Studies on the structure of 7α-hydroxytaraxerol

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The proposed structure of the natural product 7α-hydroxytaraxerol (D-friedoolean-14-en-3β, 7α-diol) 1 has been established by its synthesis from a known compound, multifloretol (D-C-friedoolean-7-en-3β-ol) 2.

Waterman et al.1 isolated 7α-hydroxytaraxerol from the leaves of Baistingu brassii and suggested its structure as D-friedoolean-14-en-3β, 7α-diol 1 on the basis of mass fragmentations and detailed NMR spectral studies. The compound was; however, not synthesized or correlated with any known compound. We establish herein the proposed structure of 1 by its synthesis from multifloretol 2, a compound of known2 structure and stereochemistry obtainable from the barks of the Indian plant, Gelonium multiflorum.

Multifloretol acetate 3, isolated from the barks of G. multiflorum, was treated with m-chloroperbenzoic acid in chloroform to furnish 7α, 8α-epoxy-multifloretol acetate 4 in ca 70% yield. The mass spectrum of 4 showed the molecular ion peak at m/z 484 which is 16 units higher than the molecular weight of 3. The 90 MHz 1H NMR spectrum of 4 showed, among other peaks, a broad singlet (1H) at δ 3.11 ppm assigned to the β-(equatorial) proton3 at C7. The oxirane ring formation at C7-C9 position must be α-oriented due to the facile approach of the reagent from the more exposed α - phase owing to the boat conformation 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 7α, 8α - 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 4 with BF3·Et2O in dry benzene at room temperature for 30 min. gave a product which on chromatography over a column of AgNO3-impregnated silica gel was resolved into three components. The least polar fraction (ca 11%) was found to contain two compounds (in TLC) and could not be investigated further for its very poor yield. The second component (ca 50%) was identified as β-acetoxyl-D-friedoolean-14-en-7α-ol 5 from its elemental analysis and spectral data (see Experimental). The hydroxyacetate 5, on hydrolysis with 5% methanolic KOH afforded D-friedoolean-14-en-3β, 7α-diol or, 7α-hydroxytaraxerol 1. The physical and spectral data of 1 were in excellent agreement with those reported in the literature1.

The most polar component (ca 25%) obtained in the reaction was characterised as 3β-acetoxyl-olean-12-en-7α-ol or, 7α-hydroxy-β-amyrin acetate 6. The 1H NMR spectrum of 6 showed a triplet at δ 5.21 ppm characteristic5,7 for the C12 olefinic proton of Δ12-oleanene triterpenes. The carbinolic proton at C7 appeared at δ 3.94 (1H, t-like). The mass spectrum of 6 exhibited the base peak at m/z 218 which could be attributed to the ion formed by typical r-DA cleavage of ring-C characteristic8 for olean-12-ene triterpenes with no functional substitution at ring D and E. Treatment of 6 with acetic anhydride and pyridine at 100° for 3 hr afforded unreacted 6 in quantitative yield indicating that the hydroxyl group at C7 has α-(axial) orientation and remains unacetylated8 due to the steric hindrance rendered by the axial methyl group at C14 and the axial hydrogens at C5 and C6. Formation of the 7α-hydroxy derivatives, 5 and 6, from the epoxide also supports the fact that the oxirane ring in 4 was indeed 7α, 8α.

The epoxide 4, reacted with BF3·Et2O to form an intermediate 7 or its equivalent species with a cationic centre at C5. A sequence of 1, 2-shift(s) of methyl group(s) then followed to give the cations 8 and 9 in the rearrangement stages which on deprotonation afforded the rearranged alcohols 5 and 6 respectively (Scheme I). Since 7α-hydroxytaraxereryl acetate 5 is obtained in this reaction, the conversion of 4 to 6 is not fully a concerted one, at least in our reaction condition. It may be pointed out that in the reported2
conversion of 3 to β-amyrin acetate 10 under the action of HCl (g) in chloroform, taraxeryl acetate 11 could not be isolated and 10 was the only product obtained in that reaction. Taraxeryl acetate 11 is very unstable under acidic conditions[6,7] and it is known that 11 on treatment with HCl (g) in chloroform completely isomerized to β-amyrin acetate 10 in less than 3 minutes[8] indicating that Δ\(^{13}\)-taraxene skeleton is thermodynamically less stable than the Δ\(^{15}\)-oleanene skeleton. In the conversion of 4 to 5 and 6, an intermediate 8 with cationic centre at C13 or its equivalent species was formed at the beginning. At this stage migration of the methyl group from C12 to C13 was not much favoured because in this migration, the migrated methyl group at C13 assumes I, 3-diaxial relationship with the axial (\(\alpha\)) substituent (-OH) at C7.

The structure of 1 as proposed by Waterman et al.[3] is thus established. To our knowledge, the work describes the first successful synthesis of a naturally occurring C7-oxygenated pentacyclic triterpene from a known compound. Work is now in progress to study the rearrangements of 4 under the action of other acidic reagents.

**Experimental Section**

**General.** 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 with iodine vapours. The IR spectra were recorded using KBr pellets on a Perkin-Elmer 1330 spectrophotometer (\(\nu_{\text{max}}\) in cm\(^{-1}\)) and \(^1\)H NMR spectra on Varian-90MHz and Bruker – 300 MHz spectrometers using TMS as internal standard (chemical shifts in δ, ppm). Analytical samples were routinely dried in vacuo over P\(_2\)O\(_5\) for 24 hr at room temperature. All solvents were purified, distilled and dried before use.

**Epoxidation of multiflorenyl acetate 3.** To a solution of 3 (2.0 g) in dry and distilled chloroform (70 mL) \(m\)-chloroperbenzoic acid (2 g) in chloroform (30 mL) was added and the mixture was stirred for 6 hr at room temperature when TLC showed no further consumption of the starting material. The reaction was then stopped by addition of 10% \(aq\). sodium sulphite solution and the organic layer was washed with saturated sodium bicarbonate solution (3 \(\times\) 100 mL). Usual work up yielded a residue (1.9 g, two spots in TLC) which was chromatographed over a column of neutral alumina. Petrol-benzene (4:1) eluents yielded unreacted 3 (0.4 g), m.p. 231-32°. Further elution of the column with petrol-benzene (3 : 2) afforded 4 (1.46 g) which was crystallized from a mixture of CHCl\(_3\)-MeOH to afford colourless crystals of 4 (1.02 g), m.p. 234°(Found : C, 79.23; H, 10.75; M\(^+\) 484. \(C_{32}H_{52}O_{15}\) requires C, 79.28; H, 10.81%; M\(^+\) 484), IR: 1720, 1240, 8750 cm\(^{-1}\); \(^1\)H NMR (90 MHz) :
\[ \delta 0.85 \text{ (s, 3H), 0.87 \text{ (s, 3H), 0.90 \text{ (s, 6H), 0.98 \text{ (s, 3H), 1.02 \text{ (s, 3H), 1.08 \text{ (s, 6H), 2.05 \text{ (s, 3H), 3.11 \text{ (brs, 1H, C\text{\textsubscript{2}} - BH), 4.46 \text{ (dd, 1H, J = 4.8 and 10.2 Hz, C\text{\textsubscript{2}}-c\text{\textsubscript{2}}H)}, 4.96 (\text{brs, 1H, C\text{\textsubscript{2}} - BH), 5.21 (t, 1H, C\text{\textsubscript{2}}-c\text{\textsubscript{2}}H})}, 3.94 (s, 3H), 3.11 (s, 3H), 2.05 (s, 3H), 1.18 (s, 3H), 3.30 \text{(dd, 1H, J = 5.0 and 12 Hz, C\text{\textsubscript{2}}-c\text{\textsubscript{2}}H}), 3.99 (\text{brs, W\textsubscript{v/2} = 6Hz, C\text{\textsubscript{2}}-BH), 5.70 (\text{dd, 1H, J = 3.0 and 7.5 Hz, C\text{\textsubscript{2}}-BH})}, 1.5-2.0 (\text{some multipletes, methylene protons at C\text{\textsubscript{2}}-C\text{\textsubscript{2}} and C\text{\textsubscript{2}}). MS\text{\textsuperscript{+}}: 464 (M\text{\textsuperscript{+}}), 442 (M\text{\textsuperscript{+}}), 420, 320, 300, 294, 25, 204, 197, 123, 129, 119, 95.} \]

Solid-C, crystallised from hot methanol (0.15 g), m.p. 260-65\degree was characterized as 6 (Found: C, 79.36; H, 10.74; M\textsuperscript{+} 484. C\textsubscript{2}H\textsubscript{4}O\textsubscript{2} requires C, 79.28; H, 10.81%; M\textsuperscript{+} 484; IR: 3525, 1710, 1245 and 820 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz): \( \delta 0.86 - 1.17 \) (overlapped singlets, 24H, 8 \texttimes Me), 3.94 (t-like, 1H, C\textsubscript{2} - BH), 4.57 (dd, 1H, J = 4.8 and 10.8 Hz, C\textsubscript{2} - c\textsubscript{2}H), 5.21 (t, 1H, C\textsubscript{2}-c\textsubscript{2}H\textsuperscript{-1}), MS: 484, 466, 451, 425, 406, 266, 249, 248, 218 (base peak), 206, 203, 191, 189, 133, 131, 107, 95.

**Alkaline hydrolysis of 5.** Compound 5 (0.09 g) was hydrolysed with 5% methanolic KOH for 6 hr over a steam bath. Usual work up with ether afforded a solid (0.067 g, single spot in TLC), crystallised from CHCl\textsubscript{3} - acetone as colourless flakes of 1 (0.05 g), m.p. 275-78\degree (lit m.p. 275-79\degree). IR: 3400 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300MHz): \( \delta 0.81 \) (3H), 0.88 (3H), 0.90 (3H), 0.93 (3H), 0.94 (3H), 0.96 (3H), 0.99 (3H), 1.18 (s, 3H), 3.30 (dd, 1H, J = 5.0 and 12 Hz, C\textsubscript{2}-c\textsubscript{2}H), 3.99 (brs, W\textsubscript{v/2} = 6Hz, C\textsubscript{2}-BH), 5.70 (dd, 1H, J = 3.0 and 7.5 Hz, C\textsubscript{2}-BH), 1.5-2.0 (some multipletes, methylene protons at C\textsubscript{2}, C\textsubscript{2} and C\textsubscript{2}). MS\textsuperscript{+}: 442 (M\textsuperscript{+}), 427, 409, 318 (base peak), 303, 285, 252, 236, 204, 147, 145, 123, 121, 109, 95, 93, 91, 81, 69.

**Attempted acetylation of 6.** A mixture of 6 (0.04g), pyridine (1 mL) and acetic anhydride (1 mL) was heated over a steam bath at 100\degree for 6 hr and allowed to stand overnight at room temperature. Usual work up afforded unreacted 6 in quantitative yield.

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**References**