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ACID-CATALYSED CYCLISATION OF SUBSTITUTED BENZYLCYCLOHEXANOLS. FACTORS INFLUENCING THE NATURE OF CYCLISATION PRODUCTS.

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The formation of condensed cyclic hydrocarbons, believed[1] to be substituted hydrofluorenes, by the phosphoric anhydride induced cyclisations of 6-benzyl-3-methyl-cyclohexanol and benzylmenthol, were described by Wallach[2]. Later investigations[3,4] clearly revealed that the acid-catalysed cyclisation of simple and substituted benzylcyclohexanols or the corresponding olefins, lead to the strain-free[5] bicyclo-(3.3.1)nonene system involving a six-membered ring formation, in preference to the relatively strained[6] hydrofluorene derivatives. As a part of a programme devoted to the synthesis of B-nor-diterpenoids, related to gibberellins; we have recently described[7] the synthesis of a substituted hydrofluorene (I, R=H and Me), which, to our knowledge, provided the first definite example of the formation of a hydrofluorene system through the cyclialkylation of a benzylcyclohexanol. In this communication we report few examples of this cyclisation revealing the influence of the structure and stereochemistry of the starting benzylcyclohexanol derivative and of the cyclisation reagent; on the nature of the cyclised products.

Polyphosphoric acid induced cyclisation of 2-benzyl-1,3-dimethyl-cyclohexanol (II)* b.p. 132-135°/0.4 mm., prepared by the condensation of methylmagnesium iodide with 2-benzyl-3-methyl-cyclohexanone[4], yielded the saturated hydrocarbon (III), b.p. 86-87°/0.4 mm.; λ_{max} 260 mμ (log ε 2.95), 266 mμ (log ε 3.08) and 273 mμ (log ε 3.08) in excellent yield. The structure of this hydrocarbon was established by its dehydrogenation with Pd-C (10%) to 1-methylfluorene and isolation of the ketone (IV); b.p. 105-108°/0.4 mm.; ν_{max} 1708 cm^{-1} (five-membered[8] aromatic conjugated C=O); λ_{max} 248 mμ (log ε 4.12) and 291 mμ (log ε 3.3), through oxidation with chromic anhydride-acetic acid. On cyclisation with $AlCl_3$-HCl in boiling benzene[9] the alcohol (II) yielded saturated hydrocarbon (V), b.p. 135-136°/14 mm.; λ_{max} 260 mμ (log ε 3.03), 266 mμ (log ε 3.02) and 274 mμ (log ε 2.92); in 72% yield. This hydrocarbon was recovered unchanged on attempted dehydrogenation and on oxidation yielded only the ketone (VI), b.p. 160°/12 mm.; ν_{max} 1680 cm^{-1} (six-membered[8] aromatic conjugated C=O); λ_{max} 254 mμ (log ε 4.12) and 292 mμ (log ε 3.3) in 65% yield. 1-Benzyl-3,5-dimethyl-cyclohexanol, b.p. 134-135°/0.5 mm.; prepared by the condensation of benzylmagnesium chloride with cis-3,5-dimethyl-cyclohexanone, with

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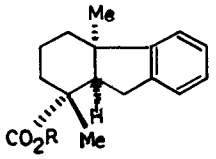
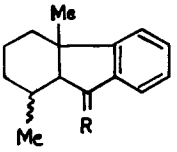
* All new compounds for which melting and boiling points are reported have been characterised by microanalytical data and the homogeneity of the solid compounds have been checked by thin layer chromatography using silica-gel G. Infra-red spectra were determined in chloroform solution and the ultraviolet spectra in 95% ethanol solution.

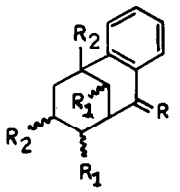


I



III , R = H_2

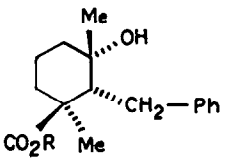
IV R = O



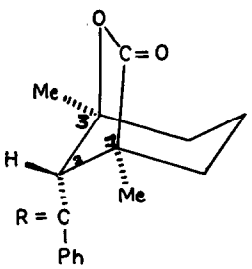
V , R = H_2 ; R_1 = Me ; R_2 = H

VI, R = O ; R_1 = Me ; R_2 = H

VII, R = O ; R_1 = H ; R_2 = Me

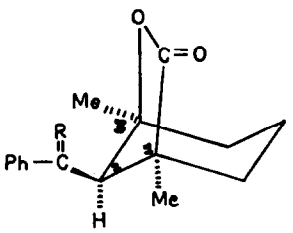


VIII



IX, R = H_2

XII, R = O



X , R = H_2

XI , R = O

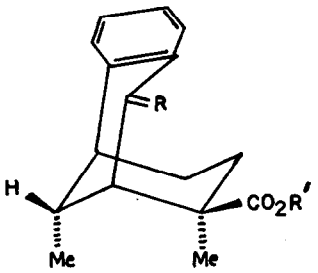
PPA cyclisation yielded saturated hydrocarbons along with substantial amount of uncyclised olefin, (removed by repeated washing with cold concentrated sulphuric acid) which on oxidation and chromatography over acid-washed alumina yielded the ketone (VII), b.p. 165°/12 mm.; ν_{max} 1680 cm^{-1} (six-membered aromatic conjugated C=O) λ_{max} 254 mμ (log ε 4.07) and 292 mμ (log ε 2.95); scarlet-red 2,4-dinitrophenylhydrazone, m.p. 183-184°; in 20-25% overall yield and a small amount of a yellowish liquid having I. R. band at 1705 cm^{-1} (five-membered ketone), which could not be characterised further; whereas the hydrocarbon from $AlCl_3$-HCl cyclisation on oxidation yielded only the ketone (VII) in about 25% yield.

Stereochemistry of the hydroxy-ester (VIII, R=Me), m.p. 73°, described previously[7], has now been established from the properties of the corresponding hydroxy acid (VIII, R=H), m.p. 148°, and the γ-lactone (IX), m.p. 80.5°, ν_{max} 1765 cm^{-1}; obtained from the acid (VIII, R=H), with toluene-p-sulphonic acid in boiling benzene or by treatment of cold-benzene solution of the ester (VIII, R=Me) with sulphuric acid. The structure of the lactone[7], m.p. 106° has been established as (X). These stereochemical assignments have been made from the n.m.r. studies (in $CDCl_3$ solution) of the keto-lactones (XI), m.p. 132-133°, ν_{max} 1768 cm^{-1}, λ_{max} 250 mμ (log ε 4.1) and (XII), m.p. 142-143°, ν_{max} 1770 cm^{-1}, λ_{max} 250 mμ (log ε 4.0); obtained through oxidation of the lactones (X) and (IX) respectively with chromic anhydride-acetic acid. The axially oriented proton at C-2 in the

keto-lactone (XI), appeared as a singlet at τ 6.20, whereas the corresponding equitorially disposed proton in (XII) showed this singlet at τ 6.04; in agreement with the observed[10] differences of such proton signals in cyclohexane ring.

As reported earlier[7], the PPA induced cyclisation of the hydroxy-ester (VIII, R=Me) at 80-82°, yielded the hydrofluorene derivative (I, R=Me) in good yield, whereas the lactone (X), though was mostly recovered under this condition, yielded a neutral hydrocarbon at elevated temperature, having a hydrofluorene skeleton. The isomeric lactone (IX) showed similar behaviour with PPA and produced a neutral hydrocarbon which on dehydrogenation afforded 1-methylfluorene. On cyclisation with $AlCl_3$-HCl, the lactone (X) yielded the acid (XIII), m.p. 180-181°, ν_{max} 1700 cm^{-1}, n.m.r. [$(CD_3)_2SO$ solution] showed a methyl doublet at τ 9.17 and 9.05 and a methyl singlet at 8.65; in 48% yield. The methyl ester (diazomethane) (XIV), m.p. 95-96°, ν_{max} 1720 cm^{-1}, on oxidation afforded the keto-ester (XV), m.p. 89-90°, ν_{max} 1678 cm^{-1} and 1728 cm^{-1}; λ_{max} 254 (log ε 3.9) in 82% yield. The equitorial orientation of the carboxyl group in the acid (XIII) was assigned from the relatively easy hydrolysis[11] of the ester (XIV) (e.g., with refluxing 10% aqueous-ethanolic potassium hydroxide for about 3½ hours) and also from the participation of the keto-group in the hydrolysis[12] of the keto-ester (XV). The axial orientation of the C-9 methyl group has been tentatively assigned from consideration of

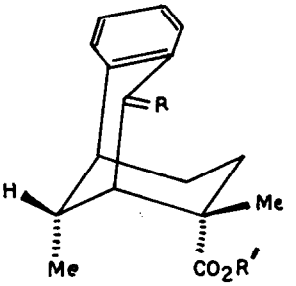
the mechanistic path of its formation (vide infra). The isomeric lactone (IX), on similar cyclisation yielded the acid (XVI), m.p. 210°, ν_{max} 1695 cm^{-1}, n.m.r. ($CDCl_3$), methyl doublet at τ 9.12 and 9.0 and a methyl singlet at τ 8.7 and (I, R=H) in 42% and 15% yields respectively. The methyl ester (XVII) (diazomethane) m.p. 98-99°, ν_{max} 1722 cm^{-1}, on oxidation yielded the keto-ester (XVIII), m.p. 95-96°, ν_{max} 1678 cm^{-1} and 1728 cm^{-1}, λ_{max} 255 mμ (log ϵ 4.16) in 71% yield. The stereochemistry of this acid was assigned from the marked resistance[11] showed by its methyl-ester (XVII) towards hydrolysis, which could only be



XIII, R = H_2 ; R' = H

XIV, R = H_2 ; R' = Me

XV, R = O ; R' = Me



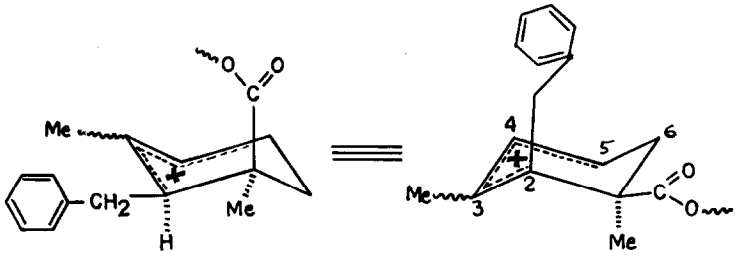
XVI, R = H_2; R' = H

XVII, R = H_2; R' = Me

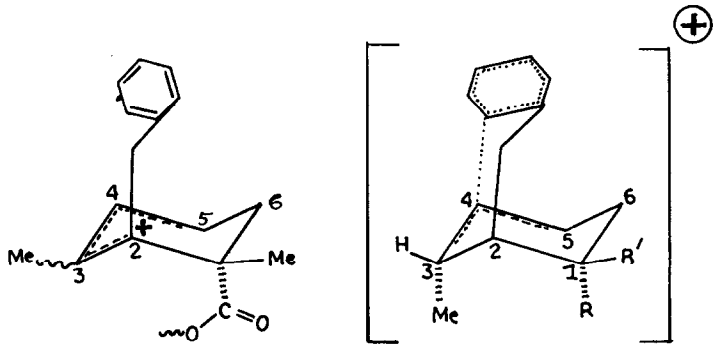
XVIII, R = O ; R' = Me

hydrolysed under drastic conditions (e.g., with boiling solution of potassium hydroxide (10%) in ethylene glycol for 4 hours). The $AlCl_3$-HCl induced cyclisation of the hydroxy-ester (VIII, R=Me), on the otherhand yielded the acid (XIII) in 29% yield, along with a neutral fraction; from which the acids (I, R=H) and (XVI) were obtained in about 22% and 16% yields respectively after hydrolysis.

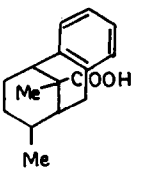
The formation of the acid (XIII) from the lactone (X) can be rationalised by assuming an intermediate carbonium ion such as (XIX) (actual nature is, however, unknown) followed by its flipping to (XX), and cyclisation at C-4. Similarly a carbonium ion (XXI), derived from the lactone (IX) and the ester (VIII, R=Me), having suitably oriented benzyl group can cyclise through an axial attack at C-4, leading to the compounds (XVI and XVII). The acid (XIII) in the cyclisation of the ester (VIII, R=Me) eventually originates from the lactone (X), formed through the carbonium ion (XXI), by epimerisation of the benzyl group prior to its cyclisation to (I, R=Me) and (XVII). These cyclisations can be reasonably represented by a transition state, such as (XXII) with sterically favoured trans orientation of the C-3 methyl group with respect to the axially approaching aromatic nucleus at C-4, giving rise to the products (XIII) and (XVI), having axial C-9 methyl group. The possibility that the acids (XIII) and (XVI), both or either of them may have the structure (XXIII) arising from cyclisation at C-6 in the



XIX XX



XXI XXII



XXIII

carbonium ions (XX) and (XXI), though could not be discarded from the evidences available so far, however, seems highly improbable, as in bringing the benzene ring at C-6 in the transition state would involve unfavourable steric interaction with cis-oriented group at C-1.

In all these examples PPA induced cyclisation mostly produced the compounds involving the alkylation at the tertiary cyclohexane carbonium ions, irrespective of the stabilities of the final products (kinetically controlled). The $AlCl_3$-HCl catalysed cyclisation, on the otherhand, proceeded through a favourable transition state leading to the strain-free benzobicyclo(3.3.1)nonene derivatives, (thermodynamically controlled), except in the case of lactone (IX) and ester (VIII, R=Me), where substantial amount of the hydrofluorene derivative was also formed. This may be due to the decrease in energy difference between the two transition states in the formation of bicyclo(3.3.1)nonene system (XVI) and the hydrofluorene(I).

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