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On Mesuol and Isomesuol. A Regiospecific Synthesis of Isomesuagin

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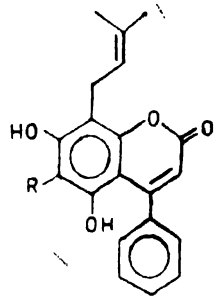
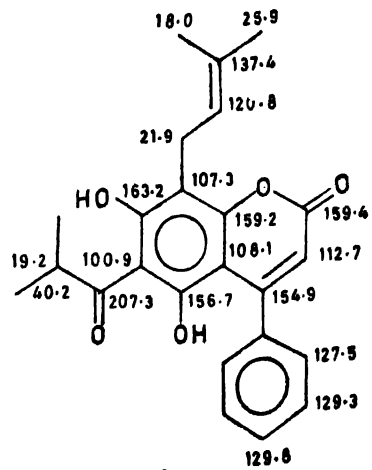
MESUOL[1], an optically inactive, bitter antibiotic[2] coumarin[3] of *Mesua ferrea* Linn. (Fam. : Guttiferae) was isolated by Dutta *et al.*[2] in 1940. They assigned its molecular formula as $C_{28}H_{22}O_5$, and its dimethyl ether as $C_{25}H_{26}O_5$. Further investigations by Chakraborty and Bose[3] revealed that mesuol and its dimethyl ether derivative responded to Seshadri's test[4] for 4-phenylcoumarins. Catalytic hydrogenation of mesuol gave a tetrahydro derivative, m.p. 181°. From the studies of the spectral properties and degradation reactions the part structure (1) for mesuol was advanced: The C_5-fragment (C_5H_5O) was assumed to contain a double bond and the fifth oxygen function.



(1) R=C_5H_5O

On the basis of revised molecular formula of mesuol as $C_{24}H_{24}O_5$ (M^+ 392) and of its dimethyl ether derivative as $C_{26}H_{28}O_5$ (M^+ 420), Chakraborty and Das[5] proposed the structure 2 and 3 for mesuol and its isomer isomesuol, respectively.



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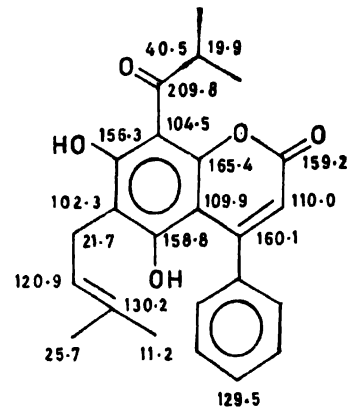


(3)

In the present report, we present the details of the previous report[5] and further results leading to the assignment of the structure of tetrahydromesuol in addition to a regiospecific synthesis of isomesuagin in support of the structure of isomesuol.

The pmr spectrum of mesuol (60 Hz, $CDCl_3$) showed the presence of signals for two chelated phenolic hydroxyls (δ 10.94 and 9.64, disappeared on deuteration), a diffuse singlet for five aromatic protons (δ 7.48), a singlet (δ 5.92), for a proton at C-3 of the coumarin nucleus, a one-proton multiplet (δ 5.28) for an olefinic proton, two proton doublets (δ 3.55, J 7 Hz) for two benzylic protons, two three-protons singlets (δ 1.88 and 1 75), each for the methyl groups of the isopropylidene function. A six-proton doublet (δ 1.10, J 7 Hz) together with a one-proton multiplet (δ 3.75) account for an isobutyryl residue (C_4H_7O). It shows the remaining four carbons of mesuol constitute an isobutyryl residue. ^{13}C nmr data of 2 and 3 not previously reported as shown on their structures, provided further support to the above conclusions.

The uv spectral data of dimethyl ether of mesuol λ_{max} 204, 230 (sh), 300 nm with log ϵ 4.50, 4.32, 4.1L support the presence of a 4-phenylcoumarin nucleus. Besides the ir bands for the lactone carbonyl, it showed a band at 1 698 cm^{-1} for an acyl function which is chelated in mesuol, and appears at the range 1 620-25 cm^{-1}, like many other acylated 5,7-dihydroxy-4-phenylcoumarins[6].

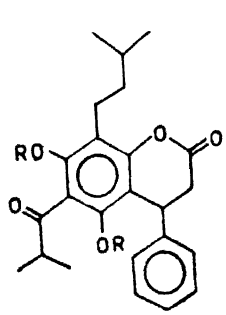
The pmr .data of dimethyl ether of mesuol showed the presence of five aromatic protons of

** In parts.

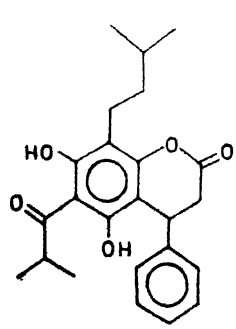
the phenyl group at C-4 (δ 7.37), a singlet (δ 6.7), for the proton at C-3 of the coumarin nucleus, the ethylenic protons of the isopropylidene group (δ 5.2), six protons of two aromatic methoxyls (δ 3.78 and 2.92), two singlets (δ 1.18 and 1.08), for 6-methyl protons of the isopropylidene group. The two benzylic protons of the isopentenyl chain (δ 3.62 and 3.5) are merged with the remaining protons of the butyryl residue. The signal of the protons of the methoxyl group at C-5 (δ 2.92) is shifted upfield due to the shielding effect of the phenyl nucleus at C-4.

With the revision of the molecular formula of mesuol, the structure of tetrahydromesuol reported by Chakraborty and Bose necessitated its proper assignment. Tetrahydromesuol, m.p. 181° reported by them was found to be homogeneous by paper chromatography but not by mass spectrometry. Besides the peak at *m/z* 396 for the tetrahydro-derivative (**4**), it had a small peak at *m/z* 402, which could be due to contamination of a decahydro-derivative (**5**) formed during hydrogenation. On further purification, it melted at 185° and gave this molecular ion peak at *m/z* 396. The nmr data of the pure tetrahydro compound showed the absence of the proton at C-3 of the coumarin nucleus, indicating the saturation of the α-pyrone double bond. In consideration of the intensity of absorption of the uv spectrum of tetrahydro mesuol (λ_{max} (EtOH) 285 and 340 nm with log ε 4.08 and 3.48) previously it was assumed that the α-pyrone double bond was in taot in tetrahydromesuol[7]. Since mesuol has an acyl function, the uv data of tetrahydromesuol could be reconciled by assuming the presence of a C-methylphloroacetophenone like chromophore[8] (λ_{max} 295 and 330 nm with log ε 4.25 and 3.39, respectively) in it. According to Crombie[9] the hydroxyl at C-5 of some 5,7-dihydroxy-6-acylcoumarin twist the phenyl ring slightly out of plane. Probably due to such a situation in mesuol, a minor amount of decahydromesuol (**5**) is formed during hydrogenation of mesuol.

Tetrahydromesuol on methylation or dimethyl ether of mesuol on hydrogenation furnished the dimethyltetrahydromesuol (**6**). The characteristic ir band for the acyl function (ν_{max} (KBr) 1 697 cm^{-1}) was readily discernible which was however



(4) R=H
(6) R=CH_3



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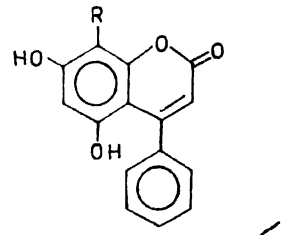
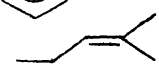
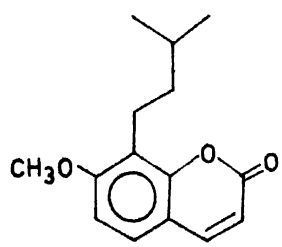


(7) R = 
(8) R = $-CH_3$

merged in the region ν_{max} 1 620 cm^{-1} in the ir spectrum of tetrahydromesuol itself.

On degradation with aqueous 40% KOH, mesuol yielded acetone, acetophenone, isovaleric acid and two constituents (a) $C_{20}H_{18}O_4$, m.p. 268° and (b) $C_{16}H_{12}O_4$, m.p. 189°. The compound $C_{20}H_{18}O_4$ was alkali-soluble and did not respond to ferric test for phenols, like 5,7-dihydroxy-4-phenylcoumarin[10]. Its uv absorption spectrum, λ_{max} 261, 340 nm (log ε 4.1, 3.30) and negative response to Gibbs test for the compound suggest structure **7** (lit. m.p. 208-14°). The compound $C_{16}H_{12}O_4$ showed ν_{max} (nujol) at 3 460, 1 688 (δ-lactone) and 710 cm^{-1} (a monosubstituted-benzene derivatives). It was soluble in alkali and like 5,7-dihydroxy-4-phenylcoumarin did not respond to ferric reaction. The uv absorption spectrum of the compound. λ_{max} (EtOH) 260, 340 nm (log ε 4.03, 4.04) and negative response to Gibbs' test led to the formulation of the compound as **8**. The formation of acetone and acetophenone could be mechanistically rationalised after the explanation of Polonosky[10] about degradation of calophyllolide, while for the formation of isovaleric acid the mechanistic interpretation by Yates and Stout[11] on the isolation of isovaleric acid from mangostin would be applicable. The driving force of the formation of acetophenone, acetone and isovaleric acid lies in the transformation of phloroglucinol unit to its keto form to facilitate reversed aldol elimination of the appropriate fragments. This has been proved by the stability of dimethyl ether of mesuol towards 40% alkali for 6 h as the dimethyl ether derivative cannot give rise to the keto form.

Dimethyl ether of tetrahydromesuol on being subjected to alkaline hydrogen peroxide oxidation, like dihydroosthol (**9**) and tetrahydromangostin (**10**), furnished isocaproic acid (**11**) confirming the presence of γ, γ-dimethylallyl residue in mesuol.



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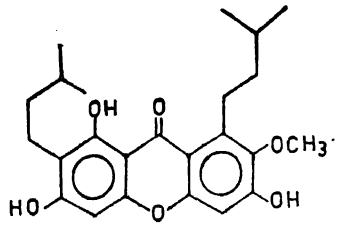


(10)

$(CH_3)_2-CH_2-(CH_2)_2-COOH$

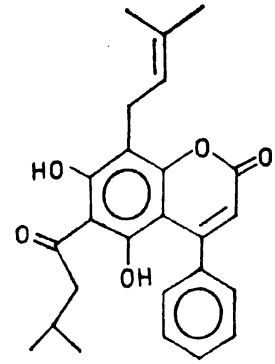
(11)

All these data suggest that mesuol has a 5,7-dihydroxy-4-phenylcoumarin with an isobutyryl and an isopentenyl residue at C-6 and C-8, respectively. Definite assignment of the positions of these side chains was made from the results of isomerisation studies with KOH solution. Mesuol on treatment with methanolic 5% KOH or aqueous 10% KOH at room temperature for 14-18 h yielded the pale yellow isomesuol[5], $C_{24}H_{24}O_5$, (M^+·392), m.p. 171°. It showed uv absorption, λ_{max} 235, 260, 338 nm (log ϵ 4.2, 4.05, 4.10) resembling that of 5,7-dihydroxy-4-phenylcoumarin. The ir spectrum of the compound showed bands at 3 300 (chelated hydroxyl), 1 735 (δ-lactone) and 710 cm^{-1} (monosubstituted benzene derivative). One of the hydroxy groups in isomesuol is more strongly hydrogen bonded than that of mesuol (ν_{max} 3 400 cm^{-1}). The compound gives a red ferric reaction like many 8-acyl-5,7-dihydroxy-4-phenylcoumarins.

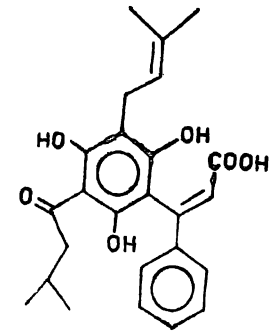
The pmr spectrum of isomesuol (60 Hz in $CDCl_3$) showed a strongly chelated phenolic hydroxy proton (δ 14.70), the other phenolic hydroxyl proton resonating at δ 5.99. The spectrum also revaled a one-proton singlet (δ 6.08) for H-3, a diffuse singlet (δ 7.60) for five aromatic protons, a one-proton multiplet (δ 5.16) for the ethylenic proton, a six-proton signal (δ 1.70) for the isopropylidene group, a six-proton doublet (δ 1.30, J 7 Hz) and a one-proton multiplet (δ 3.90) for the isobutyryl chain.

The foregoing spectral data of isomesuol are in conformity with 8-isobutyryl-6-isopentenyl-5,7-dihydroxy-4-phenylcoumarin structure (**3**) for the compound. This was also supported by ^{13}C nmr data of isomesuol as shown on its structure. Evidently, mesuol and isomesuol should be formulated as **2** and **3**, respectively. From these, structures of tetrahydromesuol and decahydromesuol follows as **4** and **5**.

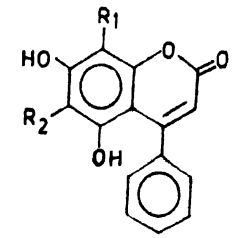
The isomerisation of 5,7-dihydroxy-6-acylcoumarin to an 8-acyl isomer had not been encountered before. Finnegan *et al.*[12] reported that mameisin (**13**) which has an acyl function at C-6 on treatment with methanolic 5% KOH remained unchanged. Similarly, Clarke *et al.*[16] reported that mammea A/AA (**14**) gave the major quantity of the unchanged material and traces of A/BA (**15**) which could be detected only by thin layer chromatography. According to Crombie, in this reaction,

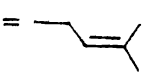
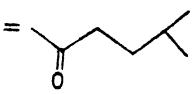


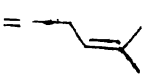
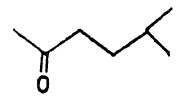
(13)



(16)

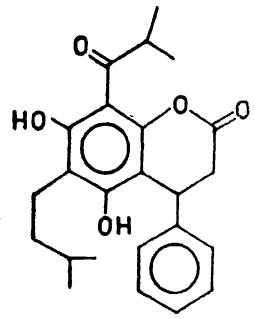


(14) R_1 =  , R_2 = 

(15) R_2 =  , R_1 = 

the equilibrium is in favour of 6-acyl species. It has been suggested by Finnegan *et al.*[12] that the coumarinic acid (**16**) obtained after hydrolysis of the 6-acylcoumarin could not rearrange as the hydroxyl at C-5 was chelated with the 6-acyl substituent. From our experiments we found that isomerisation of mesuol could be effected with methanolic 5% KOH as well as with aqueous 10% KOH. With aqueous caustic potash the yield was nearly 70%. Further evidence in support of the structure of isomesuol are furnished below.

On methylation isomesuol furnished the dimethyl ether derivative (**12**). The uv spectral data support its 5,7-dimethoxy-4-phenylcoumarin structure. The ir spectrum of dimethyl ether of isomesuol showed the band at 1 690 cm^{-1} for the acyl function. Hydrogenation of isomesuol furnished tetrahydro derivative (**17**) and from its spectral data (λ_{max} 230, 263 nm ; log ϵ 4.10, 4.09, 4.38) was assigned the structure (**17**). Crude tetrahydroisomesuol, like the corresponding product **4** obtained from mesuol, also contained a small amount of decahydro derivative (**18**) detected mass spectrometrically (M^+402). The data are convincing enough to show that isomesuol is 8-acyl isomer of mesuol. So, the tetra- and deca-hydroisomesuol could be represented as **17** and **18**, respectively.



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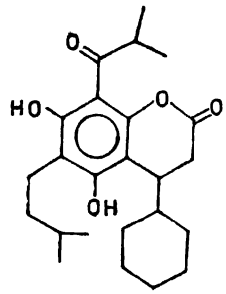
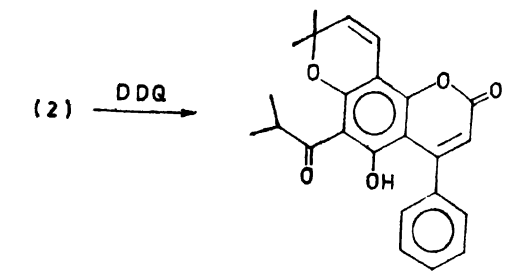


(18)

Further confirmation of the structure of isomesuol has been provided by a regiospecific synthesis of angular isomer (**21**) of mesuagin (**19**), the second antibiotic from *Mesua ferrea*[8] earlier reported by Chakraborty and Chatterjee[13]. Its structure was confirmed by its total synthesis by Chakraborty *et al.*[14] and partial synthesis by Bala and Seshadri[15]. In case of isomesuol, the cyclisation of the isopentenyl chain could be conceived to give rise to isomers of mesuagin, one linear (**20**) and another angular (**21**) ; the formation of (**21**) would be more probable from the consideration of regiospecifity[16] and would further substantiate the structure of isomesuol.



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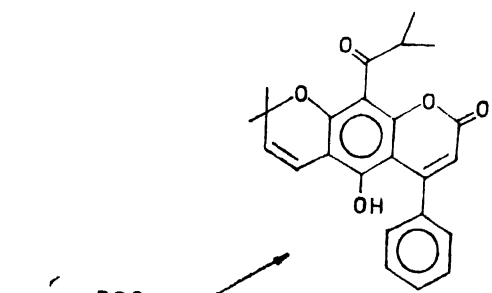

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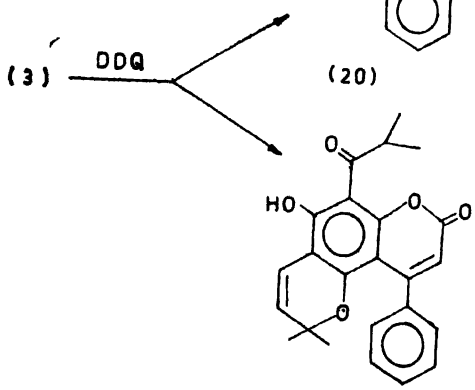

(21)

On cyclisation with DDQ (in molar quantity) at room temperature, isomesuol (**3**) gave crystalline light yellow compound, $C_{24}H_{22}O_5$ (M^+ 390), m.p. 215°. Like 8-acylcoumarin it gave a brown purple colour with $FeCl_3$ solution. The ir spectrum of the product showed a strongly chelated hydroxyl group (3 060), a δ-lactone system (1 735), chelated carbonyl (1 640) and a mono-substituted benzene moiety (700 cm^{-1}). The uv spectrum of isomesuagin (λ_{max} 235, 270, 310 nm ; log ε 4.42, 4.20, 3.50) was suggestive of the presence of a chromene ring[17] in it. The mass spectral data of isomesuagin show molecular ion peak at *m/z* 390 with a high intensity peak at (M-15) which could be represented by a benzopyrillium ion formed by loss of one of the methyl groups of the chromene ring. The peak at (M-43) may be reconciled by due to the loss of an isopropyl radical from the isobutyryl residue. The pmr spectrum of isomesuagin showed signals for five protons of the phenyl group (δ 7.24-7.40). The one-proton doublets at δ 5.42 and 6.62 (*J* 10 Hz each) together with the six-proton singlet at δ 0.96 for 2-methyl groups account for the presence of the 2,2-dimethyl-Δ^3-pyran ring in isomesuagin. The signal at δ 1.32 (*J* 10 Hz) for six protons together with a multiplet for deshielded methine proton at δ 4.15 account for the isobutyryl residue. The hydroxyl proton resonance at δ 15.42 is similar to those recorded in several 8-acyl-5,7-dihydroxycoumarin system and distinctly different from mesuagin (**19**). The pmr signal for the *gem*-dimethyl group of 2,2-dimethyl-Δ^3-pyran system in **21** unlike those of mesuagin[13], apetalolide and tomentolide[18] (δ 1.40-1.50) is shielded like those in calophyllolide and inophyllolide[18] (δ 0.94 ; 0.90 ; 0.96). This is due to the proximity of the phenyl ring at C-4. These data confirm the structure (**21**) for the angular isomesuagin.

The synthesis of mesuagin by Bala and Seshadri from **2** and the regiospecific synthesis of isomesuagin from **3** confirm both the structures of mesuol and isomesuol as reported by us earlier[5].

Evidently, the isomerisation of mesuol (**2**) to isomesuol (**3**) could presumbly be due to the steric effect of the hydroxyl at 5 on the phenyl ring at 4 twisting the latter out of plane. This effect is probably further assisted by the isobutyryl group at C-6.

Experimental

Melting points are uncorrected. Isola' n of mesuol and preparation of dimethyl ether of esuol and tetrahydromesuol and tetrahydrodimethyl ether of mesuol were carried out as described earlier.

Purification of tetrahydromesuol : Tetrahydromesuol, obtained previously was recrystallised several times from methanol, m.p. 185°.

Isomerisation of mesuol to isomesuol (**3**) *:* (i) Mesuol (100 mg) dissolved in methanolic 5% KOH (10 ml) was kept at room temperature for 18 h and then acidified with 5% hydrochloric acid and extracted with ether. On work up a pale yel o crystalline isomesuol could be obtained alt

crystallisation from methanol, (50%), m.p. 171°. (ii) Mesuol (100 mg) was dissolved in aqueous 10% KOH (10 ml) and the solution was acidified after 18 h, when a pale yellow solid precipitated. It was filtered and crystallised from methanol to get isomesuol (70%), m.p. 171° (Found : C, 73.30, H, 6.32. $C_{24}H_{24}O_5$ requires : C, 73.19, H. 6.09%).

Hydrolysis of mesuol with aqueous 40% KOH : Mesuol (500 mg) was dissolved in aqueous 40% KOH (50 ml) and refluxed for 20 min. The solution was steam-distilled, the distillate (20 ml) being collected in a solution of 2,4-dinitrophenylhydrazine sulphate when a red precipitate was obtained.

Treatment of the 2,4-DNPH fraction : The red precipitate after washing and drying was dissolved in benzene and chromatographed over a column of alumina (4 g). On working up a solid m.p. 95-100° and another melting at 230-40° were obtained from different fraction. On recrystallisation from a mixture of benzene and petroleum ether, the solid melting at 95-100°, melted at 124-26° and was identified as 2,4-DNPH of acetone by direct comparison, while the crystals melting at 230-40° melted at 245-46° and was identified as 2,4-DNPH of acetophenone by direct comparison (Found : C, 56.20, H, 4.26, N, 8.61. $C_{14}H_{12}N_4$ requires : C, 56.0, H, 4.03, N, 18.66%).

Isolation of compounds **7** and **8** *:* The solution left after steam-distillation was acidified with 5% dilute hydrochloric acid and extracted with ether. The ethereal layer on work up and repeated crystallisation from methanol yielded the compound, m.p. 267-68° (Found : C, 74.82 ; H, 6.00. $C_{20}H_{18}O_9$ requires : C, 74.52 ; H, 5.63%).

From the mother liquor left after crystallisation of **7**, a yellow compound was obtained which after several crystallisation from methanol melted at 175-78°. On sublimation at 180-210° (0.65 m) and recrystallisation of the sublimate a compound $C_{16}H_{12}O_4$, m.p. 189° (Found C, 71.39 ; H, 5.09. $C_{16}H_{12}O_4$ requires : C, 77.64 ; H, 4.5%) was obtained.

Alkaline hydrogen peroxide oxidation of dimethyl tetrahydromesuol : Dimethyl tetrahydromesuol (200 mg) was heated for 2 h with aqueous 5% KOH. Hydrogen peroxide (10% ; 15 ml) was added to it after cooling at room temperature. It was kept overnight and then heated for 6 h on water-bath. After cooling the reaction mixture, a further quantity of hydrogen peroxide was added. The mixture was heated on water-bath for 6 h. It was then cooled, acidified with dilute sulphuric acid (5%) and steam-distilled. The distillate was identified as isocaproic acid by paper chromatography using the procedure of Brown.

Attempted degredation of dimethyl ether of mesuol with 40% KOH : Dimethyl ether of mesuol (100 mg) was heated on a water-bath with aqueous 40% KOH for 6 h. On acidification of the reaction mixture in cold, dimethyl mesuol was recovered quantitatively.

Methylation of isomesuol : To a ethereal solution (25 ml) of isomesuol (150 mg) was added freshly prepared ethereal solution of diazomethane. The reaction mixture on work up furnished an oily residue which on crystallisation from aqueous methanol gave crystals homogeneous by tlc, (70%, 73 mg), m.p. 153° (Found : C, 73.03 ; H, 5.87. $C_{26}H_{28}O_5$ requires : C, 74.28 ; H, 6.67%.)

Hydrogenation of isomesuol : Isomesuol (150 mg) in ethanol (20 ml) was stirred in presence of 10% Pd/C (100 mg) at room temperature in a hydrogen atmosphere. When absorption stopped, the catalyst was filtered off and on work up yellow needless (50% yield) of tetrahydroisomesuol was obtained, m p. 166-67° (Found : C, 73.11 ; H, 6.90. $C_{24}H_{28}O_5$ requires : C, 72.72 ; H, 7.07%).

Hydrogenation of dimethylisomesuol : Dimethylisomesuol (25 mg) in spectral ethanol (10 ml) was catalytically hydrogenated using Pd/C (10-50 mg). After complete hydrogenation the catalyst was filtered off and on work up pale yellow needle shaped crystals of dimethyl tetrahydroisomesuol was obtained homogeneous by tlc (39%, 9.7 mg), m.p. 125° (Found : C, 72.87 ; H, 6.98. $C_{26}H_{32}O_5$ requires : C, 73.58, H, 7.55%).

Regiospecific synthesis of angular isomesuagin (**21**) *:* To a benzene solution (5 ml) of isomesuol (25 mg) was added DDQ (1 mol). The resulting deep orange solution was kept stirring for 2 h at room temperature (23°) when a buff coloured solid separated out. After leaving overnight, the mixture was filtered. The filtrate was concentrated and chromatographed over silica gel. From the petroleum ether-benzene (3 : 1) eluent, crystals of angular isomesuagin were obtained (90%), m.p. 215° (Found : C, 73.93 ; H, 5.82. $C_{24}H_{22}O_5$ requires : C, 73.65 ; H, 6.10%).

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