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Synthesis of 3,4 , - dihydroxy -7- methoxy -3,6-dimethyl isocoumarin and studies of Pinacol - Pinacolone rearrangement upon them.

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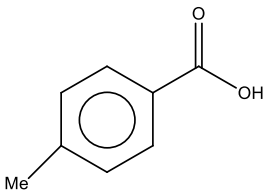
Abstract : P- Toluic acid [I] was taken as the starting material. This compound underwent sulphonation with concentrated sulphuric acid and fused with potassium hydroxide to 3 - hydroxy -3 - methylbenzoic acid [II]. The compound [II] underwent methylation with dimethyl sulphate and NaoH (aq) under reflux to give 3- methoxy - 4 methylbenzoic acid [III]. Experiment with a homogeneous solution of [III], Chloralhydrate and H_2SO_4 (conc.) afforded 6- methoxy-5-methyl-3- trichlorophthalide [IV] which was reduced with Zn - dust and glacial acetic acid to furnish 2- (ββ-Dichloroethyl)-4- methyl-5- methoxy benzoic acid [V]. The compound [V] was heated with H_2SO_4 (conc.) On water bath till no more hydrochloric gas had evolved then 2- carboxy -4 methoxy -5-methylphenylacetic acid [VI] was furnished . The compound [VI] underwent cyclization with acetic anhydride and pyridine in dry ether to give 4- acetyl - 7- methoxy -6- methylisochroman -1,3- dione [VII]. The dione underwent rearrangement with 80% H_2SO_4 to give a mixture of 4-carboxy -7-methoxy-3,6-dimethylisocoumarin [VIII]. The [VIII]-carboxy compound was separated from [VIII] by treatment with $NaHCO_3$ solution by acidification. Subsequent decarboxylation of this carboxy compound yielded 7- methoxy -3,6 dimethylisocoumarin [IX]. The present work embodied in the dissertation of focuses on the new synthesis of 3,4 - dihydroxy - 7 methoxy -3,6- dimethyl isocoumarin [XI] and pinacol pinacolone rearrangement of [XI] by heating with $KBro_3$ / H_2SO_4 (dil) yielded the 7- methoxy -3,6 dimethylisocoumarin -1 ,4 - dione [XII].

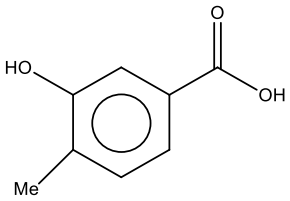
Index Term *Substituted Dihydroxyisocoumarin, synthesis, Pinacol-Pinacolone rearrangement.*

[I] ***Introduction*** P - Toluic acid [I] was taken as the starting material . Sulphonation of compound [I] with concertrated sulphuric acid and fused with potassium hydroxide furnished 3- hydroxy -4- methylbenzoic acid [II] [1].

The compound [II] underwent methylation with dimethylsulphate and aqueous sodium hydroxide under reflux to give 3- methoxy -4-methyl benzoic acid [III][1] .



[I]



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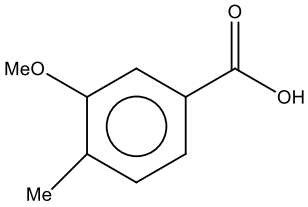

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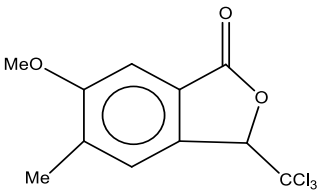

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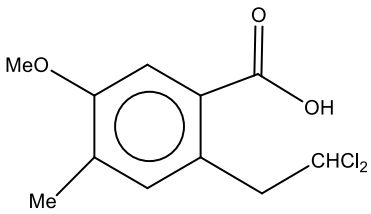
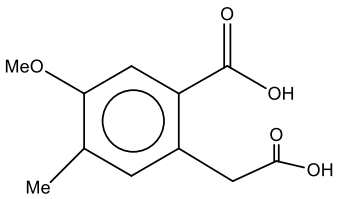
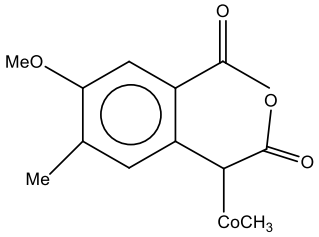


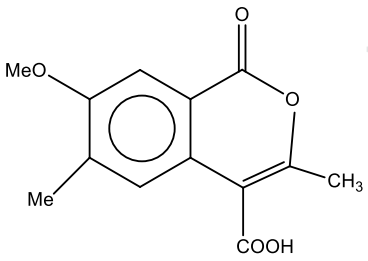
[V]



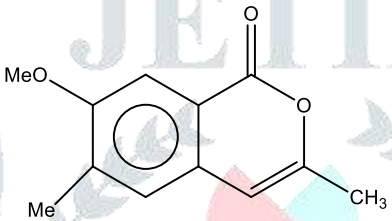
[VI]



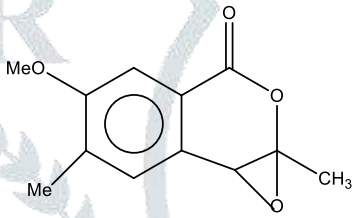
[VII]



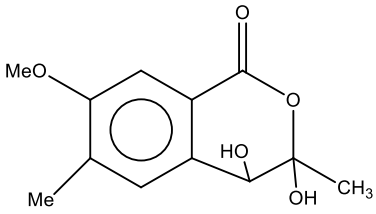
[VIII]



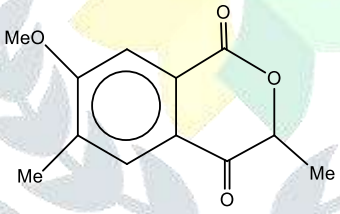
[IX]



[X]



[XI]



[XII]

Experiment with a homogeneous solution of [III] chloralhydrate and concentrated sulphuric acid afforded 6-methoxy -5-methly -3- trichlorophthalide [IV][2] which was reduced with Zn-dust and glacial acetic acid to furnish 2- (ββ- Dichloroethyl) -4-methyl -5- methoxybenzoic acid [V][3] .The compound [V] was heated with concentrated sulphuric acid on water both till no more hydrogenchloride gas had evolved then 2- carboxy -4-methoxy -5- methylphenylacetic acid [VI][4] was furnished . The compound [VI] underwent cyclization with acetic anhydride and pyridine in dry ether to give 4- acetyl -7- methoxy -6- methylisochroman -1,3 dione [VII][4] . The dione underwent rearrangement with 80 % concentrated H_2So_4 to give a mixture of 4-carboxy -7- methoxy -3,6-dimethylisocoumarin [VIII][4] . The 4- carboxy compound was separated from compound [IX] by treatment with sodium bicarbonate solution followed by acidification . Subsequent decarboxylation of this carboxy compound yielded 7 - methoxy -3,6 - dimethylisocoumarin [IX][5,6,7] .

As mentioned earlier, in order to prepare the 3,4-diol-7 - methoxy -3,6 - dimethylisocoumarin was subjected to epoxidation with m- chloroperbenzoic acid [8] in dichloromethane to form 3,4- epoxy -7- methoxy - 3, 6-dimethyl isocoumarin. The compound [X] gave the following signals in its IR , UV and NMR spectra .

UVλ_{max}^{MeOH} 252 and 349nm

IR (KBr, cm^{-1}) 1720 (>c=o of lactone), 3026 (aromatic) 2832(-OMe), 1430(C_6 – Me), 1176(δ – lactone). 1427 (C_3 - Me) and 1258 (epoxy)

^{1}HNMR (DMSO)

2.52(3H, s, 3-C<u>H</u>$_3$), 0.83 - 0.93 (1H, *s*, 4-C<u>H</u>-O-), 2.5(3H, s, 6-C<u>H</u>$_3$), 3.88 (3H, s, 7-OC<u>H</u>$_3$), 7.5 – 8.0 (2H, m,<u>H</u>-5 and <u>H</u>-8)

Hydrolysis of the epoxy compound [X] with 70% Concentrated H_2So_4 afforded the vicinal diol [XI] in reasonable good yield . The diol sured the following signals in its IR , UV and the NMR spectra.

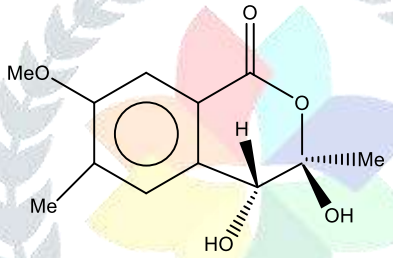
UVλ_{max}^{MeOH} 280 and 335nm

IR (KBr, cm^{-1}) 1717 (>c=o of lactone), 1172 (δ - lactone), 2658(vicinal diol), 1437 (6 - C<u>H</u>$_3$), 3028(aromatic), 2834 (-OCH$_3$) and 1421 (3-CH$_3$)

^{1}HNMR (DMSO)

2.38(3H, s, 3-C<u>H</u>$_3$), 1.31 (1H, s, 4-CO<u>H</u>-CH$_3$), 1.38(1H, *S*, 6-CHO<u>H</u>), 1.41 (1H, *s*, 7- C<u>H</u>OH), 2.49(3H, *s*, 6-C<u>H</u>$_3$), 3.86(3H, *s*, 7-OCH$_3$), 7.2 – 7.8 (2H, *m*, H-5 and H-8)

This compound [XI] was tentatively assigned to have the *trans* configuration which is indicated in the NMR spectrum by the coupling constant value J = 4Hz due to C_3- oH and C_4 -oH



[XI]

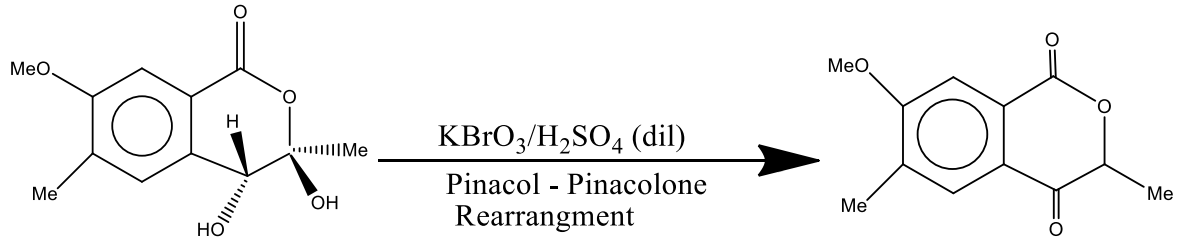
Pinacol - pinacolone rearrangement of [XI] by heating with KBro$_3$ / H_2So_4 (dil[9,10] yielded the 7- methoxy - 3,6 dimethylisocoumarin -1,4 - dione [XII] as evidenced by the following UV,IR and the NMR spectral data .

UVλ_{max}^{MeOH} 275 and 385nm

IR (KBr, cm^{-1}) 1718 (>c=o of lactone), 1426 (-CH$_3$) 2837(-OCH$_3$), 1173(δ – lactone), 1757((>c=o at C_4). and 2997 (aromatic)

^{1}HNMR (DMSO)

2.98(3H, *d*, 3-C<u>H</u>$_3$), 2.64 (1H, *q*, 3-C<u>H</u>CH$_3$), 2.48(3H, *s*, 6-C<u>H</u>$_3$), 3.88(3H, s, 7-OC<u>H</u>$_3$), 7.3 – 7.9(2H, *m*, H-5 and <u>H</u>-8)



[XI] [XII]

[II] Experimental section -

[A] 3- Hydroxy -4 - methylbenzoic acid [II]

P- Toluic acid (50g) was heated with H_2So_4 (conc.) at 155-60°c for 8 hours. It was left over night and then poured into crushed ice when 5- carboxy -2- methylbenzene sulphonic acid was precipitated out . It was filtered washed and crystallised from hot water as prismatic needles (76.5g, 90%) lit[4]yield 99%)

5 carboxy -2-methylbenzene sulphonic acid (50g) was fused with KOH (100g) of 250 -60° for an hour .

The mass obtained was dissolved in water and the solution was just acidification with concentrated sulphuric acid when potassium sulphate was separated out. It was filtered and filtrate on acidification furnished 3- hydroxy -4 - methylbenzoic acid [II] which was crystallised from water as needles (180.0 g; 50%) m.p 205-06^{o}c (Lit[4]m.p 206-07^{o}c, yield 57%)

Found : C: 63.11% ; H: 5.17%

Calculation for $C_8H_8O_3$:C:63.15%;H:5.26%

[B] 3- Methoxy -4- methylbenzoic acid [III] The compound [II] (12.5g) was methylated with dimethyl sulphate (33.0ml) and aqueous sodium hydroxide (105.0 ml ; 10%) at reflux temp. for 7 hours . The resulting solution on acidification furnished 3- methoxy -4 - methyl benzoic acid [III] . It was crystallised from aqueous methanol (12.0g) mp 162 -63°c (Lit[5] ,m.p 164-65^{o}c ,yield 13.0 g).

Found C:64.98% ; H: 5.96% calculation for $C_9H_{10}O_3$; C:65.06% ; H:6.02%

[C] 6- Methoxy -5- methyl -3- trichlorophthalide [IV]

A homogeneous solution of 3- methoxy -4- methylbenzoic acid [III] (5.5g) chloralhydrate (6.0 g) and concentrated sulphuric acid (17.0 ml) was left for three days and the reacting mixture was poured into crushed ice when a white solid was separated . It was filtered and triturated with aqueous sodium bicarbonate . It was washed with ice water and crystallised from glacial acetic acid as cluster of needles (4.8g) m.p 139 -40°c

Found C:44.58 % ; H: 2.90 %

Calculation For $C_{11}H_9O_3Cl_3$: C : 44.68 % ; H : 3.04 %

[D] 2-(ββ- Dichloroethyl) -4- methyl -5- methoxybenzoic acid [V]

The compound [IV] (5.2g) was dissolved in glacial acetic acid (27.0 ml) and to Zn - dust (3.0g) was added in small lots with constant stirring . After addition was completed stirring was continued for 1 hour. It was then heated on a water bath and filtered hot to remove zinc acetate crushed ice was added to the filtered solution when white 2- (ββ - Dichloroethyl)-4 - methyl -5- methoxy benzoic acid [V] was separated. It was treated with aqueous solution of sodium bicarbonate when the dichloro compound went into the solution . It was filtered and acidified to get back the dichloro compound . It was filtered and crystallised from ethanol as white needles (3.9g) m.p 191-92°c

Found : C: 52 .6 % ; H : 4.46 %

Calculation. For $C_{11}H_{12}O_3Cl_2$: C : 52.20 % ; H: 4.56 %

[E]2- carboxy -4- methoxy -5- methylphenylacetic acid [VI]

The compound [V] (5.0 g) was added in small lots to 98 % Sulphuric acid (40.0 ml) The addition of dichloro compound was so adjusted that the second lot was added only after the first lot had dissolved completely . After the addition was completed (1/2 hour) the reaction mixture was heated on a Water bath at about 65-70°c till no

more hydrogen chloride gas had evolved .It was poured on crushed ice. The solid separating on pouring the mixture on crushed ice was dissolved in sodium bicarbonate solution and the pasty mass remaining insoluble was removed . It was then reprecipitated and crystallised from aqueous methanol as crystals of 2-carboxy -4- methoxy -5- methylphenyl acetic acid [VI] in prismatic rods (2.0g) ; m.p 206- 7°c.

Found : C : 63 .37 % ; H :5.66 %

Calc. For $C_{11}H_{12}O_4$: C : 63.46 % ; H : 5.76 %

[F]4- Acetyl -7 - methoxy -6- methyl isochroman -1, 3 - dione [VII]

A mixture of compound [VI] (2.0g) acetic anhydride (4.5ml) and dry pyridine (4.0ml) was mechanically stirred . The acid slowly dissolved to form yellowish solution and then a yellow solid was obtained . Dry ether (10.0ml) was then added to the mixture to facilitate the stirring and after 1 .5 hours the solid was filtered washed well with ether and dried . It was crystallised from petroleum ether (60- 80°c) benzene as colourless crystals of 7- Acetyl -7- methoxy-6- methylisochroman -1,3 dione [VII] , yield : 1.0g. , m.p 108-09°

Found : C : 62 .75 % ; H: 4.73 %

Calculation For $C_{13}H_{12}O_5$: C: 62 .91. % ; H :4 84 %

[G] Rearrangement of 4- Acetyl -6- methyl -7- methoxyisochroman -1, 3 - dione [VII]

(a) The compound [VII] , (0.4g) was added portion wise to 80 % sulfuric acid (3.0ml) with constant shaking at (0-5°c). The reaction mixture was kept in ice chest overnight. It was then poured into crushed ice and the product obtained was triturated with sodium bicarbonate solution and filtered. The alkaline filtrate on acidification with concentrated hydrochloric acid furnished 4- carboxy -7-methoxy -3,6- dimethylisocoumarin [VIII] . It was crystallised from ethyl acetate petroleum ether (60-80°) ; (0.08g) . m.p. 199-200°c an admixture of this with the authentic specimen prepared by the previous method shown no. desperssion of m.p . The solid remain undissolved was filtered washed with water and was crystallised from ethylacetate petroleum ether (60-80°c) mixture as colourless needles of 7- methoxy -3,6- dimethylisocoumarin[IX] m.p. 139-40°c , yield 0.035 g
Found : C : 70 .63 % ; H: 5.76 %
Calculation For $C_{12}H_{12}O_3$: C: 70 .58. % ; H :5.88 %

UV λ_{max}^{MeOH} 284 and 345nm

IR (KBr, cm^{-1}) 1715 (>c=o of lactone), 2975, 1620, 1460,1100 (CH_3, OCH_3 and aromatic)

^{1}HNMR (60 MHz; $CDCl_3$)

2.35(3H, *s*, 3-C<u>H</u>$_3$), 2.50 (3H, *s*, CH_3-6), 3.89(3H, *s*, OCH_3 - 7), 6.0(1H, s, C-4), 7.2 - 8.0(2H,m, H-5, H-8, aromatic)

(b) The compound [VII] (0.2 g) was heated with 80% sulphuric acid (1.2 ml) on a water bath at 90-95°c for 1 hour the reaction mixture was then poured into crushed ice . The white solid obtained was triturated with $NaHCO_3$ solution and filtered . Acidification of the filtrate furnished 4-carboxy-7-methoxy-3-6-dimethylisocoumarin [VIII] . It was crystallised from benzene as colourless needless (0.04 g) m.p 200-01°c and admixture of this with the previous specimen shown no despresion in m.p. The solid that remained undissolved was washed in sodium bicarbonate solution well with ice water and crystallised from ethyle acetate petroleum ether (60-80°) as colourless needle (0.09 g) m.p 139-

40° shown no depression in m.p when admixture with the authentic specimen prepared by the previous method . It was identified as 7-Methoxy-3,6-dimethyle-isocoumarin [IX].

[H] Decarboxylation of the 4-carboxy-7-methoxy-3,6-dimethylisocoumarin [VIII]

(a) A solution of [VIII] (0.1g) in methanol (7.0ml) was refluxed for 10 hours with concentrated sulphuric acid (0.5 ml) . Methanol was then distilled off and the reaction mixture was poured into crushed ice when white solid was separated out. It was filtered, washed and triturated with sodium bicarbonate solution. The solid remained was filtered washed and crystalised from ethyl acetate petroleum-ether (60-80°c) of 7-methoxy-3,6- dimethylisocoumarin [IX] as colourless crystal (0.0.25g) and admixture of this the previous specimen method of 138-39°c .

Found C:76.48%: ; H:6.27 %

Calculation for $C_{12}H_{12}O_2$: C:76.59 % ; H:6.38 %

(b) The compound [VIII] (0.2g) heated at 210-12^{0}c in an oil both for 0.5 hour. It was then cooled and the residue was triturated with sodium bicarbonate solution, filtered and crystallised from ethyl acetate – Petroleum ether (60-80^{0}c) as colorless crystals of 7-methoxy – 3,6- dimethyiscoumarin [IX], m.p. 139-40^{0}c yield 0.06g. mixed m.p. with the previous specimen should no depression in m.p.

[I] 3,4- Epoxy-7- methoxy – 3,6- dimethylisocoumarin [X]

The compound [IX] (0.40g) was treated with a solution of m-chloroperbenzoic acid ((0.45g) and dichloromethane (6.5ml) keep the reaction mixture of (0 -5^{0}c) shake frequently during the first hour. It was kept overnight 0 -5^{0}c at the end of 24 hours only a slight excess of m-chloroperbenzoic acid (0.1g) remains confirmed this by mixing an aliquot portion with excess of acidified potassium iodide solution and titrated with standard sodium thiosulphate solution.

Separate the m- chlorobenzoic acid from the dichloromethane solution by shaking with and 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 coloumn. After the dichloromethane has been removed the 3,4- epoxy -7-methoxy – 3,6- dimethyl isocoumarin [X]. The solid product was washed with distilled water and dried . It was crystallised from conductivity water as colourless needles.

Yield :0.28g, m.p.148-49^{0}c, found : C:65.34%, H:5.35% $C_{12}H_{12}O_4$ required :C:65.46%; H:5.46%

UVλ_{max}^{MeOH} : 252 and 349 nm

IR(KBr , cm^{-1}) : 1720 (>C=0 of lactone), 3026 (aromatic)
2832(- 0CH_3); 1430 (6- CH_3)
1176 (δ- lactone), 1427 (3- CH_3) and
1258 (epoxy)

^{1}HNMR(DMSO): 2.52 (3H, s,3- C$\underline{H}_3$)
0.83-0.93 (1H,s,4-C$\underline{H}$-0-)
2.5 (3H, s,6- C$\underline{H}_3$)
3.88 (3H,s,7-OC$\underline{H}_3$)
7.5-8.0 (2H,m, H-5 and H-8)

[J] 3,4- Dihydroxy-7-methoxy-3,6- dimetheylisocoumarin [XI]

A compound [X](1.0g) in 70% concentrated sulphuric acid (20ml) was refluxed for 2 hours on a boiling water both and cooled at room temperature then poured into ice water. The 3,4- Dihydroxy-7- methoxy – 3,6- dimethylisocoumarin [XI] was furnished. It was washed well with water and crystallised from distilled water grey crystals was obtained

Yield - 0.6g, m.p:153- 54^0c

Found :C:60.40% ; H:5.78%

$C_{12}H_{14}O_5$, requires : C:60.51%; H:5.89%

Allylic bromination of the dihydroxy compound with NBS failed confirming the absence of an ethylenic linkage of 3,4- position.

UVλ^{MeOH}_{max} 280 and 335nm

IR(KBr , cm^{-1}) 1717(>C= 0 of lactone), 1172 (δ- lactone)
2658 (vicinal diol), 1437 (6- CH_3)
3028 (aromatic), 2834 (- OCH_3) and
1421 (3- CH_3)

^{1}HNMR (DMSO) 2.38 (3H, s, 3- C<u>H</u>$_3$)
1.31 (1H, s, CO <u>H</u> CH_3)
1.38(1H,s, CHO<u>H</u>)
1.41(1H,s, C<u>H</u>O<u>H</u>)
2.49 (3H, s, 6- C<u>H</u>$_3$)
3.86 (3H, s,7 O C<u>H</u>$_3$)
7.2-7.8(2H, m,H-5 and H-8)

[K] 7- Methoxy – 3,6- dimethyisocoumarin -1, 4- dione [XII]

A mixture of [XI] (0.2g), potassium bromate (0.11g) concentrated sulphuric acid (5.0 ml) and water (10.0 ml) is slowly heated to 60^0c, in a water bath. After a few minutes , the temperature was raised to 80^0c, and maintained for 30minutes. The reaction mixture was cooled in ice- bath . The separated ketone was filtered, washed with cold water and dried in Vacuum dessicator over fused calcium chloride . It was crystallised from petroleum either (60-80^0c)

Yield - 0.15g, m.p:173- 74^0c

Found :C:60.94% ; H:5.01%

$C_{12}H_{14}O_5$, requires : C:61.02%; H:5.809%

UVλ^{MeOH}_{max} : 275 and 385nm

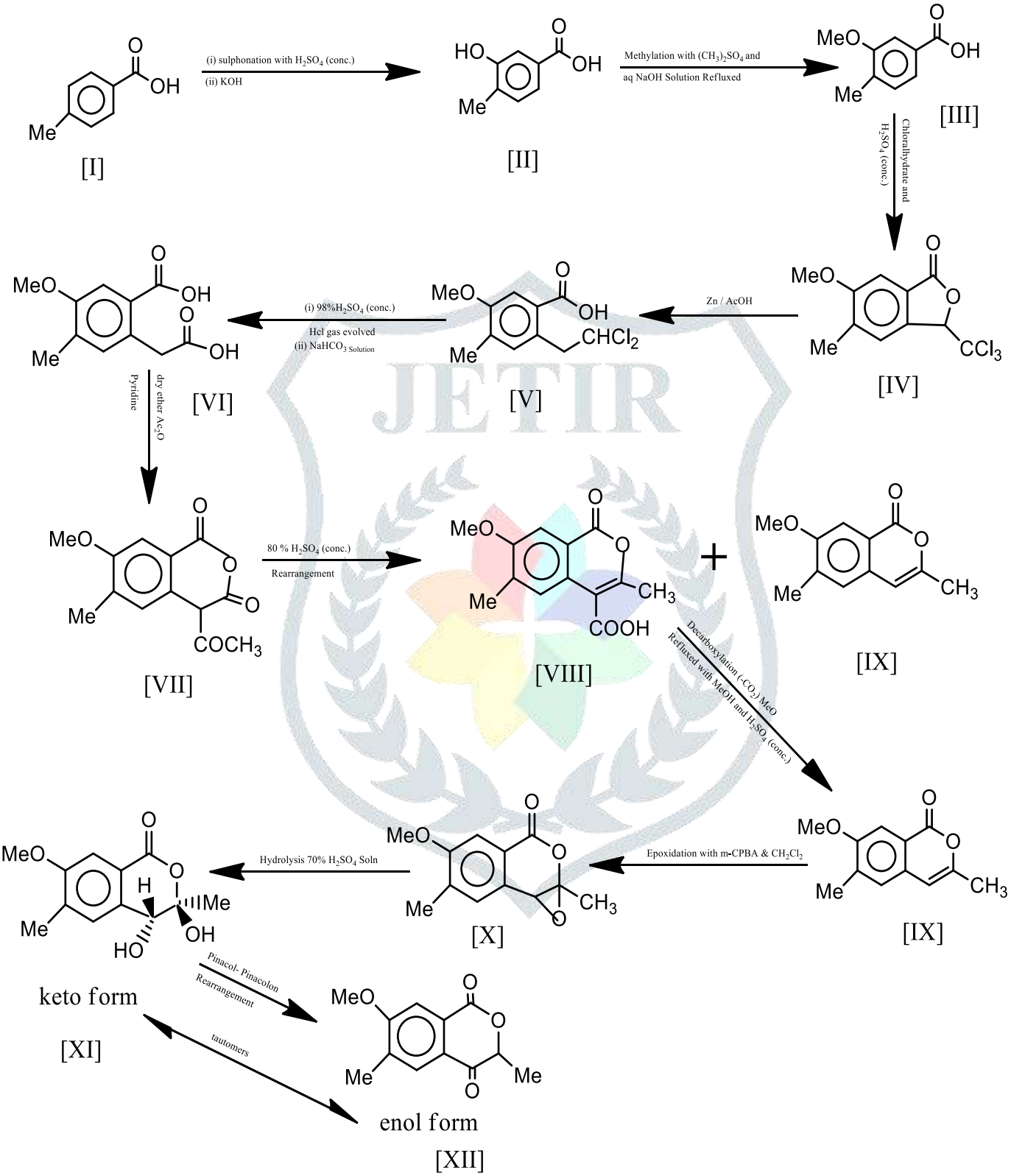
IR (KBr, cm^{-1}) : 1718 (>C= O of lactone) ; 1426(CH_3)
2837(OCH_3); 1173 (δ- lactone)
1757 (>C= at C-4) and 2997 (aromatic)

^{1}HNMR(DMSO):

2.98 (3H, d, 3- C$\underline{H}_3$)
2.64 (1H, q, 3C$\underline{H}$ CH_3)
2.48 (3H, s, 6- C$\underline{H}_3$)
3.88 (3H, s, 7- OC$\underline{H}_3$)
7.3-7.9(2H,m,H-5 and H-8)

2.4-DNP derivative of compound (XI) was prepared in the usual way a in tiny orange needles m.p. 195-96^{0}c, (decomp)

III. Results and Discussion :- The foregoing steps conclusively that 3,4- diol is obeying Pinacol – Pinacolone rearrangement under the acidic condition . The compound [XI] and [XII] are tautomers (enol to keto form) to each other.



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