Synthesis of 3,4-dihydroxy-3-methylisocoumarin and Pinacol- Pinacolone Rearrangement on it

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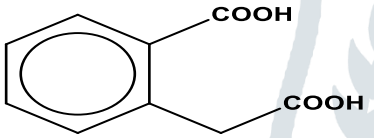
Abstract: Interaction of homophthalic acid [I] with acetic anhydride in the presence of dry pyridine at room temperature furnished 4-acetylisochroman-1, 3-dione [II]. This isochromandione was converted quantitatively on treatment with 80% H_2SO_4 into 4-carboxy-3-methylisocoumarin [III] getting partly decarboxylated during the reaction to 3-methylisocoumarin [IV] depending on the temperature of the reaction. The present work embodied in the dissertation of focuses on the new synthesis of 3, 4-dihydroxy-3-methylisocoumarin [VI] and Pinacol-Pinacolone rearrangement of [VI] by heating with $KBrO_3/H_2SO_4$ (dil) yielded the 3-methylisocoumarin-1, 4-dione [VII] Attempted epimerisation of 3, 4-dihydroxy-3-methylisocoumarin [VI] in aqueous NaOH solution, the reaction mixture was acidified with concentrated hydrochloric acid and extracted with ether. The stereochemistry involved with a view to establish the conformation of the 3, 4-diol as also the pinacol-pinacolone rearrangement on it.

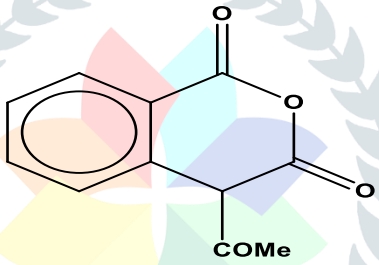
***Index terms*: Dihydroxyisocoumarin, synthesis, conformation, pinacol-pinacolone rearrangement**.

I. Introduction

Condensation of homophthalic acid with acetic anhydride in the presence of dry pyridine yields. 3-methylisocoumarin [1, 2, 3, 4] commercially available homophthalic acid [I] served as the starting material which was Condensed with acid chlorides at 200°C to afford the 3-(substituted) isocoumarins [5,6,7,8]. These compounds were required in a programme aimed at the elaboration of the synthesis of 3,4-diol via epoxide formation and their stereochemistry.



[I]



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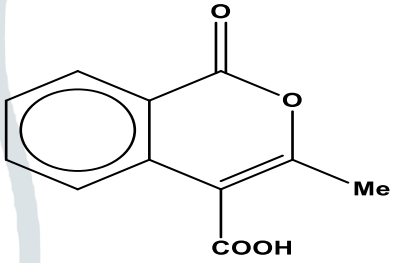

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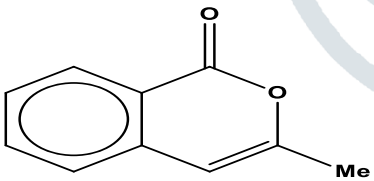

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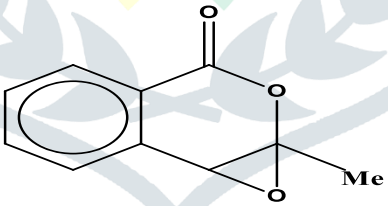
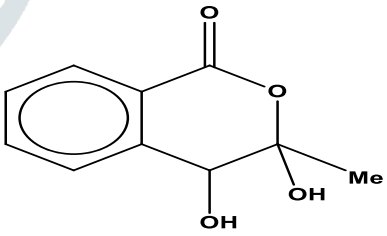
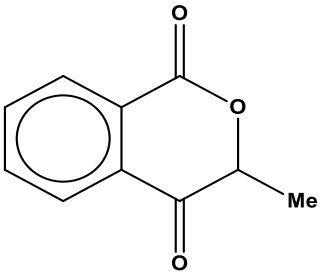


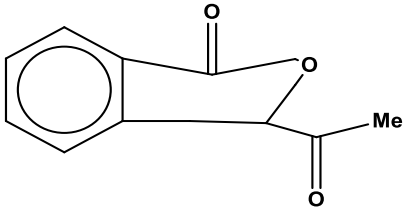
[V]



[VI]



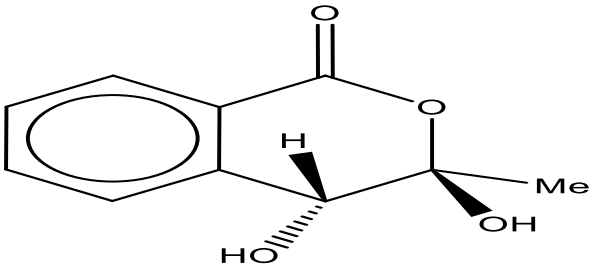
[VII]



[VIII]

Thus, homophthalic acid [I] was taken as the starting material. This compound underwent cyclization with acetic anhydride and dry pyridine in dry ether to 4-acetylisochroman-1, 3-dione [II]. The dione [II] underwent rearrangement with 80% concentrated H_2SO_4 to give a mixture of 3-methylisocoumarin [IV] and 4-carboxy-3methylisocoumarin [III]. The 4-carboxy compound was separated from [IV] by treatment with sodium bicarbonate solution followed by acidification subsequent decarboxylation of this carboxy compound again yielded the 3-methylisocoumarin [IV].

As mentioned earlier, in order to prepare the 3, 4-diol-3-methylisocoumarin was subjected to epoxidation with m-chloroperbenzoic acid in dichloromethane to form 3, 4-epoxy-3-methylisocoumarin [V]. Hydrolysis of the epoxy compound [V] with 70% concentrated H_2SO_4 afforded the vicinol diol [VI] is reasonably good yield.



[VI]

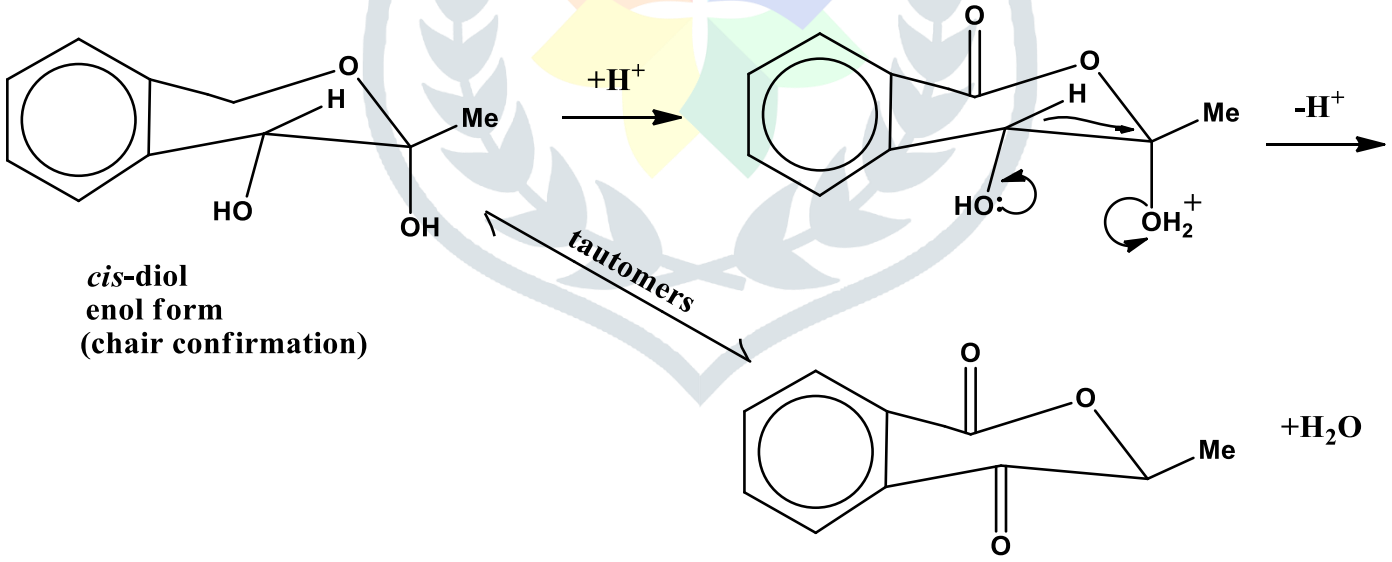
The compound [VI] was tentatively assigned to have the *trans* configuration which is indicated in the NMR spectrum ^{1}HNMRδ (300 MHz; DMSO); 2.33 (3H, s, C<u>H</u>$_3$) 1.10 (1 H, s, CO<u>H</u>CH$_3$), 1.18 (1H, s, CHO<u>H</u>), 1.21 (1 H, s, CHO<u>H</u>) and 7.5-7.8 (3H, m, Ar<u>H</u>), by the coupling constant value J = 4 Hz due to C_3-OH & C_4-H.The epimerization of C_4-H by prolonged treatment with alkali did not succeed.

Pinacol-Pinacolone rearrangement of compound [VI] by heating with $KBrO_3/H_2SO_4$ (dil) [9] yielded the 3-methylisocoumarin-1, 4-dione [VII].

II. Stereo analysis of 3,4 diol

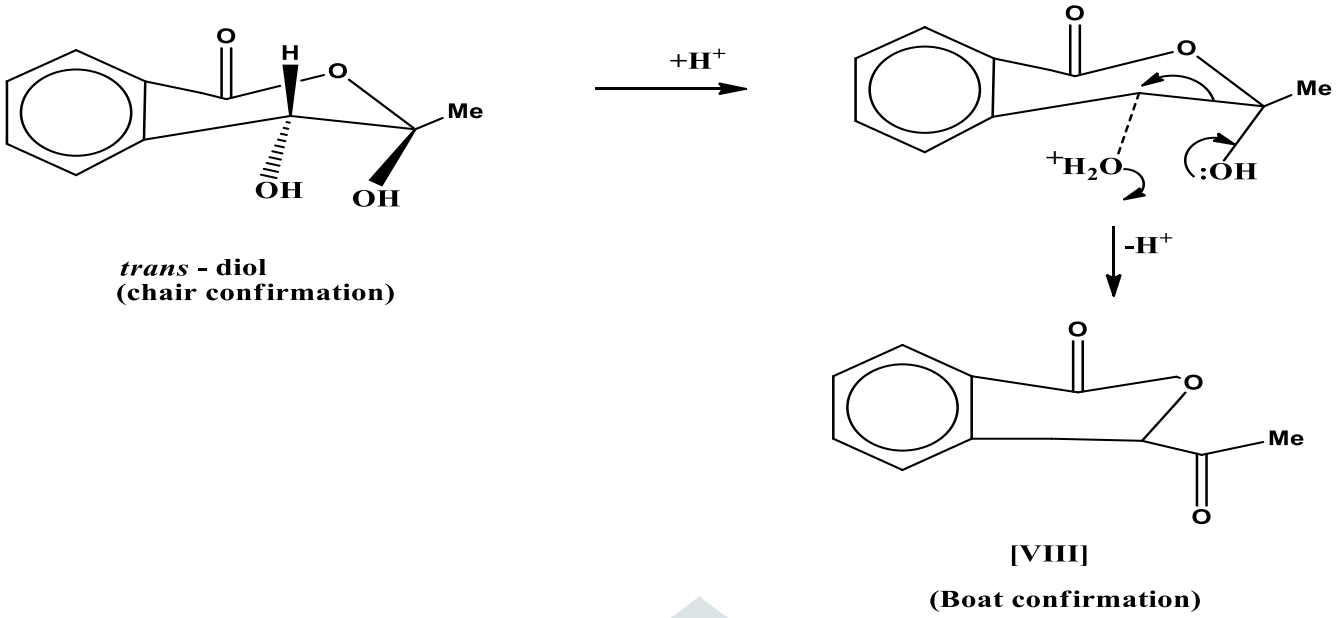
In this rearrangement the migrating group (OH) enters the *trans* to the departing group through a definite stereochemical course [10]. The *cis*-diol of 3,4-dihydroxy-3-methyisocoumarin in which the two hydroxyl groups are *trans* to each other undergoes a hydrogen shift to give 3-methylisocoumarin-1, 4-dione [VII].The 3, 4-dihydroxy derivative of compound [IV] will have a rigid conformation (i.e. chair conformation).

The *trans*-diol of 3,4-dihydroxy-3-methyisocoumarin with the two hydroxy groups in *cis*-configuration undergoes ring contraction to yield 3-acetylisocoumarin [VIII] (boat conformation). The compound [VI] and [VII] are tautomers to each other. It is expected that these compounds undergo pinacol-pinacolone rearrangement under acidic condition. All the compounds have been characterised by various spectral studies. The *cis*-diol rearranges faster than the *trans* isomer probably because of steric repulsion of two equatorial hydroxy groups.



[VII]

keto form



trans - diol
(chair confirmation)

[VIII]

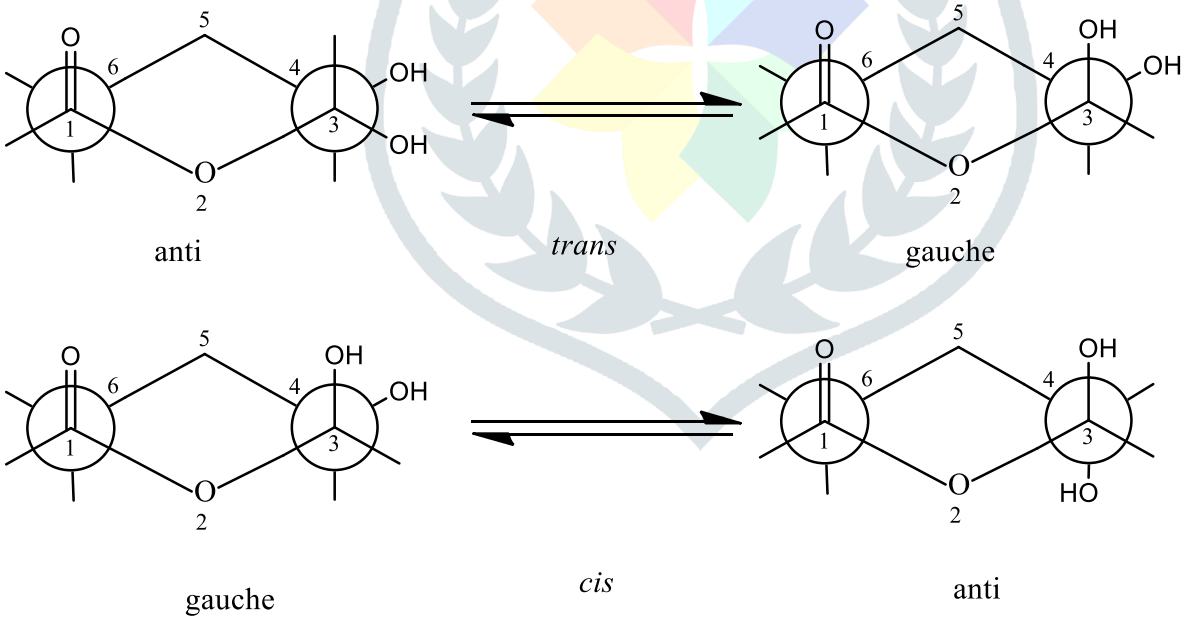
(Boat confirmation)

Conformation-Transannular effect of 3, 4-dihydroxy-3methyl-isocoumarin

Some of the chemical sequences of the peculiar geometry of isocoumarin (like other six membered ring). The two isomers form intramolecular hydrogen bonds of about the same strength [11].The greater the distance Δῡ between bonded and unbounded hydroxyl stretching frequencies.

The stronger is the intramolecular hydrogen bond. In turn, this bond is strongest when the hydroxyl groups are eclipsed or nearly eclipsed. The *cis*-diol shows stronger bonding than the *trans*-diol. This indicates that it is easier to bond the cis-group towards each other than the *trans*-group.

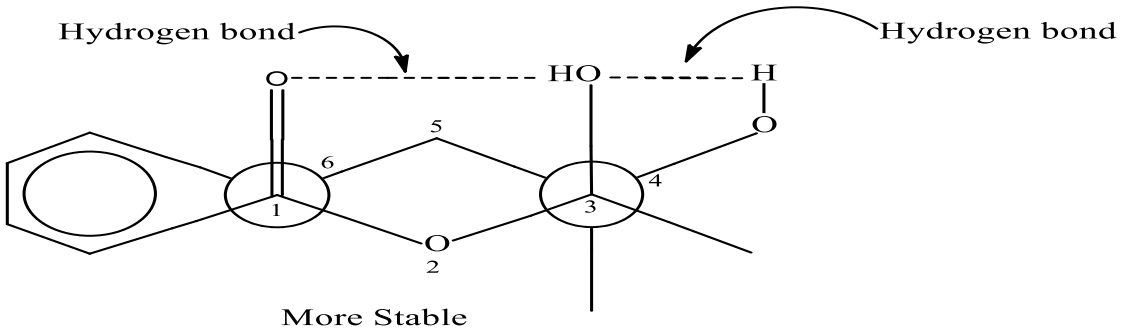
The prototype of the chair form are to be isocoumarin-3, 4-diol [VI] and bonds linking the hydroxyl groups to the ring make a dihedral angle of about 60º with each other in both the *cis* and *trans* isomer (i.e. they are staggered).



The *cis*-OH group can approach each other somewhat more readily than *trans*-OH group and therefore show stronger hydrogen bond and higher rate of glycol cleavage.

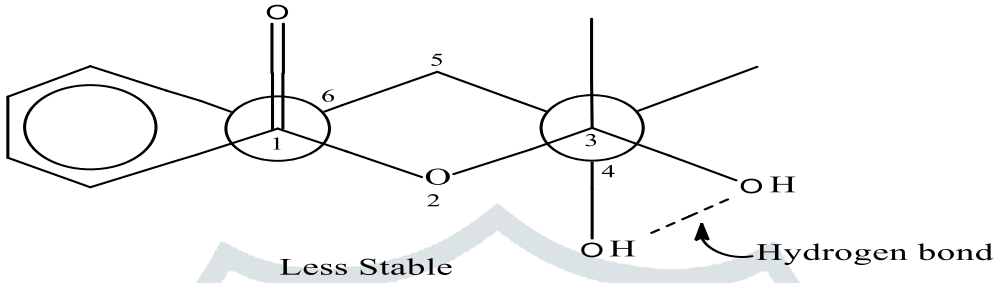
The Newman Projection Formula of 3, 4-diol :(i.e. 3, 4-Dihydroxy-3-methylisocoumarin)

One part of the present work underlines the stereochemistry in isocoumarin (two rings fused together) it is imperative to outline the stereochemistry in the fused six-membered-ring system [12]



More Stable

Due to formation of two hydrogen bonds between O-H atom.



Less Stable

Due to formation of one hydrogen bond between O-H atom.

III. EXPERIMANTAL SECTION

(A) 4-Acetylisochroman-1, 3-dione [II]

Homophthalic acid (2.0 g) was added slowly during 15 minutes to a mixture of acetic anhydride (4.0 ml) and dry pyridine (1.0 ml) with constant stirring.

After adding more of acetic anhydride (1.0 ml). The reaction was carried out. The acid slowly dissolved to form yellowish green solution and then a yellow solid slowly precipitated. Dry ether (8.0 ml) was added to the mixture to facilitate the stirring and after 1.5 hours the solid was filtered washed well with ether and dried in vacuum. It was recrystallised from petroleum-ether (60-80°) benzene as colourless crystal of 4-acetyl-isochroman-1, 3-dione (II), m.p. 160-61°, (Lit[2]. m.p. 162°C), yield 1.0 g (Found : %C = 64.58, %H = 3.78; $C_{11}H_8O_4$ requires : %C = 64.70, %H = 3.92).

(B) Rearrangement of 4-acetylisochroman-1, 3-dione [II]

[II] (0.5 g) was added portionwise to 80% sulphuric acid (3.5 ml) with shaking at 0-5°C. The reaction mixture was left in a refrigerator overnight. It was then poured on to crushed ice and the product obtained was triturated with aqueous sodium bicarbonate solution and filtered. The alkaline filtrate on acidification with concentrated hydrochloric acid furnished 4-carboxy-3-methlylisocoumarin [III]. It was recrystallised from ethylacetate-petroleum ether (60-80°). m.p. 220-221°, yield, 0.11 g (Found : %C = 64.60, %H = 3.81; $C_{11}H_8O_4$ requires : %C = 64.71, %H = 3.92).

The solid remained undissolved was filtered washed with water and was recrystallised from the mixture of ethylacetate-petroleum ether (40-60°) as colourless needless of 3-methylisocoumarin [IV]. m.p. 71-72°, (Lit [2] m.p. 73-74°), yield 0.04 g. (Found : %C = 74.89, %H = 4.90; $C_{10}H_8O_4$ requires :%C = 75.00, %H = 5.0)

(C) Decarboxylation of 4-carboxy-3-methylisocoumarin [III]

a) A solution of [III] (0.2 g) in methanol (7.0 ml) was refluxed for 16 hours with concentrated sulphuric acid (0.5 ml). The methanol was then distilled off and the reaction mixture was poured on to crushed ice when white solid was separated out. It was filtered, washed and triturated with a saturated solution of sodium bicarbonate. The solid remained was filtered, washed well and recrysatallised from ethylacetate-petroleum ether(40-60°) of 3-methylisocoumarin [IV] as colourless crystals m.p. 71-72°, yield 0.08g.

b) The [III], (0.2 g) heated at 210-12°C in an oil bath for half an hour. It was then cooled and the residue was triturated with aqueous solution of sodium bicarbonate, filtered and recrystallised from ethyl-acetate-petroleum ether (40-60°) as colourless crystals of 3-methylisocoumarin [IV] m.p. 71-72°, yield 0.04 g. mixed m.p. with the previous specimen shown no depression in m.p.

(D) 3,4-Epoxy-3-methylisocoumarin [V]

The [IV], (.04g) was treated with a solution of m-chloroperbenzoic acid (0.45 g) and dichloromethane (6.5 ml). Keep the reaction mixture at 0-5°C and shake frequently during the first hour. It was kept for 24 hours at 0-5°C. At the end of 24 hours only a slight excess of m-chloroperbenzoic acid remains unreacted which was examined by mixing an aliquot portion unreacted with excess of acidified potassium iodide solution and titration with standard sodium thiosulphate solution.

Separate the m-chloroperbenzoic acid from the dichloromethane solution by shaking with an excess of 10% sodium bicarbonate solution, removed the residual alkali by washing well with distilled water and dried the dichloromethane solution with magnesium sulphate. Distilled with the aid of an efficient fractionating column. After the dichloromethane has been removed the 3, 4-epoxy-3-methylisocoumarin [V] was obtained. The solid product was washed with distilled water and dried. It was recrystallised from conductivity water as colourless needless. m.p. 128-29°, yield 0.28 g. (Found :%C = 68.07, %H = 4.43; $C_{10}H_8O_3$ requires :%C = 68.18, %H = 4.54).

UV λ_{max}^{MeOH} : 245 and 332 nm
IR (KBr, cm^{-1}) : 1710 (>C=O of lactone), 3073 (aromatic),1428 (CH_3), 1170 (δ-lactone), 1462 (epoxy)
^{1}H NMR (DMSO) : 2.31 (3H,s, C<u>H</u>$_3$), 0.73 – 0.81 (1H,s, 4-C<u>H</u>O), 7.5 – 7.7 (3H, m, Ar<u>H</u>)

(E) 3,4-Dihydroxy-3-methylisocoumarin [VI]

Hydrolysis of a solution of [V] (1.0 g) in 70% sulphuric acid (20 ml) was refluxed for two hours on a boiling water bath and cooled at room temperature then poured on to ice water. A precipitate of 3, 4-dihydroxy-3-methylisocoumarin [VI] was furnished. It was filtered washed well with water and recrystallised from distilled water. m.p. 132-33°, yield 0.6 g.

Allylic bromination of the [VI] with NBS failed, confirming the absence of an ethylenic linkage at 3, 4-position.

UV λ_{max}^{MeOH} : 265,342 and 332 nm
IR (KBr, cm^{-1}) : 1715 (>C=O of lactone), 3075 (aromatic),1417 (CH_3), 2660 (vicinal diol) and1180 (δ-lactone)
^{1}H NMR (DMSO) : 2.33 (3H, s, C<u>H</u>$_3$),1.10 (1H,s, CO<u>H</u>CH$_3$), 1.18 (1H, s, CHO<u>H</u>), 1.21 (1H, s, C<u>H</u>OH), 7.5-7.8 (3H, m, Ar<u>H</u>)

Attempted epimerisation of [VI] (0.1 g) in aqueous NaOH solution (5.0 ml) kept in refrigerator for 72 hours. After 72 hours the reaction mixture was acidified with concentrated hydrochloric acid and extracted with ether. The ether extract was washed with water and dried (Na_2SO_4). Removol of the solvent afforded a colourless oil (0.04 g) which did not crystallise.

(F) 3-Methylisocoumarin-1, 4-dione [VII]

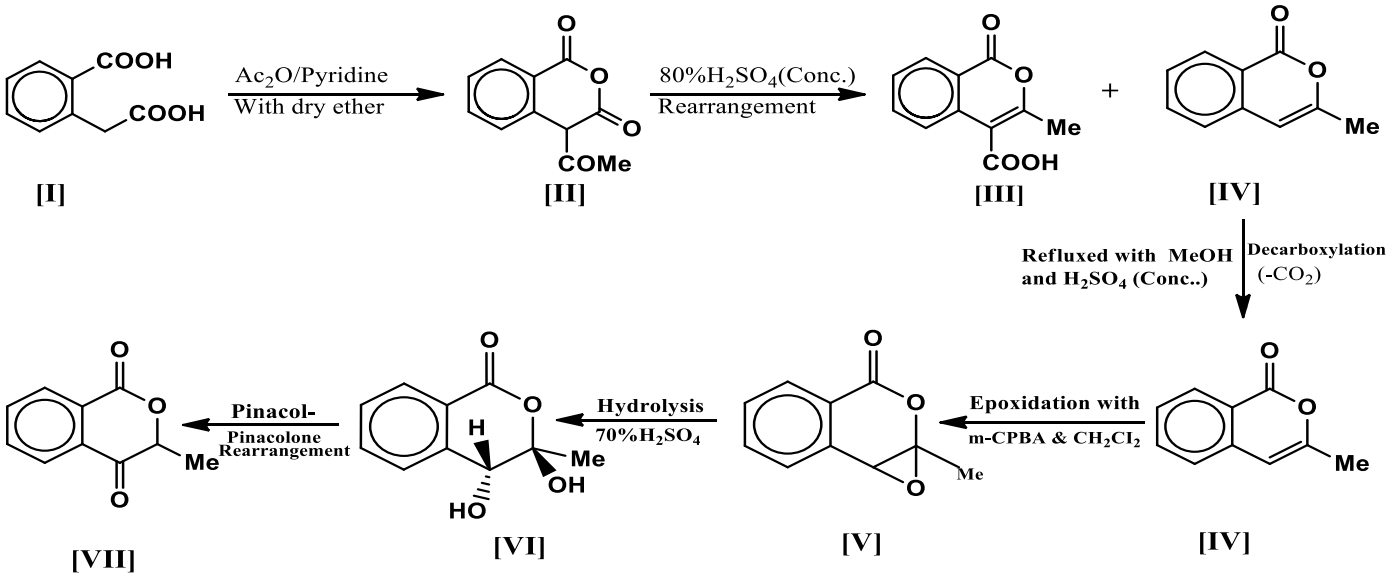
A mixture of [VI], (0.2 g), potassium bromated (0.11 g), sulphuric acid (5 ml) and water (10 ml) was slowly heated to 60° on a water bath. After a few minutes, the temperature was raised to 80° and maintained for 30 minutes. The reaction mixture was cooled in ice-bath. The separated ketone [VII] was filtered, washed with cold water and dried in an vacuum dessicator over fused calcium chloride. It was recrystallised from petroleum ether (60-80°). m.p. 118°, yield 0.14 g.

(Found :%C = 62.41, %H = 4.07; $C_{10}H_8O_4$ requires :%C = 62.50, %H = 4.17%) 2, 4-DNP derivative of [VII] was prepared in the usual way in tiny orange needles m.p. 171-72° (decomp).

UV λ_{max}^{MeOH} : 255 and 375 nm
IR (KBr, cm^{-1}) : 1718 (>C=O of lactone), 2975 (aromatic),1485 (CH_3), 1720 (>C=0 group) and 1186 (δ-lactone)
^{1}H NMR (DMSO) : 2.32 (3H, d, C<u>H</u>$_3$), 2.44 (1 H, q, C<u>H</u>CH$_3$), 7.5-7.9 (3H, m, Ar<u>H</u>)

IV. Results and Discussion

The fore going steps conclusively stabilized that 3,4 diol (*cis* and *trans* form) is obeying pinacol-pinacolone rearrangement.



Acknowledgements

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