidation, rearrangement and ring expansion by a second Baeyer-Villiger oxidation step.

Scheme I

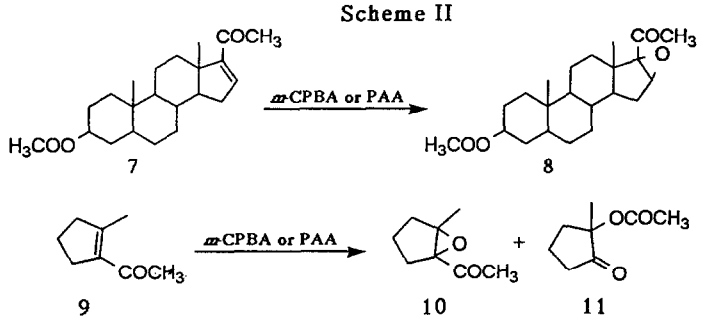


4 5 6

This study of peracid oxidation was extended to five membered enones as well. The reaction of **7** with 2 molar equivalents of *m*-CPBA or peracetic acid (2.0 mol) gave the epoxide, **8** [9,10] only. Use of an excess of *m*-CPBA or longer time of reflux (24h) of reaction mixture did not cause further oxidation of **8** (Scheme II). The resonance signal for 16β-H in **8** showed no coupling with the C-15 methylene protons and appeared as a sharp singlet at δ 3.66 in its ^{1}H-NMR spectrum![11] Under similar conditions 1-acetyl-2-methyl-1-cyclopentene (**9**),

however, afforded the 1,2-epoxy-1-acetyl-2-methylcyclopentane (10) and 2-acetyloxy-2-methylcyclopentanone (11)[12] in about equal amounts (Scheme II).

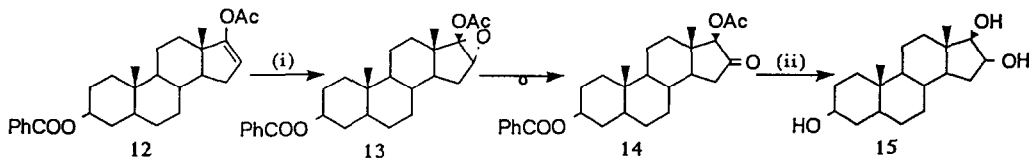
Scheme II



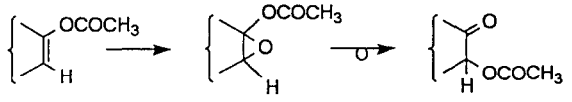
In 1984, Newaz and Tcholakian[13] reported that an enol acetate epoxide (13) obtained during the course of epoxidation of anenol acetate (12) was unstable and rearranged to a 17β-acetyloxy-16-keto derivative (14) (Scheme III). The structure assigned to 14 was based on their finding that a singlet at δ 3.88 (1H) observed in the ^{1}H-NMR spectrum of this compound could be assigned to 17α-H. LAH reduction of 14 led to 15, a compound of known structure and stereochemistry.[14,15]

Based on our own experience on terpenoids[6] and information available on steroid epoxides and α-acetyloxy ketones in the literature,[14-18] it appears that during epoxidation and rearrangement of an enol acetate (16), the vinyl carbon linked to the acetyloxy group becomes the site of the keto group in the rearranged product (17). We, therefore, felt that the proposed rearrangement of 13 into 14 needs reexamination.

Scheme III



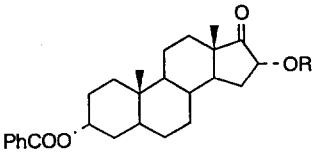
(i) $PhCO_3H$ (ii) $LiAlH_4$



We have repeated the *m*-CPBA oxidation of 12 and isolated a stable product of m.p. 153-155°C in 80% yield that shows a singlet at δ 3.88 (1H) in its ^{1}H-NMR spectrum as described earlier.[13] ^{13}C-NMR spectrum of this product provided significant structural information. Two carbonyl signals that appeared at δ 165.8 and 168.9 were suggestive of two ester carbonyls. No ketone carbonyl was detected but a quaternary carbon signal was found at 91.9 ppm. This chemical shift was in agreement with the C-17 signal expected of a 16,17-epoxy-17-acetate (13). Additional information regarding the protons and the attached carbons was obtained by one bond ^{1}H-^{13}C shift correlated (HETCOR) spectra. These studies indicated that the proton corresponding to the

signal at δ 3.88 was located on C-16 (δ 59.9). Further, the ^{13}C (16)-H coupling was found to be 190.5 Hz. Such a large coupling constant is compatible with a 16,17-epoxide.[19] The ^{13}C-NMR data do not permit discrimination between α and β stereochemistry of the epoxide ring.

Treatment of **13** with p-toluenesulfonic acid in chloroform solution led to the formation of two products **18** and **19** (in 2:1 ratio) which showed the presence of ketone carbonyls (δ 214.1 and 219.4, respectively) in their ^{13}C-NMR spectra. One of these compounds, **19**, had a free hydroxyl group. Based on spectral data the structures of these products were deduced to be 5α-androstane-17-one-3α,16α-diol 3-benzoate 16-acetate (**18**) and 5α-androstane-17-one-3α,16α-diol 3-benzoate (**19**).



18 R = $COCH_3$

19 R = H

In view of the foregoing, the ketoacetate (**14**) of Newaz and Tcholakian[13] should be assigned the epoxyacetate structure, **13**. Confirmation of the structural assignment of **13** was obtained from the single crystal x-ray diffraction study on **13**. The PLUTO diagram of **13** is shown in Fig. 1.

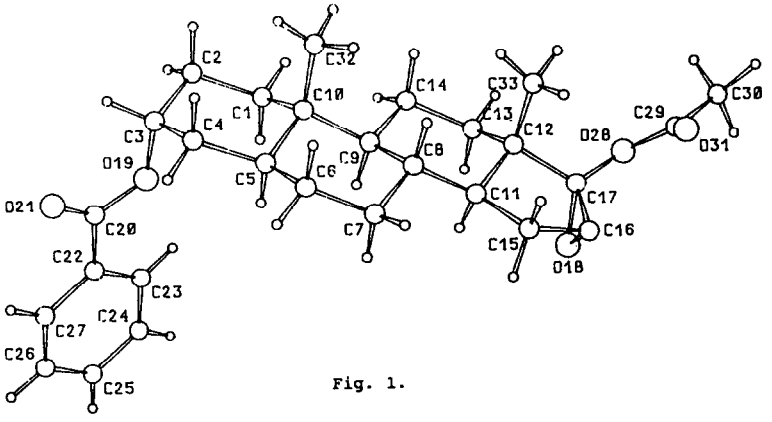


Fig. 1.

EXPERIMENTAL

5α-Androstan-3α-ol-17-one 3-benzoate and 16-pregnen-3β-ol-20-one 3-acetate were purchased from Steraloids, Inc., U.S.A. 1-Acetyl-1-cyclohexene, 1-acetyl-2-methyl-1-cyclopentene, *m*-CPBA (50-60%), and peracetic acid (32%) were obtained from Aldrich Chemical Co., U.S.A. *m*-Chloroperbenzoic acid (100%) was prepared from commercially available 50-60% pure acid by washing with a phosphate buffer. Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1760 FT-IR spectrometer as neat or nujol mulls, ^{1}H-NMR, ^{13}C-(BB, DEPT and fully coupled) NMR and HETCOR spectra were obtained on a Bruker AF-200 NMR spectrometer using $CDCl_3$, C_6D_6 or C_5D_5N as solvents and TMS as an internal standard. Chemical ionization mass spectra were recorded using a Biospect. mass spectrometer (Scientific Research Instruments Corp., Baltimore, MD) using CH_4 as carrier gas. High

resolution (EI and CI) mass spectra were obtained on Finnigan MAT-90 mass spectrometer. X-ray crystal diffraction analyses were carried out on a Enraf-Nonius CAD4 diffractometer.

Oxidation of 1-acetyl-1-cyclohexene (4): A solution of 1-acetyl-1-cyclohexene (4, 1.24g, 0.01 mol) and *m*-CPBA (50-60%, 7.0g, ca. 0.02 mol) in chloroform (60 mL) was refluxed for 6h and the reaction mixture washed with aqueous sodium hydroxide (10%) and water, successively. Removal of the solvent gave a mixture of **5** and **6** (ca 1.0g, ratio[20] 1:2, 60%). Chromatography over silica gel gave **5** (150 mg) and **6** (500mg). Repetition of the above reaction using 3.0 mole equivalents of *m*-CPBA gave **6** only.

1,2-Epoxy-1-acetylcyclohexane (5): Colorless oil; IR(neat): 1706 cm^{-1}; ^{1}H-NMR(200 MHz, $CDCl_3$) δ : 1.10-2.70 (8H,m), 2.04 (3H,s), 3.31 (1H,d,J=2Hz); ^{13}C-NMR (50 MHz,$CDCl_3$) δ : 18.8, 19.3, 22.1, 23.1, 24.3, 56.7, 63.0, 208.1; Mass(CI): m/z 141 $(M+H)^+$; HREIMS: m/z 140.0835 (Found); calc. for $C_8H_{12}O_2(M^+)$: 140.0834.

6-Acetyloxy-2-oxepanone (6): Colorless oil, IR(neat): 1745 cm^{-1}(br); ^{1}H-NMR(200 MHz, $CDCl_3$) δ : 1.60-2.30 (6H,m), 2.14 (3H,s), 2.70 (2H,m), 6.42 (1H,dd,J=6.2 Hz); ^{13}C-NMR (50MHz, $CDCl_3$) δ : 20.5, 22.4, 24.0, 32.9, 35.8, 93.4, 168.2, 171.8; HRCIMS: m/z 173.0814 (Found); calc. for $C_8H_{13}O_4$ (MH^+): 173.0814.

Oxidation of 16-pregnen-20-one-3β-ol 3-acetate (7): A solution of 16-pregnene-20-one-3β-ol 3-acetate (7, 0.18g, 0.0005 mol) and *m*-CPBA (50-60% purity, 0.35g, ca 0.001 mol) in chloroform (5mL) was refluxed for 2h. Work-up as described for the oxidation of **4** followed by recrystallization from hexane-dichloromethane gave **8** as colorless crystals (43% yield), m.p. 174-76°C. Repetition of the above reaction for longer time of reflux (24h) or use of peracetic acid did not cause any Baeyer-Villiger oxidation of **8**.

16α,17α-Epoxypregnan-20-one-3β-ol 3-acetate (8): Colorless crystals; m.p. 174-76°C; IR(nujol): 1702, 1737 cm^{-1}; ^{1}H-NMR(200 MHz, $CDCl_3$) δ : 0.83 (3H,s), 1.01 (3H,s), 0.60-2.40 (20H,m), 2.02 (6H,s), 3.66 (1H,s), 4.65 (1H,m); ^{13}C-NMR (50MHz, $CDCl_3$) δ : 12.1, 15.3, 20.6, 21.4, 25.9, 27.4(2C), 28.4, 31.4, 31.5, 33.1, 33.9, 35.6, 41.8, 44.7, 45.2, 54.5, 60.5, 70.9, 73.5, 170.6, 204.9; HREIMS: m/z 374.2451 (Found); calc. for $C_{23}H_{34}O_4(M^+)$: 374.2457.

Oxidation of 1-acetyl-2-methyl-1-cyclopentene (9): A solution of 1-acetyl-2-methyl-1-cyclopentene (9, 0.62g, 0.005 mol) and *m*-CPBA (50-60% purity, 3.5g, ca. 0.01 mol) in chloroform (45 mL) was refluxed for 12h. Work-up as described for the oxidation of **4** followed by chromatography over silica gel gave **10** and **11** (approximately in the ratio 1:1) in 60 % total yield.

1,2-Epoxy-1-acetyl-2-methylcyclopentane (10): Colorless oil; IR(neat): 1702 cm^{-1}; ^{1}H-NMR(200MHz,$CDCl_3$) δ : 1.46 (3H,s), 1.30-2.40 (6H,m), 2.23 (3H,s); ^{13}C-NMR(50 MHz,$CDCl_3$) δ : 15.1, 18.5, 27.4, 28.2, 33.0, 70.9, 73.6, 205.8; HREIMS: m/z 140.0838 (Found); calc for $C_8H_{12}O_2(M^+)$: 140.0834.

2-Acetyloxy-2-methylcyclopentanone (11): Colorless oil; IR(neat): 1737,1752 cm^{-1}; ^{1}H-NMR(200MHz, $CDCl_3$) δ : 1.32 (3H,s), 1.60-2.75 (6H,m), 2.04 (3H,m); ^{13}C-NMR(50MHz,$CDCl_3$) δ : 17.7, 20.5, 21.3, 33.8, 34.8, 81.6, 169.4, 214.2; HREIMS: m/z 156.0795 (Found); calc. for $C_8H_{12}O_3$ (M^+): 156.0786.

16α,17α-Epoxy-5α-androstane-3α, 17β-diol 3-benzoate 17-acetate (13): 5α-Androstane-3α-ol-17-on 3-benzoate was treated with isopropenyl acetate and p-toluenesulfonic acid according to the literature procedure[13] to give the enol acetate, 5α-androsta-16-ene-3α,17-diol 3-benzoate 17-acetate (12) in 50% yield, m.p. 160°C, lit.[13] m.p. 160-62°C. A mixture of enol acetate(12, 0.33g, 0.75 mmol) and *m*-CPBA (100% pure, 0.2g, 1.2 mmol) was dissolved in benzene (6.0 mL) and kept at room temperature for 5 min. TLC analysis showed the completion of the reaction. The reaction mixture was then diluted with dichloromethane (20 mL)

and washed with cold aqueous NaOH (1%) followed by water and the organic layer was dried (Na_2SO_4). Evaporation of the solvent gave 13 (0.2g, 59 %). Recrystallization from dichloromethane and methanol gave colorless crystals, m.p. 153-55°C. IR(nujol): 1766, 1716 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ : 0.86 (3H,s), 0.90 (3H,s), 0.90-2.00 (20H,m), 2.10 (3H,s), 3.87 (1H,s), 5.29 (1H,m), 7.40-7.65 (3H,m), 8.10 (2H,dd,J=8.2 Hz); (C_6D_6, 200 MHz) δ : 0.57 (3H,s), 0.83 (3H,s), 0.60-1.90 (20H,m), 1.61 (3H,s), 3.90 (1H,s), 5.35 (1H,m), 7.10 (3H,m), 8.30 (2H,m); (C_5D_5N, 200 MHz) δ : 0.72 (3H,s), 0.90 (3H,s), 1.00-2.00 (20H,m), 2.04 (3H,s), 3.97 (1H,s), 5.39 (1H,m), 7.50 (3H,m), 8.35 (2H, dd, J=8.2 Hz); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ : 11.3, 14.7, 20.2, 21.1, 26.2, 26.4, 28.1, 31.1, 31.2, 32.9, 33.1, 33.7, 36.0, 40.5, 42.9, 46.4, 54.9, 59.9, 70.5, 91.9, 128.3, 129.5, 131.1, 132.7, 165.8, 168.9; CIMS(positive, 180°C): m/z 452 (M^+), 392 ($M-CH_3COOH)^+$; 330 ($M-C_6H_5COOH)^+$.

Crystal data for 13: $C_{28}H_{36}O_5$, FW 452. The crystals are orthorhombic, a=7.935(2) Å, b=10.432(2) Å c=29.382(3) Å, $\alpha=\beta=\bar{a}=90°$, V=2430.9(6) $Å^3$, D_{calc} =1.7173 g/cm^3. Systematic extinctions, h00=2n, 0k0=2n, 001=2n, gave the space group $P2_12_12_1$ with Z=4. 1250 reflections were collected on an automated Enraf-Nonius CAD4 diffractometer using monochromated MoKα radiation in θ range 0-25°. Three standard reflections were measured every 3000 seconds and there were no significant changes in their intensities. The structure was solved by direct methods with SHELXS-86 and refined with full-matrix least-squares SHELX76 programs. The non-hydrogen atoms were refined with anisotropic thermal parameters. Nine hydrogen atoms were found from Fourier difference map calculations and the remaining were located at their expected positions but not refined. Analysis of the ring conformations showed a chair flattened at one end for the A ring, (asymmetry parameter[21] ΔC_S=1.4°), chair for B and C, (asymmetry parameters ΔC_S=0.3° and ΔC_S=7.1°, respectively), and an envelope conformation for ring D, (ΔC_S=4.8°). The final residual was 0.0403 (unit weights). Maximum fluctuation on the final $\Delta\rho$ maps was 0.29 e/$Å^3$.

Rearrangement of 16α,17α-epoxy-5α-androstane-3α,17β-diol 3-benzoate 17-acetate (13): The epoxide **13** (ca 50 mg) was dissolved in chloroform (5.0mL), added a catalytic amount of p-TSA and heated under reflux for 10 min. Usual work up of the reaction gave a mixture (40 mg) of 5α-androstane-17-one-3α,16α-diol 3-benzoate 16-acetate (**18**) and 5α-androstane-17-one-3α,16α-diol 3-benzoate (**19**) in 2:1 ratio. Compounds **18** and **19** were separated by chromatography over silica gel (solvent system: hexane-ethyl acetate, 9:1). Rearrangement of **13** in the presence of p-TSA at room temperature for 5 min gave **18** and **19** in a 1:2 ratio[20] and in almost quantitative yield.

5α-Androstane-17-one-3α,16α-diol 3-benzoate 16-acetate (18): IR(nujol): 1759, 1745 and 1716 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ : 0.87 (3H,s), 0.98 (3H,s), 1.00-2.00 (20H,m), 2.12 (3H,s), 5.30 (1H,m), 5.41 (1H,bd, J=6.5 Hz), 7.41-7.62 (3H,m), 8.06 (2H,dd,J=8.3,1.4 Hz); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ : 11.4, 14.2, 19.7, 20.8, 26.2, 27.7, 29.5, 30.4, 31.3, 32.9, 33.1, 34.9, 36.0, 40.4, 47.7, 48.7, 54.3, 70.4, 72.4, 128.3, 129.5, 131.0, 132.7, 165.8, 170.2, 214.1; CIMS (positive, 180°C): m/z 452 $(M)^+$.

5α-Androstane-17-one-3α,16α-diol 3-benzoate (19): IR(nujol): 3468, 1745 and 1695 cm^{-1}; ^{1} H-NMR ($CDCl_3$, 200 MHz) δ : 0.88 (3H,s), 0.98 (3H,s), 1.20-2.10 (20H,m), 2.37 (1H,bs), 4.38 (1H,bd,J=7.0 Hz), 5.30 (1H,m), 7.43-7.68 (3H,m), 8.04-8.08 (2H,m); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ : 11.4, 14.1, 19.7, 26.2, 28.0, 30.4, 30.5, 31.3, 32.9, 33.1, 35.0, 36.0, 40.4, 47.7, 48.3, 54.3, 70.4, 71.3, 128.3, 129.4, 131.1, 132.8, 165.9, 219.4; CIMS (positive, 180°C): m/z 392 $(M-H_2O)^+$.

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