Acid-catalyzed reactions of 7 α ,8 α -epoxy multiflorenyl acetate[†]

Mahuya Roy, Kakoli Majumdar and Saktipada Das

E-mail : sakti@klyuniv.ernet.in

Department of Chemistry, University of Kalyani, Kalyani-741 235, India

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7 α ,8 α -Epoxy multiflorenyl acetate (**1**) on reaction with hydrogen chloride in dry chloroform yielded multiflor-7,9(11)-dien-3 β -acetate (**6**) and 7-keto-multiflor-3 β -acetate (**7**) in nearly 1 : 2 ratio. Treatment of **1** with BF₃·Et₂O in dry benzene furnished 7 α -hydroxy taraxeryl acetate (**3**) and 7 α -hydroxy β -amyrin acetate (**8**) alongwith the diene (**6**) in traces. The structures of these compounds have been settled by spectroscopic evidence and the difference in the nature of the products obtained in the two reactions of **1** has been rationalised.

Molecular rearrangement in triterpenoids provides invaluable information about the structure and stereochemistry of naturally occurring triterpenoids and also renders a great insight into their biogenetic relationships. Acid-catalyzed reactions of a large variety of triterpenoid epoxides are well documented in the literature¹⁻⁹. Such reactions are partly due to unique structural and stereochemical features in the vicinity of the oxirane function and partly due to dependence of the course of such reactions on the nature of the acidic reagents and the solvents used. Chakravarty *et al.*¹⁰ studied the acid-catalysed rearrangement of the 7 α ,8 α -epoxy baurenyl acetate and obtained 7 α -hydroxy-14,27-cycloisoursan-3 β -acetate and 7 α -hydroxy-isours-14-en-3 β -acetate with several other rearranged products. Such work prompted us to believe that similar acid-catalysed rearrangement of the 7 α ,8 α -epoxide (**1**) obtainable from multiflorenyl acetate (**2**), (a migrated oleanane triterpene)¹¹ might led to the isolation of structurally analogous 14,27-cycloisoooleanane derivatives, which to our knowledge, are not reported in the literature as yet. We also expected to obtain 7 α -hydroxy taraxeryl acetate (**3**) as a possible rearranged product of **1** and were interested to prepare **3** from multiflorenol (**4**) because 7 α -hydroxytaraxerol (**5**) was isolated by Watermann *et al.*¹² from the leaves of *Basistoa brassii* but its structure was only proposed on the basis of its physical and spectral data and it was not synthesised or correlated with any compound of known structure and stereochemistry. With a view to correlate 7 α -hydroxy taraxerol (**5**) with a known compound multiflorenol (**4**)¹¹ and also to prepare some hitherto unknown 14,27-cycloisoooleananes, the title work was undertaken.

Results and discussion

Multiflorenyl acetate (**2**), isolated from the barks of

Gelonium multiflorum, was treated with *m*-chloroperbenzoic acid in chloroform to furnish 7 α ,8 α -epoxy multiflorenyl acetate (**1**) in ca. 70% yield. The mass spectrum of **1** showed the molecular ion peak at *m/z* 484 which is 16 mass units higher than the molecular weight of **2**. The 90 MHz ¹H NMR spectrum of **1** showed among other peaks a broad singlet (1H) at δ 3.11 ppm assigned to the β -(equatorial) proton at C₇. The oxirane ring formation at the C₇-C₈ position was assumed to be α -oriented due to the facile approach of the reagent from the more exposed α -phase owing to the boat conformation¹² assumed by the unsaturated ring-B and also the steric hindrance rendered by the axial methyls at C₁₀ and C₁₄. The orientation of the epoxide ring as 7 α ,8 α - was however, ascertained conclusively from the 300 MHz ¹H NMR spectra of the products obtained from its rearrangement with boron trifluoride etherate.

Treatment of the epoxide (**1**) with dry hydrogen chloride in anhydrous chloroform yielded two compounds : (A) C₃₂H₅₀O₂, (M⁺ 466), m.p. 212–15° and (B), C₃₂H₅₂O₃ (M⁺ 484), m.p. 182–84° in the ratio of about 1 : 2. The UV spectrum of compound A [$\lambda_{\max}$ (EtOH) 232.2 (log ϵ 4.10), 238.8 (log ϵ 4.17) and 247.5 (shoulder like, log ϵ 3.94) nm] indicated it to be a heteroanular diene and its IR, ¹H NMR (two olefinic protons at δ 5.15 and 5.40 ppm) and mass spectral fragmentation were in accord with the structure **6** assigned to it. This was further supported by ¹³C NMR spectral data in which the two non-protonated *sp*² carbons, viz. C₈ and C₉ appeared at δ 142.6 and 144.9 while the two *sp*² methine carbons, viz. C₇ and C₁₁ appeared at δ 118.1 and 114.9 ppm respectively.

Compound **B** contained a cyclic ring ketone as indicated by its IR spectrum (1710 cm⁻¹). It showed negative test with tetranitromethane and its ¹H NMR spectrum showed,

[†]Dedicated to the memory of Late Professor Pasupati Sengupta.

in addition to the expected signals for acetoxymethyl and acetoxymethine functions and eight tertiary methyl groups, a doublet at δ 2.26 (J 12 Hz) for the ketomethine proton at C₈ that couples with the adjacent *trans* axial proton at C₉. The two ketomethylene protons at C₆ appeared as ill-defined multiplets in the region δ 1.88–2.19 ppm. The ¹³C NMR spectrum of **B** did not show any signal for olefinic carbons but showed a signal at δ 215.8 ppm for the carbonyl carbon (C₇). The mass spectral fragmentations of **B** coupled with the above spectral data were in agreement with the structure **7** assigned to it. Compounds **A** and **B** were thus identified as multiflor-7,9 (11)-dien-3 β -acetate (**6**) and 7-keto-multiflor-3 β -acetate (**7**) respectively.

Reaction of the epoxide **1** with boron trifluoride etherate (BF₃·Et₂O) in dry benzene at room temperature for 30 min gave a mixture of products which on chromatography over a column of silvernitrate-impregnated silica gel (10%) was resolved into three compounds. The least polar fraction (*ca.* 11%) was found to contain two compounds (TLC) and on careful rechromatography yielded a product characterized as the diene (**6**) obtained earlier as described above. The second component yielded a compound (*ca.* 50%) that was identified as 3 β -acetoxy-D-friedoolean-14-en-7 α -ol i.e., 7 α -hydroxy taraxeryl acetate (**3**) from its elemental analysis and spectral data (see Experimental.) The hydroxy-acetate (**3**) on hydrolysis with 5% methanolic KOH afforded D-friedoolean-14-en-3 β ,7 α diol i.e., 7 α -hydroxy taraxerol (**5**). The physical and spectral data of **5** were in excellent agree-

ment with those reported in the literature¹³. The most polar component yielded a compound (*ca.* 25%) which was identified as 3 β -acetoxy-olean-12-en-7 α -ol i.e., 7 α -hydroxy β -amyrin acetate (**8**). The ¹H NMR spectrum of **8** showed a triplet at δ 5.21 ppm characteristic¹⁴ for the C₁₂ olefinic proton of Δ^{12} -oleanene triterpenes. The carbinolic proton at C₇ appeared at δ 3.94 (1H, t-like) ppm. The mass spectrum of **8** exhibited the base peak at m/z 218 which could be attributed to the ion formed by typical r-DA cleavage of ring-C characteristic¹⁵ for olean-12-ene triterpenes with no substitution at ring D and E. Treatment of **8** with acetic anhydride and pyridine at 100° for 3 h yielded unreacted **8** in quantitatively indicating that the hydroxyl group at C₇ has axial (α) orientation and remains unacetylated¹⁶ due to the steric hindrance rendered by the axial methyl group at C₁₄ and the axial hydrogens at C₅ and C₉. Formation of the 7 α -hydroxy derivatives (**3**) and (**8**) from the epoxide also supports the fact that the oxirane ring in **1** was indeed 7 α ,8 α .

The formation of the different nature of products obtained in the reactions of the epoxide (**1**) with HCl(g) in chloroform and BF₃-etherate in benzene may be rationalized as shown in Schemes 1 and 2. With HCl(g) the reaction proceeds through the intermediacy of the discrete carbocation (**9**) that readily loses a proton from C₉ to give the allylic alcohol (**10**) which under the strongly acidic condition eliminates a molecule of water to give the diene (**6**). Alternatively, loss of a proton from C₇ of **9** produces the enol from (**11**) of **7** which presumably isomerises by taking a proton at C₈ to give the B/C-*trans* ketone (**7**) as the only product rather than its thermodynamically less stable C₈-epimer.

Scheme 1

The reaction of the epoxide (**1**) with BF₃·Et₂O in dry

benzene (Scheme 2) initially involves the formation of an intermediate (**12**). The oxirane ring then opens up with concerted 1,2-shift(s) of the methyl group(s) followed by loss of protons to give the intermediates **13** (route-a) and **14** (route-b) which on hydrolysis with water (added during work up) afforded the rearranged alcohols **3** and **8** respectively. The formation of the diene (**6**) in the above reaction can be explained by assuming the formation of the carbocation intermediate (**15**) from **12** that loses a proton from C₉ to give another intermediate (**16**) which finally yielded the diene (**6**) in trace quantity (*ca.* 5%). Isolation of **6** in very poor yield clearly demonstrates that opening of the epoxide ring with concerted methyl migrations followed by proton loss was much favoured rather than formation of the intermediate (**15**) with a cationic centre at C₈.

Scheme 2

The structure of **5** as proposed by Watermann *et al.* is thus established. To our knowledge, the work describes the first successful synthesis of a naturally occurring C₇-oxygenated pentacyclic triterpenoid from a known compound. We however, could not obtain any 14,27-cycloisooleanane derivative from the rearrangements of **1** although we expected to get such products after going through the publication of Chakraborty *et al.*¹⁰ who obtained 14,27-cycloisoursane derivatives from the acid catalyzed rearrangements of 7 α ,8 α -epoxy bauerenyl acetate.

Experimental

All melting points reported are uncorrected. Petrol used had b.p. 60–80°. Homogeneity of compounds was checked by TLC on dried silica gel plates and spots were visualized by iodine vapours. IR spectra (KBr) were recorded on a Perkin-Elmer 1330 spectrophotometer, electronic spectra on

a Hitachi 200-20 instrument and NMR spectra on Varian-90 MHz and Bruker-300 MHz spectrometers using TMS as internal standard (chemical shifts in δ , ppm). Analytical samples were routinely dried *in vacuo* over P_2O_5 for 24 h at room temperature. All solvents were purified, distilled and dried before use.

Multiflorenyl acetate (1), m.p. 229–31° (lit.¹¹, m.p. 232–34°), was isolated from the barks of *Gelonium multiflorum* by reported procedure¹¹.

7 α ,8 α -Epoxy multiflorenyl acetate (1): A solution of *m*-chloroperbenzoic acid (2 g) in chloroform (30 ml) was added to a solution of multiflorenyl acetate (**2**; 2 g) and the mixture was stirred at room temperature for 6 h when TLC showed no further consumption of the starting material. The reaction was then stopped by addition of 10% aq. sodium sulfite solution and the organic layer was washed with saturated sodium bicarbonate solution (3 $\times$ 100 ml) and then with water until neutral. Usual work up yielded a residue (1.9 g, two spots in TLC) which was chromatographed over a column of neutral alumina (50 g). Petrol-benzene (4 : 1) eluents yielded unreacted **2** (0.4 g, m.p. 231–32°. Further elution of the column with petrol-benzene (3 : 2) afforded the epoxide (**1**; 1.46 g) which on crystallization from a mixture of CHCl_3 -MeOH gave colourless crystals of **1** (1.02 g, m.p. 234° (Found : C, 79.23; H, 10.75. $\text{C}_{32}\text{H}_{52}\text{O}_3$ requires : C, 79.28; H, 10.81%); ν_{max} 1720, 1240 and 750 cm^{-1} ; ^1H NMR δ 0.85 (3H, s), 0.87 (3H, s), 0.90 (6H, s), 0.98 (3H, s), 1.02 (3H, s), 1.08 (6H, s), 2.05 (3H, s), 3.11 (1H, br, C₇- βH), 4.46 (1H, dd, J 4.8, 10.2 Hz, C₃- αH); m/z 484 (M^+), 469, 466, 451, 391, 360, 345, 278, 218, 205, 123 (base peak), 121 and 95.

Reaction of 1 with HCl(g) in CHCl_3 : Formation of 6 and 7:

Dry hydrogen chloride was passed through a solution of **1** (0.2 g) in 40 ml of anhydrous chloroform for 45 min when TLC showed complete conversion of the starting epoxide. The organic layer was then washed with water until neutral, dried (Na_2SO_4) and evaporated to furnish the crude reaction product (0.2 g, two spots in TLC) which on chromatography over a column of silica gel (30 g) was resolved into two components. Petrol-benzene (3 : 2) eluents yielded solid-A (0.06 g) which on crystallization from a mixture of chloroform and methanol furnished colourless crystals of **6**, m.p. 212–15° (lit.¹¹, m.p. 216–18°) (Found : C, 82.27; H, 10.72. $\text{C}_{32}\text{H}_{50}\text{O}_2$ requires : C, 82.34; H, 10.80%). λ_{max} (EtOH) 232.2 (log ϵ 4.10), 238.8 (log ϵ 4.17) and 247.5 (shoulder like, log ϵ 3.94) nm; ν_{max} 1725, 1260 and 840 cm^{-1} ; ^1H NMR δ 0.79 (3H, s), 0.82 (3H, s), 0.84 (3H, s), 0.86 (3H, s), 0.88 (3H, s), 0.91 (3H, s), 0.96 (6H, s), 0.99

(3H, s), 2.01 (3H, s, OCOCH₃), 4.43 (1H, dd, *J* 4.3, 10.1 Hz, C₃- α H), 5.15 (1H, br, C₇-H) and 5.40 (1H, br, C₁₁-H). ¹³C NMR δ 36.6 (C₁), 24.1 (C₂), 81.3 (C₃), 37.4 (C₄), 48.4 (C₅), 23.7 (C₆), 118.1 (C₇), 142.6 (C₈), 144.6 (C₉), 35.2 (C₁₀), 114.9 (C₁₁), 36.7 (C₁₂), 38.45 (C₁₃), 39.7 (C₁₄), 27.6 (C₁₅), 37.4 (C₁₆), 31.7 (C₁₇), 55 (C₁₈), 35.6 (C₁₉), 38 (C₂₀), 37.3 (C₂₁), 39.6 (C₂₂), 27.7 (C₂₃), 16.7 (C₂₄), 20.8 (C₂₅), 21.0 (C₂₆), 26.2 (C₂₇), 31.7 (C₂₈), 34.0 (C₂₉), 33.8 (C₃₀), 171.3 (COCH₃), 21.1 (COCH₃), *m/z* 466 (M⁺), 451, 406, 391, 313, 299, 287, 273, 255, 205, 190, 179, 109, 95, 69 and 45 (base peak)

Further elution of the column with benzene-ethyl acetate (9 : 1) yielded solid-B (0.13 g), crystallized from a mixture of chloroform and methanol as colourless crystals, *m p* 183–85° and finally identified as **7** (Found C, 79.39, H, 10.72 C₃₂H₅₂O₃ requires C, 79.28, H, 10.81%), $\nu_{\max}$ 1710 (C=O), 1725 and 1250 (acetate) cm⁻¹, ¹H NMR δ 0.75 (3H, s), 0.78 (3H, s), 0.85 (3H, s), 0.88 (3H, s), 0.92 (3H, s), 0.93 (3H, s), 0.98 (3H, s), 1.0 (3H, s), 2.05 (3H, s), 1.88–2.19 (2H, m, C₆-methylene protons), 2.26 (1H, d, *J* 12 Hz, C₈-H), 4.25 (1H, dd, *J* 6.0, 11.8 Hz, C₃- α H), *m/z* 484 (M⁺), 483, 469, 424, 409, 360, 332, 205, 189, 123 (base peak), 121 and 95

BF₃-Etherate catalysed rearrangement of 1 Formation of 6, 3 and 8

Freshly distilled boron trifluoride etherate (5 drops) was added to a solution of **1** (0.8 g) in anhydrous benzene (60 ml) and the mixture was stirred at room temperature for 30 min. The reaction mixture was then diluted with water (50 ml), washed with saturated NaHCO₃ solution and then with water until neutral. Usual work up gave a solid (0.79 g, three spots in TLC) which was chromatographed over a column of AgNO₃-impregnated (10%) silica gel (25 g). Elution of the column with solvent systems petrol-benzene (3 : 2), benzene-ethyl acetate (19 : 1) and benzene-ethylacetate (9 : 1) furnished only solid-C (0.09 g), solid-D (0.38 g) and solid-E (0.26 g) respectively. The only solid-C on digestion with acetone yielded a white solid that showed two close spots in TLC. Rechromatography of the solid thus obtained over a column of silica gel followed by crystallization from a mixture of CHCl₃-MeOH yielded colourless crystals of the diene (**6**, 0.04 g), *m p* 210–12°, found to be identical with the sample of **6** obtained earlier from the reaction of **1** with HCl(g) in chloroform.

Solid-D, crystallized from a mixture of CHCl₃-MeOH as colourless crystals (0.25 g), *m p* 282–86°, was identified as **3** (Found C, 79.32, H, 10.71 C₃₂H₅₂O₃ requires C, 79.28, H, 10.81%), $\nu_{\max}$ 3525, 1710, 1245 and 820 cm⁻¹, ¹H NMR δ 0.81 (3H, s), 0.87 (6H, s), 0.91 (3H, s),

0.95 (3H, s), 1.0 (3H, s), 1.07 (3H, s), 1.15 (3H, s), 2.17 (3H, s), 4.53 (1H, dd, *J* 5.3, 11.0 Hz, C₃- α H), 4.01 (1H, br, C₇- β H), 5.70 (1H, dd, *J* 7.8, 3.0 Hz, C₁₅-H), *m/z* 484 (M⁺), 469, 451, 409, 328, 300 (base peak), 294, 204, 189, 123, 189, 121, 119 and 95

Solid E was crystallized from hot methanol to give colourless crystals (0.15 mg), *m p* 260–65°, which was subsequently characterized as **8** (Found C, 79.36, H, 10.74 C₃₂H₅₂O₃ requires C, 79.28, H, 10.81%), $\nu_{\max}$ 3250, 1710, 1225 and 830 cm⁻¹, ¹H NMR δ 0.86 (3H, s), 0.99 (6H, s), 1.11 (6H, s), 1.17 (3H, s), 9.94 (1H, t-like, C₇- β H), 4.57 (1H, dd, *J* 4.8, 10.8 Hz, C₃- α H), 5.21 (1H, t, C₁₂-H), *m/z* 484 (M⁺), 466, 451, 425, 406, 266, 249, 248, 218 (base peak), 206, 203, 191, 189, 133, 131, 107 and 95

7 α -Hydroxy taraxerol (5)

Compound **3** (0.09 g) was hydrolysed with 5% methanolic KOH under reflux for 6 h over a steam bath. Usual work up with ether furnished a solid (0.8 g, single spot in TLC) which was crystallized from a mixture of CHCl₃ and acetone as colourless flakes of **5** (0.05 g), *m p* 275–78° (lit¹², *m p* 175–79°), $\nu_{\max}$ 3400 cm⁻¹, ¹H NMR δ 0.81 (3H, s), 0.88 (3H, s), 0.90 (3H, s), 0.93 (3H, s), 0.94 (3H, s), 0.96 (3H, s), 0.99 (3H, s), 1.18 (3H, s), 3.30 (1H, dd, *J* 5.0, 12.0 Hz, C₃- α H), 3.99 (1H, br, *W*_{1/2} 6 Hz, C₇- β H), 5.70 (1H, dd, *J* 3.0, 7.5 Hz, C₁₅-H), 1.5–2.0 (some overlapped multiplets for the methylene protons at C₂, C₆ and C₁₆), *m/z* 442 (M⁺), 427, 409, 318 (base peak), 303, 285, 252, 236, 204, 147, 145, 123, 121, 109, 95, 93, 91, 81 and 69

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