

FLAVANOID PART 7¹ : A NOVEL PHOTOSYNTHESIS OF 3- α -HYDROXYBENZYLFLAVONES
FROM 3-ARYLIDENEFLAVANONES

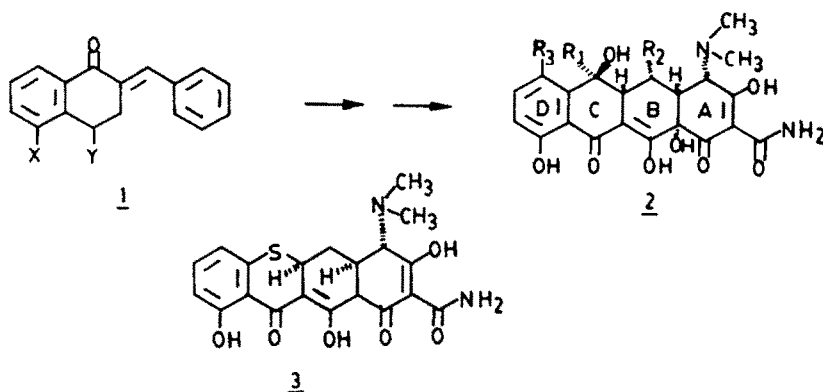
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(Received in UK 3 March 1988)

Abstract : E-3 Arylidene flavanones 4 on UV irradiation using quartzware undergo auto-oxidation to 3-aryylflavones 5. Photolysis using pyrex filter in the presence of iodoform furnishes 3- α -hydroxybenzylflavones indicating the intermediacy of the hydroperoxide 11 and form a new general method for the synthesis of these compounds not available by other routes.

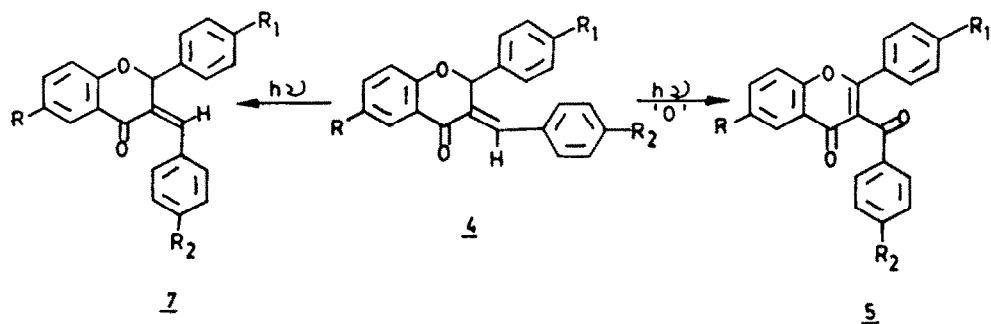
Introduction

2-Arylidene tetralones 1 have been used as key intermediates in the synthesis of ring B of tetracyclines 2². However there are no studies on the analogies with a heterocyclic ring B except for a report on the synthesis of thiatetracycline 3 superior to all known derivatives³. Similar medicinal activity can be expected for the related oxygen heterocycle and also oxa-anthracycline analogues and study in this direction is desirable as many non-natural derivatives of tetracyclines have been proved to be more useful than the products derived from microbial source⁴. With this end in view we have undertaken studies on 2-arylidene tetralones, 3-arylidene chromanones and flavanones extendable to tetra or anthracyclines. In the present paper we report photo-oxidation studies on 3-arylidene flavanones as model compounds which provide a facile synthesis of 3- α -hydroxybenzylflavones extendable to chromanones for further elaboration to tetracyclic systems.



Results and Discussion

UV irradiation of E-3-benzylidene-4"-chloro-4'-methoxy-6-methylflavanone 4a with high pressure mercury vapour lamp using quartz immersion well in the presence of air or oxygen gave 3-benzoyl-4"-chloro-4'-methoxy-6-methylflavone 5a. Its IR and ¹H-NMR spectra were not much informative, but its mass spectrum showed M⁺ at m/z = 404-406 indicating loss of two hydrogens and addition of one oxygen to 4a. ¹³C-NMR spectrum showed two carbonyl carbons at 192.58 and 176.05 δ and two downfield olefinic carbons at 162.00 and 153.98 δ . The single frequency off resonance decoupled (SPORD) spectrum clearly showed



| | a | b | c | d | e | f | g | h | i |
|----------------|------------------|-----------------|------------------|---|-----------------|------------------|---------------------|----|-----------------|
| R | CH ₃ | CH ₃ | CH ₃ | H | H | H | H | H | H |
| R ₁ | OCH ₃ | Cl | OCH ₃ | H | H | H | H | H | H |
| R ₂ | Cl | H | OCH ₃ | H | CH ₃ | OCH ₃ | OCH ₂ Ph | Cl | NO ₂ |

the expected number of singlets and doublets in addition to the high field methoxy and methyl quartets expected for 5a. Its ¹H-NMR spectrum was completely analysed by spin decoupling and Lanthanide Induced Shift (LIS) studies.

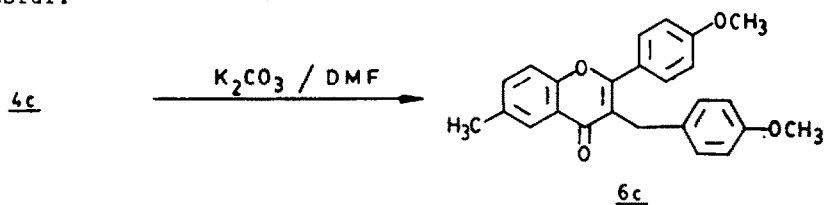
The resonance effect of 4'-methoxy group defined H-3',5' as the most high field two proton doublet at 6.75δ. Irradiation of this identified the companion doublet due to H-2'',6'' at 7.55δ (collapsed to a singlet). The most downfield one proton singlet (br) is due to H-5. The effect of chlorine on the chemical shift of benzene protons is negligible⁵. However anisotropic deshielding by C-3 carbonyl causes H-2'',6'' to appear as a clean doublet at 7.84δ and H-3'',5'' companion doublet appears at 7.36δ identified by irradiation of the former. H-7 and H-8 proton signals appear as a broad singlet due to their accidental overlap or low resolution of the instrument (90 MHz). Successive addition of Eu(fod)₃ led to the maximum relative down field shift of H-5 showing the complexation of the lanthanide at C-4 carbonyl and lanthanide induced downfield shift of H-2'',6'' comparable to that of H-5 suggested the vicinity of H-2'',6'' with C-4-C=O i.e. the exocyclic carbonyl at C-3 has S-cis conformation 5 with a free rotation of C-3-C-Ar bond, or the ring C is perpendicular to the molecular plane - i.e. H-2'',6'' are equidistant from the carbonyl group at C-4.

Similar photo-oxidation in air of E-3-benzylidene-4'-chloro-6-methylflavanone 4b and of its 4',4'' dimethoxy analogue 4c yielded 3-benzoyl-4'-chloro-6-methylflavone 5b and 3-benzoyl-4',4''-dimethoxy-6-methylflavone 5c in 27% and 31% yield. The ¹H-NMR data is given in table.

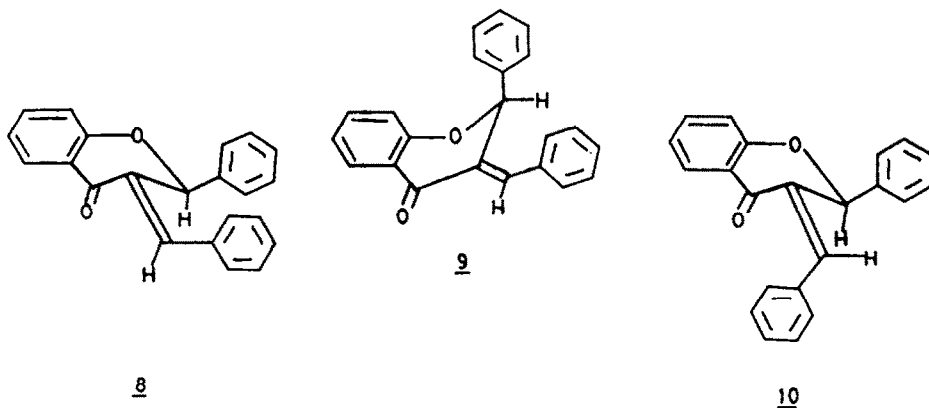
¹H-NMR data of 3-acoylflavones 5a-c

| Compd. | H-5 | H-2",6" | H-2',6' | H-3",5" | H-3',5' | H-7,8 | OCH ₃ | CH ₃ |
|-----------|---------------|------------------------------------|-----------------------------------|------------------------------------|-----------------------------------|-------|------------------|-----------------|
| <u>5a</u> | 7.98 (brs) | 7.84 (d) J _o =10 Hz | 7.55 (d) J _o =10 Hz | 7.36 (d) J _o =10 Hz | 6.80 (d) J _o =10 Hz | 7.45 | 3.8 (s) | 2.48 (s) |
| <u>5b</u> | 7.99 (brs) | 7.80 (d) J _o =10 Hz | 7.58 (d) J _o =10 Hz | 7.28 (d) J _o =10 Hz | 7.42 (d) J _o =10 Hz | 7.48 | 3.78 (s) | 2.48 (s) |
| <u>5c</u> | 7.95 (brs) | 7.84 (d) J _o =9.5 Hz | 7.58 (d) J _o =10 Hz | 6.82 (d) J _o =9.5 Hz | 6.80 (d) J _o =10 Hz | 7.42 | 3.75 (s) | 2.48 (s) |

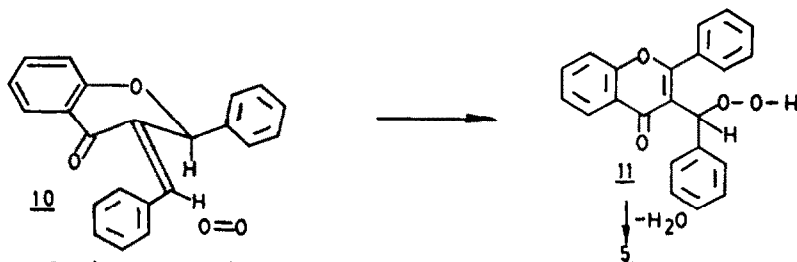
For an independent synthesis of 5c the exo double bond in 4c was isomerised by K₂CO₃-DMF⁶ to furnish 3-benzyl-4'4"-dimethoxy-6-methylflavone 6c. However oxidation of the benzylic methylene, to furnish 5c by DDQ⁷ was unsuccessful.



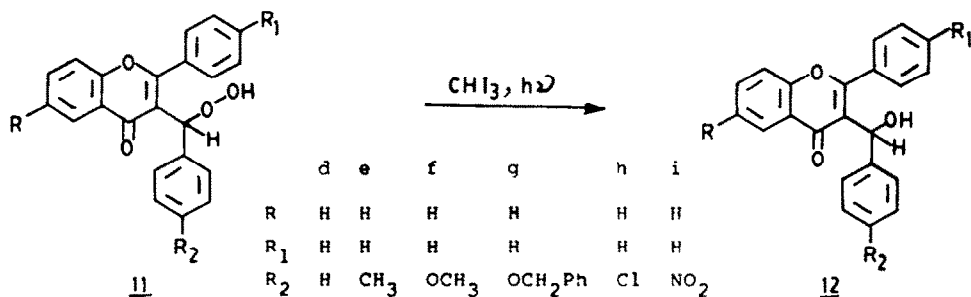
At the outset this photo-oxidation in air, with rearrangement, suggested a concerted ene reaction, with singlet oxygen under photolytic conditions acting as the enophile. The conformation of E-3-arylidene flavanone with slightly distorted half chair⁸ and/or distorted ethylene bond angles with C-2 aryl equatorial as in 8, provided the axial H-2 proton suitably disposed for ene reaction. However earlier it has been proposed⁹ that the stable conformation of 4 has C-2 aryl axial as shown in 9, to relieve the steric congestion observed in model of 4, the phenomenon generalised by Johnson as the concept of A^{1,3} strain¹⁰. In this case H-2 is equatorial and not properly disposed for abstraction. Moreover in every case prior to



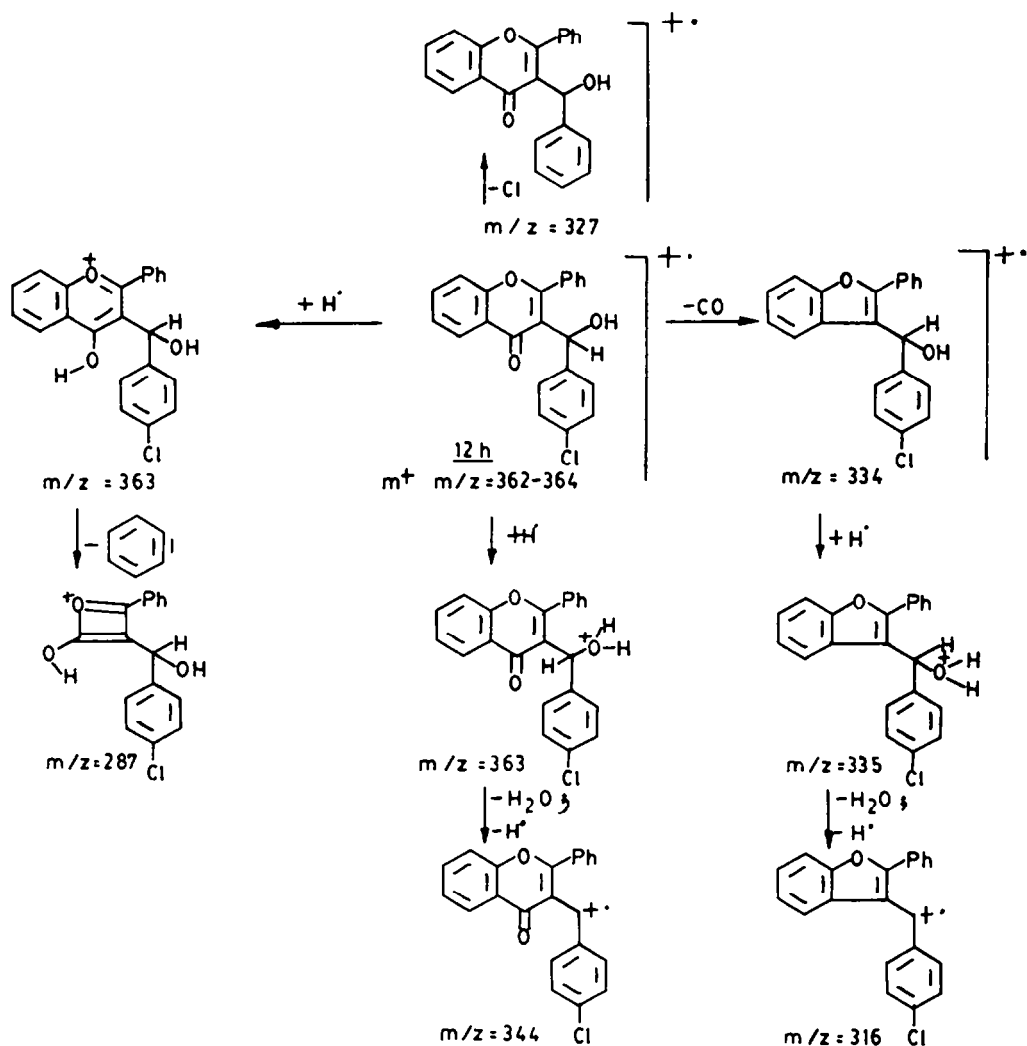
oxidation photoisomerisation was observed (tlc check vide infra). In inert atmosphere the Z isomer 7 is the only product isolated. The stable conformation of the Z-isomer as in 10 with C-2 aryl equatorial has the geometry ideal for a concerted ene reaction, leading to the hydroperoxide 11, yielding 3-benzoyl flavones 5 by spontaneous elimination of water.



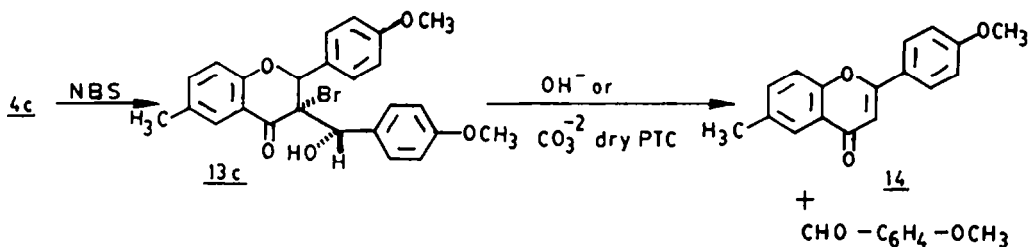
During E \rightarrow Z isomerisation studies the rate was enhanced in solvents containing halogens such as chlorobenzene bromobenzene and iodobenzene. As a follow up UV irradiation of 4d in benzene containing iodoform in inert atmosphere furnished the Z isomer 7d with reduced isomerisation time. However similar irradiation of 4d in air gave a new compound with a hydroxy group (ω_{OH} 3400 cm^{-1}). The yield was not much improved when irradiation was carried out under oxygen atmosphere. $^1\text{H-NMR}$ spectrum of the hydroxy compound revealed that in addition to fourteen protons in the aromatic region there are two one proton doublets at 5.25 and 5.72 δ . The former was exchanged with D_2O and the other collapsed to a singlet. In the light of the formation of 3-aryylflavones 5 in UV irradiation of 7 in quartz this compound was considered to be the 3- α -hydroxybenzylflavone 12d formed from the initially generated 3- α -hydroperoxybenzylflavone 11d followed by its photoreduction in the presence of iodoform accounting for the liberation of iodine. The role of iodoform causing the oxidation in air or oxygen is rather obscure. This photo-oxidation was extended to 4"-methyl, 4"-methoxy, 4"-benzyloxy, 4"-chloro and 4"-nitro-3-



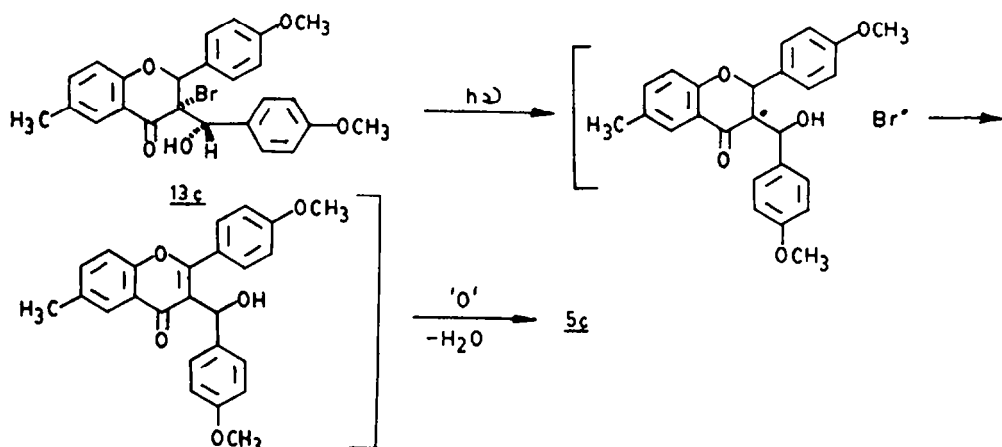
-benzylidene flavanones 4e, f, g, h and i to furnish 4"-methyl, 4"-methoxy, 4"-benzyloxy, 4"-chloro and 4"-nitro-3- α -hydroxybenzylflavones 12e-i respectively. The structure of 12h was substantiated by its mass spectrum which showed M^+ peak at $m/z = 362-364$ and other ionic fragments given below.



For an alternate synthesis of 3- α -hydroxybenzylflavone 12c, 4c was treated with aqueous NBS when 3-bromo-4',4"-dimethoxy-6-methyl-3- α -hydroxybenzylflavan (most probably 2,3 trans-3- β -erythro isomer) 13c was obtained. With aqueous NaOH in acetone or anhydrous K_2CO_3 -tetrabutylammonium iodide in



dry benzene (dry phase transfer catalysis) instead of the expected dehydrobromination to 12c¹¹, the compound 13c suffered fragmentation followed by dehydrobromination to furnish 4'-methoxy-6-methylflavone 14 and anisaldehyde. However its UV irradiation in air led to α -cleavage, β -elimination and subsequent photo-oxidation giving 4',4''-dimethoxy-6-methylflavone 5c.



The structures of 12d, 12f, 12g and 12h based on spectral studies were confirmed by their oxidation with pyridinium chlorochromate to the related 3-benzoyl, 4''-methoxy-3-benzoyl, 4''-benzyloxy-3-benzoyl and 4''-chloro-3-benzoyl flavones 5d, 5f-h respectively.

This oxidation with rearrangement apparently suggested the involvement of the concerted ene reaction with the involvement of singlet oxygen acting as the enophile. However irradiation of 4a in air in the presence of rose bengal (a singlet oxygen source)¹² in methanol-benzene did not improve the yield of 5a appreciably. On the other hand when the photolysis was carried out in dichloromethane, phase transfer catalyst and rose bengal (λ_{\max} 548 nm) or or methylene blue (λ_{\max} 661 nm) the oxidation was totally suppressed and the E to Z isomerisation alone was noticed with isomerisation rate enhancement. The isolation of the Z isomers was easier as the dye could be removed easily by rapid column chromatography. Thus this oxidation is most probably via a mero-radical transition state and these experiments provide a useful method for the synthesis of 3- α -hydroxybenzylflavones not reported by any other route.

Experimental

3-Aroylflavones :

(a) By photo-oxidation of E-3-arylidene flavanones (using quartz immersion well)

E-3-Arylidene flavanone 4 (0.5 g) in dry benzene (50 ml) was irradiated in a quartz immersion system with 125 W high-pressure mercury arc with external cooling. Reaction was complete in ca. 48 h. Removal of solvent (vacuo) afforded a gum which was purified by chromatography on silica gel (eluent benzene). The first fraction gave starting 3-arylidene flavanone, which on crystallisation from ethanol gave 3-aryloylflavone 5. Analytical data are given in table.

(b) By oxidation of 12 :

Pyridinium chlorochromate (0.005 M) was added to dry dichloromethane (100 ml) with stirring at 0° when orange-yellow colour was observed. Then 3- α -hydroxyarylflavone 12 (0.003 M) was added and stirring continued at room temperature for 2-4 h. Reaction mixture turned black in colour and was filtered over neutral alumina (eluent dichloromethane). The filtrate was evaporated under vacuo. Solid obtained was crystallised from dichloromethane-hexane to furnish 5 (ca. 80-90%). Analytical data are given in table below.

| Compound | m.p. (°C) | Yield (%) | Formula | Found | | Requires | |
|-----------|--------------|--------------|---|-------|-------|----------|-------|
| | | | | C (%) | H (%) | C (%) | H (%) |
| <u>5a</u> | 192 | 32 | C ₂₄ H ₁₇ ClO ₄ | 70.99 | 4.38 | 71.20 | 4.20 |
| <u>5b</u> | 187 | 27 | C ₂₃ H ₁₅ ClO ₃ | 73.77 | 4.20 | 73.69 | 4.00 |
| <u>5c</u> | 191 | 31 | C ₂₅ H ₂₀ O ₅ | 74.81 | 4.91 | 75.00 | 5.00 |
| <u>5d</u> | 132-33 | 90 | C ₂₂ H ₁₄ O ₃ | 81.05 | 4.41 | 80.98 | 4.29 |
| <u>5f</u> | 133-35 | 81 | C ₂₃ H ₁₆ O ₄ | 77.38 | 4.23 | 77.52 | 4.49 |
| <u>5g</u> | 150-52 | 86 | C ₂₉ H ₂₀ O ₄ | 80.37 | 4.53 | 80.55 | 4.63 |
| <u>5h</u> | 151-53 | 81 | C ₂₂ H ₁₃ O ₃ Cl | 73.07 | 4.19 | 72.83 | 4.14 |

3-Benzyl-4',4"-dimethoxy-6-methylflavone 6c :

To a solution of 4c (0.5 g) in dry DMF (10 ml) was added anhydrous K₂CO₃ (0.2 g) and the reaction mixture was refluxed for 18 h. Addition of water and crystallisation of the precipitated solid from ethanol furnished 6c (68.2%), m.p. 143° (Found : C, 77.76; H, 5.72. C₂₅H₂₂O₄ requires C, 77.70; H, 5.74%).

3- α -Hydroxybenzylflavone 12 :

A solution of 3-arylidene flavanone 4 (0.004 M), iodoform (0.001 M) in dry benzene (40 ml) was irradiated (Philips HPK-125 W mercury vapour lamp) at room temperature using pyrex immersion well for 5-20 h. Colour of the reaction mixture changed to purple indicating liberation of iodine. Purification by column chromatography on silica gel (eluent benzene), or better after a prior treatment with aqueous sodium thiosulphate and crystallisation of the product from dichloromethane-hexane furnished 12 (60-70%). Analytical data are given in table below.

| Compound | m.p. (°C) | Yield (%) | Formula | Found | | Requires | |
|------------|--------------|--------------|--|-------|-------|----------|-------|
| | | | | C (%) | H (%) | C (%) | H (%) |
| <u>12d</u> | 175-77 | 65 | C ₂₂ H ₁₆ O ₃ | 80.26 | 4.94 | 80.48 | 4.87 |
| <u>12e</u> | 132-33 | 66 | C ₂₃ H ₁₈ O ₃ | 80.53 | 5.16 | 80.70 | 5.26 |
| <u>12f</u> | 160-62 | 61 | C ₂₃ H ₁₈ O ₄ | 76.74 | 4.68 | 77.09 | 5.02 |
| <u>12g</u> | 169-70 | 60 | C ₂₉ H ₂₂ O ₄ | 79.96 | 5.23 | 80.18 | 5.07 |
| <u>12h</u> | 141-43 | 70 | C ₂₂ H ₁₅ ClO ₃ | 72.88 | 3.96 | 72.90 | 4.14 |
| <u>12i</u> | 149-50 | 88 | C ₂₂ H ₁₅ NO ₅ | 70.55 | 4.10 | 70.77 | 4.02 |

3-Bromo-4,4'-dimethoxy-6-methyl-3-(α -hydroxy)benzylflavan 13c :

NBS (0.02 M) was added to a solution of 3-benzylidene-4',4"-dimethoxy-6-methylflavanone 4c (0.001 M) in aq. acetone (30 ml, 70%) and the reaction mixture was stirred for 12 h. It was poured in ice cold water, extracted with ether, washed with water and dried. Removal of solvent furnished a solid which on crystallisation from ethanol gave 13c (58%), m.p. 172°. (Found : C, 62.04; H, 4.77. $C_{25}H_{23}BrO_5$ requires C, 62.09; H, 4.53%).

4'-Methoxy-6-methylflavone 14 :

(i) The bromohydrin 13c (0.29 g) in acetone (10 ml) was stirred with aq. NaOH (5 ml, 10%) for 10 min. Acetone layer was separated and solvent was removed (vacuo). Solid obtained was crystallised from ethanol to furnish 14 (73%), m.p. 170°. (Found : C, 76.70; H, 5.36. $C_{17}H_{14}O_3$ requires C, 76.67; H, 5.30%).

(ii) Using dry phase transfer catalyst: To a suspension of bromohydrin 13c (0.483 g) and tetrabutylammonium iodide (0.050 g) in dry benzene (10 ml) was added anhydrous K_2CO_3 (0.275 g) and the mixture was stirred for 12 h. The inorganic material was filtered. Removal of solvent from the filtrate and crystallisation of the residue from ethanol gave 14 (77%), m.p. 170° (1H -NMR and IR comparison).

3-Benzoyl-4',4"-dimethoxy-6-methylflavone 5c from 13c :

A solution of bromohydrin 13c (0.2 g) in dry benzene (10 ml) was irradiated Philips HPK-125 W mercury vapour lamp at room temperature using pyrex immersion well for 13 h. Removal of solvent afforded a gum which was purified by chromatography on silica gel (eluent : benzene-hexane 80:20). Evaporation of the eluate furnished a solid which on crystallisation from ethanol furnished 5c (47%), m.p. 190° (IR, NMR comparison).

Photolysis of E-3-arylideneflavanone 4 (in the presence of rose bengal/methylene blue) :

A solution of E-3-arylideneflavanone 4 (0.4 g) in dry dichloromethane (100 ml), with methylene blue/rose bengal (0.025 g) as a sensitizer along with a phase transfer catalyst (0.01 g) was irradiated in a pyrex immersion well for 2-8 h (tlc check) to give the Z isomers. Isomerisation was ~ 100% complete and the photoisomer was purified by column chromatography on silica gel (eluent : dichloromethane). Removal of solvent under vacuo and crystallisation from dichloromethane-hexane furnished Z-3-arylideneflavanones 7¹ (ca. 70-90%). Comparison of the time required to complete the isomerisation in different solvents is given in table below.

| Compound | Reaction time in h | | | Yield (%) |
|-----------|--------------------|---------------|--------------------|-----------|
| | Benzene | Chlorobenzene | Methylene blue/PTC | |
| <u>7d</u> | 15 | 8 | 4 | 80 |
| <u>7e</u> | 30 | 11 | 7 | 75 |
| <u>7f</u> | 40 | 15 | 8 | 70 |
| <u>7g</u> | 35 | 13 | 7.5 | 72 |
| <u>7h</u> | 10 | 6 | 3 | 85 |
| <u>7i</u> | 6 | 4 | 2 | 88 |

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