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α-HALOGENOKETONES—XI[1]

GENERALISATION OF THE WHEELER AURONE SYNTHESIS

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Abstract—α-Bromo-β-methoxydihydrochalcones were generally available from the reaction of 2'-acetoxychalcones with N-bromosuccinimide in methanol and were cyclized by base to the corresponding aurones in excellent yield. An exception was the α-bromo-β-methoxydihydrochalcone derived from phloracetophenone which gave only a moderate yield of aurone. It formed, as the major product, a chromone epoxide, the rearrangement of which, in acidic conditions, constitutes a new chromonol synthesis.

Naturally occurring aurones contain an OH substituent in the 4'-position. The Wheeler reaction[2] is a particularly useful method for the synthesis of alkoxyl ethers of such aurones. It involves the solvolysis of readily available chalcone dihalides (1) to α-halogeno-β-alkoxyl dihydrochalcones (2); cyclization of the latter by aqueous sodium hydroxide yields aurones (3). It is unnecessary and unusual to isolate the dihydrochalcone intermediate (2). In practice, the chalcone dihalide is refluxed in alcohol for some minutes before the addition of aqueous base. It has been shown, particularly by Bhide *et al.*[3] that α-halogeno-β-alkoxyl dihydrochalcones, with certain bases and solvents, give products other than aurones—mainly, flavones and 1,3-diketones. Also, if reaction conditions are so mild[4] or a solvent other than alcohol is used, the chalcone dihalide is not converted into an α-halogeno-β-alkoxyl dihydrochalcone, and the addition of base yields a flavone.

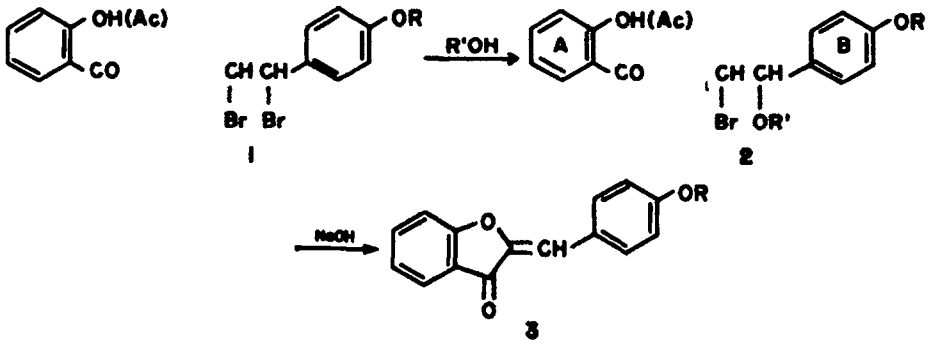
The Wheeler aurone synthesis is limited by the fact that α-halogeno-β-alkoxyl dihydrochalcones are available only from chalcone dihalides that contain an *ortho* or *para* oxysubstituent in the B-ring, i.e. from class[5] 2B chalcone dihalides; all others are unaffected by alcohol. As aurone-formation by these dihydrochalcones is due primarily to the greater effectiveness of halide, compared with alkoxide, as a leaving group and is unrelated to the alkoxyl substituent in the B-ring, it was decided to attempt the generalisation of the Wheeler reaction by converting 2'-hydroxychalcones directly into α-bromo-β-methoxydihydrochalcones using N-bromosuccinimide (NBS) in methanol.

It has been observed by Bien *et al.*[6] that 2'-hydroxychalcone undergoes nuclear halogenation on reaction with N-bromoacetamide in aqueous tetrahydrofuran. It has now been found that this chalcone reacts similarly with methanolic NBS, forming 3',5'-dibromo-2'-hydroxychalcone (4). 2'-Acetoxychalcone, however, was cleanly bromomethoxylated to give 2'-acetoxy-α-bromo-β-methoxydihydrochalcone (5) which, when cyclized with aqueous sodium hydroxide, gave aurone in excellent (88%) yield; the overall yield from chalcone was 64%. A one-pot reaction that omitted isolation of the bromomethoxyl intermediate (5) gave a 74% overall yield of aurone from chalcone.

2'-Acetoxy-α-bromo-β-methoxydihydrochalcone (5) was deacetylated by aqueous methanolic hydrogen chloride and the resulting α-bromo-2'-hydroxy-β-methoxydihydrochalcone also cyclized to aurone in excellent yield.

The Wheeler synthesis of aurones from chalcone dihalides, although much used, has sometimes been frustrated at the initial solvolysis step. For example, the simplest class 2B chalcone dihalide, 2'-hydroxy-4-methoxychalcone dibromide (1, R = Me), when refluxed in ethanol, forms[3] a flavone precursor, 3-bromo-4'-methoxyflavanone (7) as well as the aurone precursor, α - bromo - β - ethoxy - 2' - hydroxy - 4 - methoxydihydrochalcone (2, R = Me, R' = Et). It was now found that 4'-methoxyaurone (3, R = Me) can be obtained directly, in very good yield, from 2' - acetoxy - 4 - methoxychalcone by reaction with methanolic NBS followed by aqueous base, without isolating the intermediate α - bromo - β - methoxydihydrochalcone (2, R = R' = Me).

Attention was next turned to a flavonoid system with another hydroxylation pattern commonly occurring in nature, i.e. with a phloroglucinol-derived A-ring. 2' - Hydroxy - 4',6' - dimethoxychalcone reacted with methanolic NBS to give only the nuclear dihalogenated chalcone, 3',5' - dibromo - 2' - hydroxy - 4',6' - dimethoxychalcone. 2' - Acetoxy - 4',6' - dimethoxychalcone (8) also underwent nuclear halogenation but precipitation of the quantitatively formed 2' - acetoxy - 3' - bromo - 4',6' - dimethoxychalcone (9) confined the reaction to monohalogenation. This chalcone (9) unlike 3',5' - dibromo - 2' - hydroxy - 4',6' - dimethoxychalcone, was readily bromomethoxylated by further reaction with methanolic NBS, giving 2' - acetoxy - α,3' - dibromo - β,4',6' - trimethoxydihydrochalcone (15). This dihydrochalcone (15) could also be prepared directly from 2' - acetoxy - 4',6' - dimethoxychalcone (8) if chloroform was incorporated into the solvent system to prevent pre-



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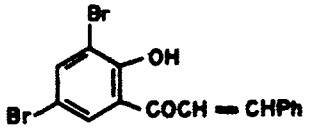

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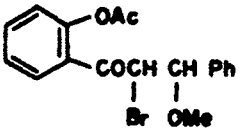

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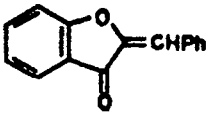

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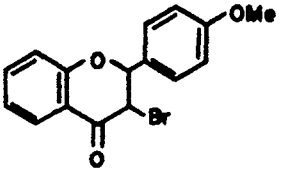

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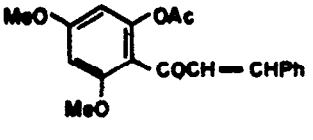
cipitation of the initially formed nuclear brominated chalcone (9). The yield (75%), however, was not as good as that (91%) from the two-step process.

Typical[7] of di-*ortho* substituted dihydrochalcones, this bromomethoxyl compound (15) reacted in an unusual and interesting fashion. It could not be deacetylated with aqueous alcoholic acid but reacted with aqueous methanolic sodium hydroxide to give three major products: two diastereomers of 8 - bromo - 5,7 - dimethoxy - 3 - (*α* - methoxybenzyl) - 2 - methylchromone epoxide (16), and 7 - bromo - 4,6 - dimethoxyaurone (18). Isolated as minor products were *cis* - 3,8 - dibromo - 5,7 - dimethoxyflavanone (11), 3,8 - dibromo - 4,5,7 - trimethoxy - 3 - flavene (12), *α*,3' - dibromo - 2' - hydroxy - 4',6' - dimethoxychalcone (13), and 8 - bromo - 5,7 - dimethoxyflavone (14).

The dehydrohalogenation (Scheme 1) of the bromomethoxyl dihydrochalcone (15) to a chromone epoxide (16) is another example of the recently observed[1] rearrangement of secondary *α* - halogeno - *o* - acyloxyacetophenones. The epoxide is stable to base but readily reacted with acid to form the chromonol, 8 - bromo - 3 - hydroxy - 5,7 - dimethoxy - 2 - methylchromone (17) and benzaldehyde. The flav-3-ene (12), isolated in trace amounts, was unstable, particularly in acid, and formed *cis* - 3,8 - dibromo - 5,7 - dimethoxyflavanone (11).

In an analogous reaction the benzoate of 2' - hydroxy - 4',6' - dimethoxychalcone, on reaction with methanolic



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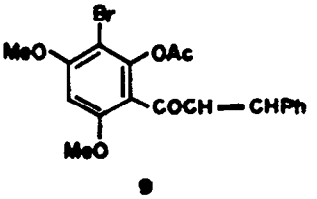

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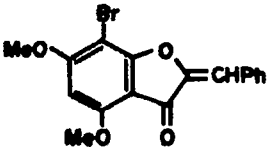

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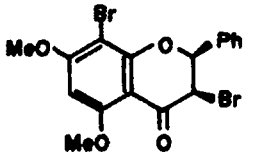

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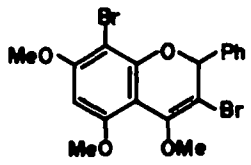

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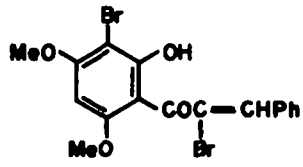

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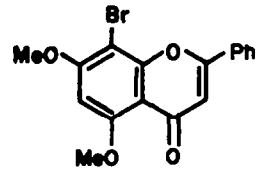

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NBS, gave 2′ - benzoyloxy - α,3′ - dibromo - β,4′,6′ - trimethoxydihydrochalcone (15). It also gave the bromodeacylated[8] product, 2,6 - dibromo - 3,5 - dimethoxyphenyl benzoate (19) and 2′ - benzoyloxy - 3′ - bromo - 4′,6′ - dimethoxychalcone (20).

The base-catalysed rearrangement of 2′ - benzoyloxy - α,3′ - dibromo - β,4′,6′ - trimethoxydihydrochalcone (15) did not yield a flavone epoxide. The main product was (Z) - 2′ - benzoyloxy - α,3′ - dibromo - 4′,6′ - dimethoxychalcone (21). Also isolated were 7 - bromo - 4,6 - dimethoxyaurone (10), 8 - bromo - 5,7 - dimethoxyflavone (14), 3,8 - dibromo - 4,5,7 - trimethoxy - 3 - flavene (12), and *cis* - 3,8 - dibromo - 5,7 - dimethoxyflavanone (11).

EXPERIMENTAL

^{1}H NMR spectra were obtained at 60 MHz with a Perkin-Elmer R12 spectrometer in $CDCl_3$ with TMS as internal reference. Chemical shifts are given in ppm (δ). M.ps were taken with a Kofler hot-stage apparatus. Solids were crystallized from aqueous ethanol (96%) unless otherwise stated. Merck silica gel was used for tlc. Satisfactory analyses (C, ±0.4%; H, ±0.2%; Hal. ±0.5%) were obtained for new compounds.

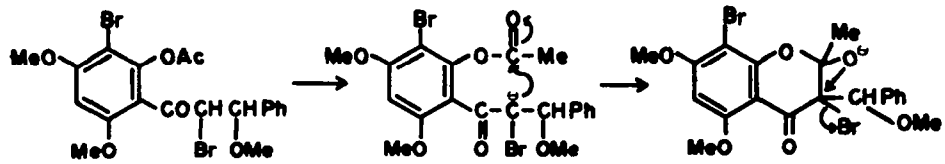
NBS (2.314 g) was added to a solution of 2′-hydroxychalcone (1.325 g) in methanol (26 ml). After 24 hr, the red solid was collected and crystallized from acetone to give orange prisms (1.55 g) of 3′,5′ - dibromo - 2′ - hydroxychalcone, m.p. 150–1° (lit.[6] m.p. 147–8°).

NBS (1.47 g) was added to a soln of 2′-acetoxychalcone (1.998 g) in MeOH (20 ml). After 2 days, during which some solvent was allowed to evaporate, the crystalline *2′ - acetoxy - α - bromo - β - methoxydihydrochalcone* (2.307 g) was collected and recrystallized from MeOH, m.p. 85–6°. PMR: 2.39 (s, Ac), 3.22 (s, OMe), 4.82 (d, β-H), 5.09 (d, α-H), 7.46 (s, Ph), $J_{\alpha\beta}$ 10 Hz.

5% NaOHaq (7 ml) was added to a soln of this dihydrochalcone (1.004 g) in MeOH (10 ml). After 2 hr, it was diluted with water. The ppt was collected and washed with water. Crystallization gave aurone (0.370 g), m.p. 110–11° (lit.[9] m.p. 108°). Column chromatography of the mother-liquor on alumina, using benzene as eluent, gave more aurone (0.146 g).

NBS (1.721 g) was added to a soln of 2′-acetoxychalcone (2.341 g) in MeOH (24 ml) and, after 3 days, 5% NaOHaq (24 ml) was added. After 1 hr, it was diluted with water. Crystallization of the ppt gave aurone (1.445 g), m.p. 110°.

10% HCl aq (1 ml) was added to a soln of 2′ - acetoxy - α - bromo - β - methoxydihydrochalcone (0.420 g) in MeOH (10 ml). The mixture was heated on a steambath for 2.5 hr before it was made cloudy with a few drops of water. On cooling, lime crystals



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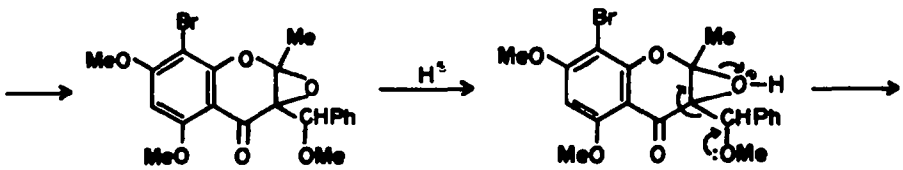

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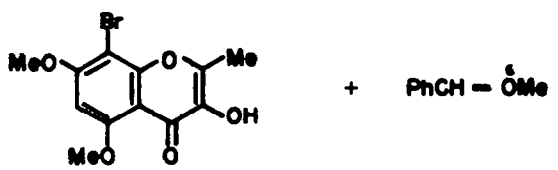

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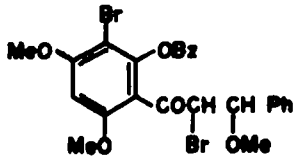
Scheme 1.



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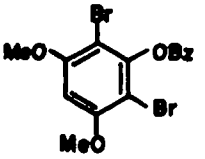

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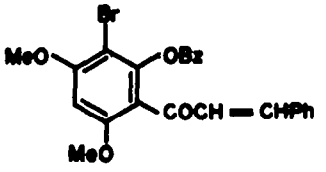

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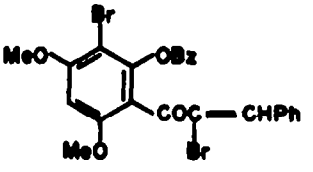

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(0.362 g) of *α - bromo - 2' - hydroxy - β - methoxydihydrochalcone*, m.p. 86–7°, were obtained. PMR: 3.24 (s, OMe), 4.92 (d, *β*-H), 5.26 (d, *α*-H), 7.53 (s, Ph), 12.04 (s, OH), $J_{\alpha\beta}$ 9.5 Hz.

5% NaOH aq (2.5 ml) was added to a soln of this dihydrochalcone (0.332 g) in MeOH (7 ml). After 1 hr, it was diluted with water and the ppt collected and washed with water. Crystallization gave aurone (0.180 g). Column chromatography of the mother-liquor on alumina, using benzene as eluent, gave more aurone (0.026 g), m.p. 110–11°.

NBS (0.331 g) was added to a soln of *2' - acetoxy - 4 - methoxychalcone* (0.501 g) in MeOH (10 ml). After 24 hr, 5% NaOH aq (3 ml) was added and, 1 hr later, the mixture was diluted with water, and extracted with diethyl ether. The ether extract was washed, dried, and evaporated to dryness. Crystallization of the residue gave *4'-methoxyaurone* as yellow needles (0.313 g), m.p. 135–6° (lit.[10] m.p. 134–5°).

NBS (0.693 g) was added to a soln of *2' - hydroxy - 4',6' - dimethoxychalcone* (0.503 g) in $CHCl_3$ (15 ml) containing MeOH (15 ml). After 5 days, the solvents were removed on a steambath. The residue crystallized in orange needles of *3',5' - dibromo - 2' - hydroxy - 4',6' - dimethoxychalcone* (0.473 g), m.p. 121°. PMR: 3.85 (s, 4'-OMe), 4.02 (s, 6'-OMe), 8.00 (s, *α*- and *β*-H), 13.73 (s, OH). This reaction was better carried out using CCl_4 alone as solvent.

NBS (0.301 g) was added to a soln of *2' - acetoxy - 4',6' - dimethoxychalcone* (0.502 g) in MeOH (25 ml). After 24 hr, the white needles of *2' - acetoxy - 3' - bromo - 4',6' - dimethoxychalcone* (0.622 g), m.p. 188–9° (lit.[5] m.p. 187–8°) were collected. PMR: 2.25 (s, OAc), 3.89 (s, 4'-OMe), 4.00 (s, 6'-OMe), 6.53 (s, 5'-H), 7.05 (d, *β*-H), 7.53 (d, *α*-H), $J_{\alpha\beta}$ 16 Hz.

NBS (1.201 g) was added to a soln of *2' - acetoxy - 4',6' - dimethoxychalcone* (1.001 g) in $CHCl_3$ (30 ml) and MeOH (30 ml). After 7 days, the solvents were removed on a steambath. Addition of MeOH to the warm residue gave white crystals of *2' - acetoxy - α,3' - dibromo - β,4',6' - trimethoxydihydrochalcone* (1.190 g), recrystallized from benzene in prisms, m.p. 165°. PMR: 2.39 (s, OAc), 3.25 (s, *β*-OMe), 3.93 (s, 4'-OMe), 3.97 (6'-OMe), 4.76 (d, *β*-H), 5.08 (d, *α*-H), 6.49 (s, 5'-H), 7.46 (s, Ph), $J_{\alpha\beta}$ 10 Hz. This dihydrochalcone was also synthesised as follows. NBS (0.265 g) was added to a soln of *2' - acetoxy - 3' - bromo - 4',6' - dimethoxychalcone* (0.548 g) in $CHCl_3$ (12 ml) and MeOH (12 ml). Work-up as above after 7 days gave the dihydrochalcone (0.637 g), m.p. 166°.

NaOH (0.47 g) in water (12 ml) was added to a soln of *2' - acetoxy - α,3' - dibromo - β,4',6' - trimethoxydihydrochalcone* (2.0 g) in MeOH (300 ml). After 1 hr it was diluted with water (300 ml). Crystallization of the ppt from acetone gave *7 - bromo - 4,6 - dimethoxyaurone* (0.295 g), m.p. 258° (lit.[5] m.p. 258–9°). The mother-liquor was fractionated by tlc and the following products were isolated in order of decreasing R_f value. *3,8 - Dibromo - 4,5,7 - trimethoxy - 3 - flavene* (0.072 g), m.p. 162–4°; PMR, 3.76 (s, 4-OMe), 3.87 (s, 5- and 7-OMe), 6.14 (s, 2-H), 6.18 (s, 6-H), 7.27–7.75 (m, Ph); (Found, C, 47.1; H, 3.9; Br, 35.9. $C_{18}H_{16}Br_2O_4$ requires: C, 47.4, H, 3.5, Br, 35.0%). *7 - Bromo - 4,6 - dimethoxyaurone* (0.055 g), m.p. 257° (lit.[5] m.p. 258–9°).

8 - Bromo - 5,7 - dimethoxy - 3 - (α - methoxybenzyl) - 2 - methylchromone epoxide (0.31 g), m.p. 189°; PMR: 2.11 (s, 2-Me), 3.48 (s, *α*-OMe), 3.94 (s, 5- and 7-OMe), 5.47 (s, CHOMePh), 6.28 (s, 6-H), 7.18–7.72 (m, Ph). A *second diastereomer* (0.25 g) of the above chromone epoxide, m.p. 183°; PMR: 1.94 (s, 2-Me), 3.54 (s, *α*-OMe), 4.00 (s, 5- and 7-OMe), 5.73 (s, CHOMePh), 6.34 (s, 6-H), 7.48 (s, Ph). *7 - Bromo - 4,6 - dimethoxyaurone* (0.10 g), m.p. 257°. *8 - Bromo - 5,7 - dimethoxyflavone* (0.13 g), m.p. 259–260° (lit.[5] m.p. 256–7°). The initial aqueous methanolic filtrate (after removal of the ppt) was acidified and extracted with ether. The extract was washed and dried. Removal of the solvent and fractionation of the residue by tlc gave the following products, in order of decreasing R_f value. *3,8 - Dibromo - 4,5,7 - trimethoxy - 3 - flavene* (0.075 g). *cis - 3,8 - Dibromo - 5,7 - dimethoxyflavanone* (0.04 g), m.p. 230–2° (lit.[11] 232–3°). (Z) - *α,3' - Dibromo - 2' - hydroxy - 4',6' - dimethoxychalcone* (0.02 g), m.p. 169° (lit.[11] 168–170°). *8 - Bromo - 5,7 - dimethoxyflavone* (0.03 g), m.p. 259° (lit.[5] 256–7°).

A soln of the diastereomers of *8 - bromo - 5,7 - dimethoxy - 3 - (α - methoxybenzyl) - 2 - methylchromone epoxide* (0.2 g) in benzene (10 ml), containing *p*-toluenesulphonic acid (a few crystals) was heated on a steambath for 20 min. On cooling, the precipitated *8 - bromo - 3 - hydroxy - 5,7 - dimethoxy - 2 - methylchromone* (0.1 g), m.p. 235° was collected; PMR: 2.53 (s, 2-Me), 4.09 (s, 5- and 7-OMe), 6.10 (s, OH), 6.51 (s, 6-H). The benzene filtrate was fractionated by tlc and gave additional chromone (0.03 g) and benzaldehyde (0.015 g).

p-Toluenesulphonic acid (a few crystals) was added to a soln of *3,8 - dibromo - 4,5,7 - trimethoxy - 3 - flavene* (0.2 g) in benzene (10 ml). After 0.5 hr, the solvent was removed. Crystallization of the residue gave *cis - 3,8 - dibromo - 5,7 - dimethoxyflavanone* (0.2 g), m.p. 232–3° (lit.[11] m.p. 232–3°).

Benzoyl chloride (2 ml) was added to a soln of *2' - hydroxy - 4',6' - dimethoxychalcone* (3 g) in pyridine (15 ml). After 0.5 hr, the mixture was poured into HCl aq (400 ml; 3%). Crystallization of the ppt gave *2' - benzoyloxy - 4',6' - dimethoxychalcone* (3.8 g), m.p. 107–9°; PMR: 3.88 (s, 4'-OMe), 3.91 (s, 6'-OMe), 6.59 (s, 3'- and 5'-H), 7.07 (d, *β*-H), 7.32–8.31 (m, Ph and *α*-H), $J_{\alpha\beta}$ 16 Hz.

NBS (2.0 g) was added to a soln of *2' - benzoyloxy - 4',6' - dimethoxychalcone* (1.5 g) in MeOH (100 ml) and $CHCl_3$ (100 ml). After 1 week, the ppt was crystallized giving *2' - benzoyloxy - 3' - bromo - 4',6' - dimethoxychalcone* (0.78 g), m.p. 202–3°; PMR: 3.92 (s, 4'-OMe), 4.06 (s, 6'-OMe), 6.60 (s, 5'-H), 6.90 (d, *β*-H), 7.28–8.37 (m, Ph and *α*-H), $J_{\alpha\beta}$ 16 Hz. The methanolic chloroform filtrate was diluted with water and extracted with $CHCl_3$. The extract was washed and dried before the solvent was removed. The residue was fractionated by tlc and the following

products were isolated in order of decreasing R_f value. 2,6 - *Dibromo* - 3,5 - *dimethoxyphenyl benzoate* (0.16 g), m.p. 211–2°; PMR: 3.97 (s, 3- and 5-OMe), 6.58 (s, 4-H), 7.61–8.50 (m, Ph). *2' - Benzoyloxy - 2,3' - dibromo - 3,4',5' - trimethoxy - 3 - phenylpropiophenone* (0.51 g), m.p. 169–170°; PMR: 3.08 (s, 3-OMe), 3.99 (s, 4'-OMe), 4.02 (s, 6'-OMe), 4.70 (d, 3-H), 5.13 (d, 2-H), 6.58 (s, 5'-H), 7.36–8.50 (m, Ar), J_{23} 10 Hz.

NaOH (0.165 g) in water (4 ml) was added to a soln of *2' - benzoyloxy - 2,3' - dibromo - 3,4',5' - trimethoxy - 3 - phenylpropiophenone* (0.8 g) in MeOH (300 ml). After 1 hr, it was diluted with water and the ppt was fractionated by tlc. The following products were isolated in order of decreasing R_f value. *3,8 - Dibromo - 4,5,7 - trimethoxy - 3 - flavene* (0.03 g). *(Z) - 2' - Benzoyloxy - α,3' - dibromo - 4',5' - dimethoxychalcone* (0.27 g), m.p. 155–7°; PMR: 3.92 (s, 4'-OMe), 4.06 (s, 6'-OMe), 6.73 (s, 5'-H), 7.26-8.36 (m, Ar and β-H). Substrate (0.08 g). *7 - Bromo - 4,6 - dimethoxyaurone* (0.07 g). *8 - Bromo - 5,7 - dimethoxyflavone* (0.03 g). The initial aqueous methanolic filtrate was acidified and extracted with diethyl ether. The ether extract was washed and dried. Removal of the solvent and fractionation of the residue by tlc gave the following products in order of decreasing R_f value. *cis - 3,8 - Dibromo - 5,7 - dimethoxyflavanone* (0.03 g). Benzoic acid (0.047 g), m.p. 122°.

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