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HYDROXY TRITERPENOIDS—I

Conversion of Methyl Oleanonate to Methyl 2α, 3β-Dihydroxyolean-12-Ene-28-Oate and 2α, 3β, 23-Trihydroxyolean-12-Ene and their Epimers

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ABSTRACT

Methyloleanonate (I) is converted to methyl 2α, 3β-dihydroxyolean-12-ene-28-oate (IV *a*), its 2β-epimer (V), 2α, 3β, 28-trihydroxyolean-12-ene (VI *a*) and its 3α-epimer by acetoxylation with Pb (OAc) 4 followed by reduction with metal hydrides.

HYDROXYLATION in ring A of triterpenoids is accomplished by four methods, (i) reaction of olean-2-enes with OsO_4[1], (ii) hydroboration of the enol-3-acetates followed by oxidation with H_2O_2[2], (iii) reaction of the enolisable ketones with Pb $(OAc)_4$ followed by reduction with metal hydrides[3], and (iv) autooxidation of C-3 ketones to the diosphenols followed by catalytic hydrogenation and reduction[4]. We now report the partial synthesis of methyl 2α, 3β-dihydroxyolean-12-ene-28-oate (IV *a*), its 2β-epimer (V), 2α, 3β, 28-trihydroxyolean-12-ene (VI *a*) and its 3α-epimer from methyloleanonate (I).

Treatment of methyloleanonate (I) with Pb $(OAc)_4$ in glacial acetic acid at 100° or in benzene using $BF_3.(OC_2H_5)_2$ as catalyst gave a product which showed three spots on tlc. Crystallisation of the crude product from methanol afforded the 2α-acetoxy-3-ketone (II), m.p. 224–25° (lit.[7] m.p. 226–28°), $(\alpha)_D$ + 65° in about 30% yield. In this reaction the acetoxyl group approaches from the less hindered rear face of the molecule. Its IR and ^1H NMR spectral data [ν_{max} 1750 (ester C=O), 1720 (ring C=O) cm^{-1}; δ 5·57 a pair of doublets $J_{a,a}$ = 13 Hz, $J_{a,e}$ = 6 Hz, H-2] suggest an equatorial conformation for the acetoxyl at C-2 *in* II. The acetoxy ketone (II), when adsorbed on basic alumina, was found to rearrange to the 2-oxo-3β-acetate (III), m.p. 190–92° (lit.[7] m.p. 197–98°), $(\alpha)_D$ + 105°. From the spectral data (ν_{max} 1745, 1720 cm^{-1}; δ 4·95 s, H-3), it is inferred that the acetoxyl at C-3 is equatorial. A precedent for this isomerisation is found in the work of Ganguli *et al.*[4] who suggested a plausible mechanism.

Reduction of the acetoxy ketone (II) with $NaBH_4$ in methanol gave in high yield methyl maslinate (IV *a*), m.p. 228–30° (lit.[5] m.p. 227–28°), $(\alpha)_D$ + 75°; diacetate (Ac_2O-pyridine), m.p. 175–77° (lit.[5] m.p. 166–68°), $(\alpha)_D$ + 39°. The ^1H NMR spectral data of the diacetate (IV *b*) (δ 4·75 *d*, J = 11 Hz, H-3, 5·05 qd, H-2) suggest that H-2 and H-3 are *trans* diaxial and the hydroxyls in IV *a* are therefore *trans* diequatorial[3,6]. Similar reduction of the ketone (III) with $NaBH_4$ afforded the *cis* diol (V), m.p. 268–73° (lit.[7] m.p. 278–80°), $(\alpha)_D$ + 72° in high yield (70%).

The 2α-acetoxy-3-ketone (II) on reduction with $LiAlH_4$ in dry ether gave a mixture of two compounds (tlc), the olean-12-ene-2, 3, 28-triols, which were separated by chromatography on acid washed alumina and purified by preparative tlc. The more polar triol (75% yield) is identified as 2α, 3β, 28-trihydroxy-olean-12-ene (VI *a*), m.p. 272–76°, (lit.[9] m.p. 275–79°), $(\alpha)_D$ + 70°, ν_{max} 3400 cm^{-1}; δ 3·65 m, H-2; 3·60 d, J = 10 Hz, H-3. The ^1H NMR spectrum of its triacetate (Ac_2O-pyridine) m.p. 183–85°. (lit.[8] 187–88°) $(\alpha)_D$ + 20°, (δ 3·90 AB 5, J = 10·5 Hz,-CH_2-OAc; 5·00 m, H-2; 4·77 d, J = 10·5 Hz, H-3) indicated that the hydroxyls in ring A of the triol (VI *a*) possess *trans* diequatorial orientation. The less polar triol (yield 15%), m.p. 245–50°, $(\alpha)_D$ + 45° is probably the 3-epimer of VI *a*. Its ^1H NMR data (δ 4·10 m, $W_{1/2h}$=22 Hz, H-2β; 3·45m, $W_{1/2h}$=4 Hz resolved as doublet J=4 Hz, H-3β; 3·40 AB q J=11Hz, -CH_2OH) suggest that H-2 and H-3 are axial and equatorial

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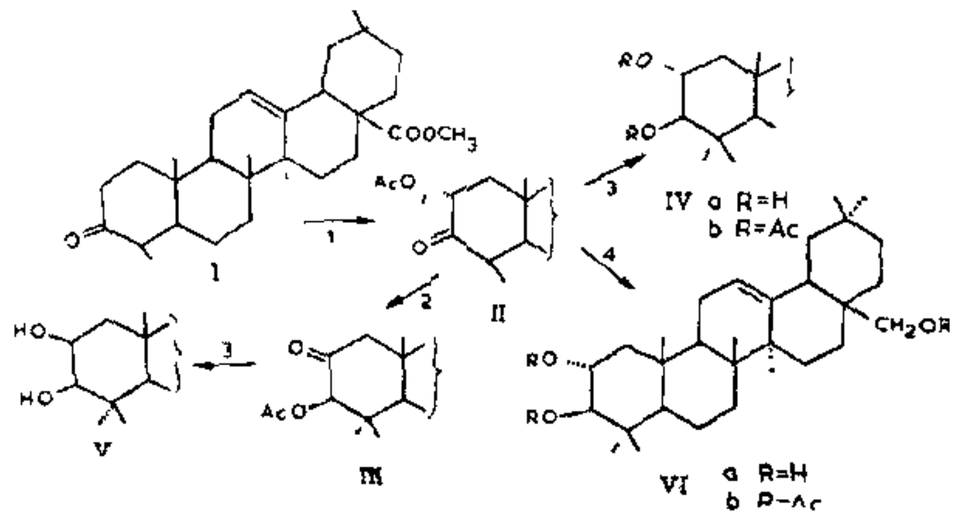
respectively[8]. There is so far no report in literature on the natural occurrence of these triols and it is likely that they may be found along with the corresponding C-17 carboxylic acids.



1. $Pb(OAc)_4$-HOAc or $Pb(OAc)_4$-BF_3. $(OC_2H_5)_2$.
2. Basic Al_2O_3.
3. $NaBH_4$-CH_3OH.
4. $LiAlH_4$-dry ether.

All compounds reported in this paper gave satisfactory C and H analyses. IR spectra were taken in KBr on Perkin Elmer Model 137 spectrophotometer and ^1H NMR spectra in $CDCl_3$ (MeS_4i as internal standard) on Varian A-60 instrument. Optical rotations were measured in methanol solution at room temperature.

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PROF. G. N. RAMACHANDRAN, F.R.S.

Professor G. N. Ramachandran, who has been recently elected a Fellow of the Royal Society, was a student of Prof. Sir C. V. Raman, with whom he worked for his doctorate at the Indian Institute of Science, Bangalore. After this, he went to the University of Cambridge, England, where he worked with Prof. Sir Lawrence Bragg from 1947 to 1949. He has been the Professor and Head of the Department of Physics at the University of Madras from 1952 to 1970 where he initiated work on the structure of biological macromolecules, studied essentially by methods of X-ray diffraction. This work initially was centred on the protein collagen, which forms the essential constituent of the connective tissue (skin, tendon, bone, etc.). Prof. Ramachandran has also been one of the earliest persons in the world to start studies on *molecular bio-physics—in particular, on protein conformation* and the structures of other biological macromolecules. In this, he and his colleagues introduced the method "dihedral angles" for working out the full three-dimensional structures of these biopolymers and related compounds.

In addition to being a Fellow of the Indian Academy of Sciences and Indian National Science Academy, Prof. Ramachandran is an Honorary Member of the American Society of Biological Chemists, an Honorary Foreign Member of the American Academy of Arts and Sciences and also a Fellow of the Royal Society of Arts, London. He has edited 8 volumes on different aspects of biopolymer structure, and has written two books on crystallography. He was the Editor of *Current Science* from 1951 to 1957, and has been, on the Editorial Board of several International Journals.

During the last six years at the Indian Institute of Science, he has set up a Department of Molecular Biophysics, which is working on the whole range of biopolymers, using a wide range of techniques. Among the achievements of this Laboratory are the finishing touches to the triple-helical structure of collagen—the role of hydroxyproline in this *protein—and the development of a new method* of solving crystal structures using packing considerations. They are also working on a new structure of DNA, which is rather different from the well-known Watson-Crick double helix. Among other important studies are those on protein-polysaccharide complexes, on membranes and on antibiotics.