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SYNTHESES AND STEREOCHEMISTRY OF (±)-4α-METHYL-10β-HYDROXY-*trans*-1,2,3,4,5,6,7,10-OCTAHYDROPHENANTHRENE-4β-CARBOXYLIC ACID LACTONE AND THE FOUR EPIMERS OF (±)-4-METHYL-1,2,3,4,5,6,7,10-OCTAHYDROPHENANTHRENE-4-CARBOXYLIC ACID*.

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In connection with the stereochemical and synthetic studies in diterpenoids related to rosenonolactone, gibberellins and their congeners, we have developed the syntheses of the lactones (I and II)** and all the four possible epimeric acids (III, IV, V and VI) with assigned stereochemistry. The communication of these results in the present stage is desirable in view of a recent publication by Mori, Matsui and Tanaga[1], reporting a synthesis of the lactone (I), following a different route, and stereochemical assignment to the acid (IV), prepared by Haworth and Barker[2].

Methyl 4-methyl-1,2,3,4,6,7-hexahydrophenanthrene-4-carboxylate (VII), b.p. 158-62°/0.4 mm., λ_{max} 264 mμ (logϵ 4.09),

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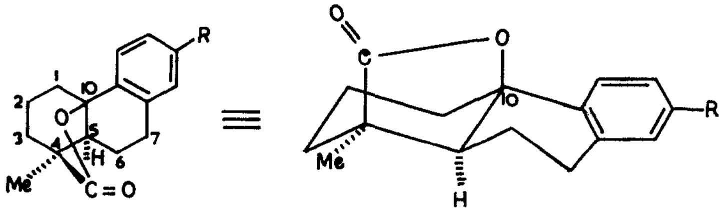
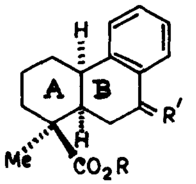
* Part of these investigations was presented at an International Symposium on "Recent Advances in Terpenoids", Poona, India, June (1965).

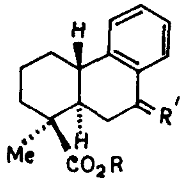
** Although formulas of one enantiomer are drawn, they are taken to represent a recemate. All new compounds for which melting and boiling points are reported have been characterised by micro-analytical data and their homogeneity have been checked by T.L.C. Infrared spectra were determined in chloroform solution and Ultraviolet spectra in 95% ethanolic solution.



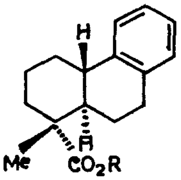
I, $R = H$
II, $R = OMe$



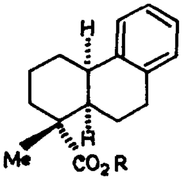
III, $R = H; R' = H_2$
XI, $R = Me; R' = H_2$
XII, $R = Me; R' = O$



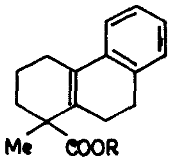
IV, $R = H; R' = H_2$
XIII, $R = Me; R' = H_2$
XIV, $R = Me; R' = O$



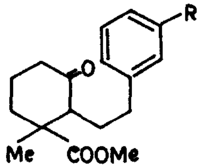
V, $R = H$
XV $R = Me$



VI, $R = H$



VII $R = Me$
IX $R = H$

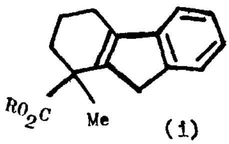


VIII, $R = H$
X, $R = OMe$

ν_{max} 1716 cm^{-1}, obtained in 77% yield, through cyclisation*** of the ketoester (VIII)[4] with concentrated sulphuric acid in benzene solution at ice-salt bath temperature[5], on alkaline hydrolysis yielded unsaturated acid (IX), m.p. 179-80°, λ_{max} 266 mμ (logϵ 4.11) in 95% yield. The acid (IX) yielded 1-methylphenanthrene on dehydrogenation with Pd-C (10%) and was converted to the lactone (I), m.p. 130-31° (lit.[1] m.p. 129-30°), ν_{max} 1760 cm^{-1}, in 70% yield, through treatment with concentrated sulphuric acid at -10~-5°. Following an identical series of reactions the lactone (II), m.p. 154-56°, ν_{max} 1761 cm^{-1}, was obtained from the ketoester (X), b.p. 183-85°/0.5 mm., yellow 2:4-dinitrophenylhydrazone, m.p. 199-200°; prepared from 2-(β-*m*-methoxyphenylethyl)-3-methyl-Δ^2-cyclohexenone[6], through the conjugate addition of hydrogen cyanide followed by alkaline hydrolysis and esterification[4].

In the first case we have based the assignment of the stereochemistry to lactone (I), on the mechanistic path of its formation and conformational analysis. This stereochemical assignment has been definitely established on the basis of the direct chemical transformations of this lactone, described in the following sections.

*** Similar cyclisation of 2-benzyl-3-methyl-3-carbomethoxy *cyclo*hexanone[3] yielded the cyclised ester (i, R = Me), b.p. 145-50°/0.3 mm., λ_{max} 260 mμ (logϵ 4.12), ν_{max} 1720 cm-1; acid (i, R = H), m.p. 145-46°, λ_{max} 260 mμ (logϵ 4.0). Through a series of transformations similar to those described in the present communication, a number of hydrofluorene derivatives have been synthesised from (i) and will be reported in a separate communication.



(i)

The catalytic hydrogenolysis (Pd-C, 10%) of the lactone (I) in ethanol yielded the acid (III), m.p. 193-94^{o}, λ_{max} 266mμ (logϵ 2.71) and 273 mμ (logϵ 2.77), methyl ester (XI) (diazomethane), m.p. 83-84^{o}, λ_{max} 266 mμ (logϵ 2.62), 274 mμ (logϵ 2.69), in excellent yield. The same acid (III) or the corresponding ester (XI) were also obtained in good yields ($\sim$80%) through catalytic hydrogenation (Pd-C, 10%) of the unsaturated acid (IX) or the ester (VII), either in neutral (ethanol) or acidic medium (acetic acid). On oxidation with chromic acid-acetic acid[4] the methyl ester (XI) yielded the ketoester (XII), m.p. 91-92^{o}, λ_{max} 248 mμ (logϵ 4.08), 294 mμ (logϵ 3.27), ν_{max} 1679 and 1722 cm^{-1}, in over 50% yield (*purified through chromatography over acid-washed alumina*). Formation of the acid (III)[7] through catalytic reduction[8] of IX established its *cis* A/B-ring junction. This fact, together with the generation of the acid (III) from the lactone (I), under hydrogenolysis condition proceeding through inversion[9] at C-10, convincingly established the assigned stereochemistry. The equatorial orientation of the carboxyl group is revealed from the complete hydrolysis[10] of the ester (XI), with 7% aqueous ethanolic potassium hydroxide at reflux for 2-3 hours.

Attempted hydrogenolysis of the lactone (I) with Raney nickel under conditions which are known to proceed with retention of configuration[11,9] either led to the recovery of the starting material or the acid (III), arising through *inversion* at C-10. However, reductive cleavage of the benzylic C-O bond[12] of the lactone (I) through short treatment with lithium liquid-ammonia in tetrahydrofuran followed by decomposition with solid ammonium chloride, proceeded with complete retention**** at C-10 and yielded (95%) the acid (IV), m.p. 189-90°, λ_{max} 267 mμ (logϵ 2.73) and 274 mμ (logϵ 2.69), methyl ester (diazomethane) (XIII), m.p. 75-77°, undepressed when mixed with the acid, m.p. 189-90° (lit.[2] 187-88°) and the corresponding methyl ester, m.p. 76-77° (lit.[2] 75-76°), prepared according to Haworth et al[2]. The methyl ester (XIII) on oxidation with chromic acid-acetic acid[4] yielded the corresponding ketoester (XIV), m.p. 102° (lit.[1], m.p. 102-103°), λ_{max} 250 mμ (logϵ 4.11) and 290 mμ (logϵ 3.33), ν_{max} 1678 and 1724 cm^{-1}, in about 30% yield. The stereochemistry assigned to this acid readily follows from its formation from lactone (I) and also confirmed from the marked resistance showed by its methyl ester (XIII) towards hydrolysis[10] (e.g., it was recovered practically unchanged on refluxing with 10% aqueous-ethanolic potassium hydroxide for over 2 hours).

The third epimeric acid (V), m.p. 209-10°; λ_{max} 266 mμ (logϵ 2.5), 274 mμ (logϵ 2.5), methyl ester (XV) (diazomethane), m.p. 54-55°; λ_{max} 266 mμ (logϵ 2.74), 274 mμ (logϵ2.67); was obtained in excellent yield through reduction[13] of the unsaturated acid (IX) with lithium liquid-ammonia in tetrahydrofuran-ether co-solvent. While equatorial nature of the carboxyl group has been established from the hydrolysis[10] (hydrolysed completely with 7% aqueous-ethanolic potassium hydroxide at reflux for 2-3 hours)

**** To our knowledge this provides the first example of a metal-ammonia induced reductive cleavage of a benzylic C-O bond with complete retention at the benzylic asymmetric centre. The scope of this novel stereospecific reductive cleavage reaction is being investigated in our laboratory.

of its ester (XV), we have based the complete stereochemical assignment to the acid (V) on consideration of the conformational, steric and also stereoelectronic factors controlling the protonation of the intermediate dianion and monoanion, involved in the course of metal-ammonia reduction of the styrenoid double bond of the acid (IX), following arguments developed by Smith[13].

The cyclisation of ethyl 1-methyl-2(β-phenylethyl)-Δ^2-cyclohexene carboxylate[2] with $AlCl_3$-HCl in boiling benzene[10] afforded a crystalline acidic and a liquid neutral material . The neutral material on alkaline hydrolysis yielded further quantity of crystalline acid. The combined acidic material (80% yield) on fractional crystallisation from ethyl acetate followed by conversion to the methyl ester (diazomethane), chromatographic separation over acid-washed alumina, and controlled alkaline hydrolyses yielded the ester (XIII), m.p. 77°, the acid (V), m.p. 210-211°, alone or mixed with the samples described above; and the remaining epimeric acid (VI), m.p. 206°, λ_{max} 266 mμ (logϵ 2.58), 273 mμ (logϵ 2.58) in ratio of about 1:7:5.

The catalytic hydrogenation (Pd-C, 10%) of the unsaturated acid (IX) in ethanol in presence of triethylamine yielded (~5%) the acid (VI) m.p. 205-206°, alone or mixed with the sample described above, which was separated through fractional crystallisation (from ether) from the mother liquor left after the separation of the acid (III) (~70% yield). The formation of the acid (VI) through catalytic hydrogenation[8] established the assigned *cis* stereochemistry to the ring-junction.

Acknowledgement : We thank Prof. P. C. Dutta for his kind interest in this work.

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(12) (a) For a recent review on reductive fisson with metal-ammonia reagents, see H. Smith, "*Organic Reactions in Liquid Ammonia*", in "Chemistry in Nonaqueous Ionizing Solvents", Interscience Publishers (New York), **I**, Part 2, p. 156 and p. 304 (1963); (b) H.E. Zimmerman, *Tetrahedron*, **16**, 169(1961).

(13) For an excellent critical review on the reduction of styrenoid systems with metal-ammonia reagents, see Reference 12a, p. 227.