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α-HALOGENOKETONES-XII[1]

EXTENSION OF THE RASODA SYNTHESIS OF DIHYDROFLAVONOLS

J. A. DONNELLY* and M. J. FOX
Chemistry Department, University College, Dublin 4, Ireland

and

T. C. SHARMA
School of Studies in Chemistry, Vikram University, Ujjain 456010, M. P., India

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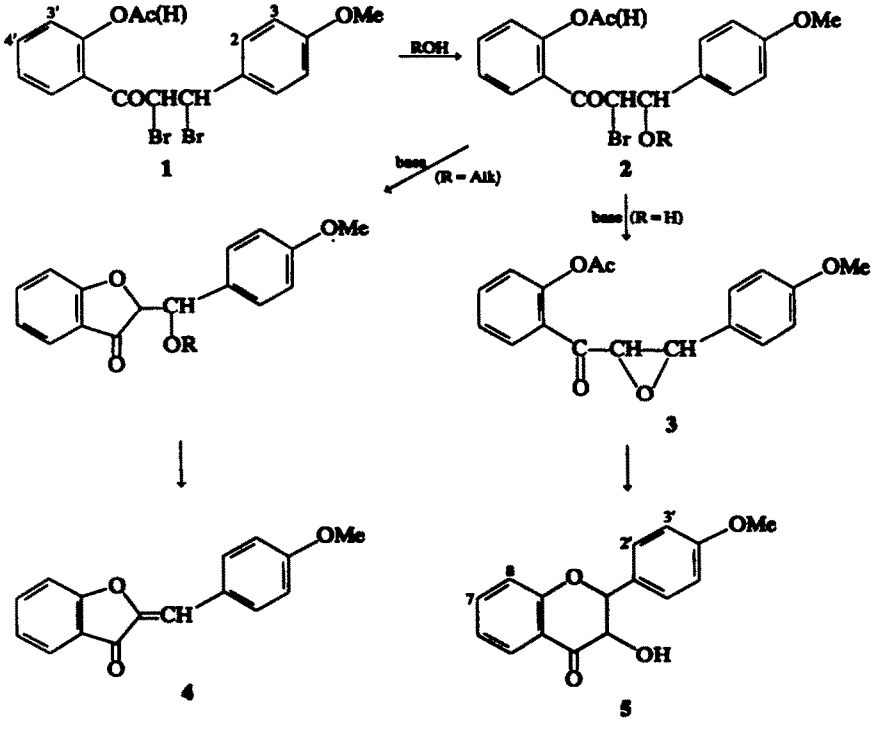
Abstract—α-Bromo-β-hydroxydihydrochalcones, the intermediates in the Rasoda reaction, were generally available from the reaction of 2'-acetoxychalcones with N-bromo-succinimide in aqueous BuOH and readily cyclized to chalcone epoxides. The base-catalysed recyclization of a 6'-substituted chalcone epoxide gave an aurone and not a *trans*-dihydroflavonol as was obtained in the absence of a 6'-substituent.

Chalcone dihalides that have a 2- or a 4-alkoxyl substituent (e.g. **1**) are converted[2] into α-halogeno-β-alkoxyl dihydrochalcones (**2**, R = alkyl) when refluxed in alcohol. The dihydrochalcones, if they possess a 2'-acetoxyl or hydroxyl substituent, are cyclized by base in the Wheeler reaction[1] to aurones (**4**). In contrast, it was discovered by Limaye[3] that these[4] 2B chalcone dihalides react with aqueous acetone and sodium carbonate to form dihydroflavonols (**5**). This, the Rasoda reaction,[3,5-9] is a particularly useful synthesis of these flavonols.

It has been shown by Marathey[6] that 2B chalcone dihalides (e.g. **1**) are converted by aqueous acetone into α-halogeno-β-hydroxyl dihydrochalcones (**2**, R = H) which cyclize not to aurones but to chalcone epoxides (**3**). The epoxides, rarely isolated, recyclize to *trans*-dihydroflavonols. The stereochemistry of these reactions has been investigated by Fischer and Arit.[8] Recently, Kelkar and Kulkarni[7] have isolated *cis*-dihydroflavonols as well as the more usual *trans* products.

The Rasoda reaction at present is limited to the



synthesis of 2'- and 4'-alkoxydihydroflavonols as only these 2B chalcone dihalides (i.e. those which have a 2- or 4-oxysubstituent) are hydrolysable to bromohydrins; all others are unaffected by water. The present work describes the extension of this reaction to the two other dihydrochalcone systems, class 1 and class 2A, important with regard to naturally occurring flavonoid hydroxylation patterns. It was found that the bromohydrin intermediates could be prepared by reaction of the corresponding 2'-acetoxychalcones with N-bromosuccinimide (NBS) in aqueous t-butanol.

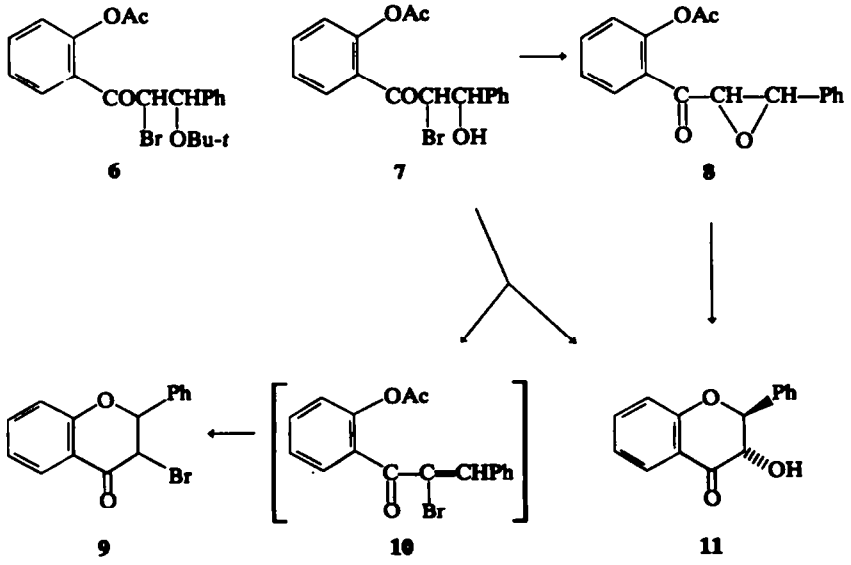
As representative of class 1 dihydrochalcone (i.e. those unsubstituted in the 2-, 4-, or 6'-positions), 2'-acetoxy-α-bromo-β-hydroxydihydrochalcone (**7**) was chosen. It was obtained by the reaction of 2'-acetoxychalcone with aqueous t-butanolic NBS; also obtained as minor products were 2'-acetoxy-α-bromo-β-t-butoxydihydrochalcone (**6**) and 2'-acetoxychalcone dibromide. The bromohydrin (**7**), when treated with potassium carbonate in aqueous t-butanol, gave *trans*-dihydroflavonol (**11**) in excellent yield together with traces of *cis*- and *trans*-3-bromoflavanone (**9**), which probably arose from dehydration of the bromohydrin (**7**) to the α-bromochalcone (**10**) followed by cyclization. The chalcone epoxide precursor (**8**) of dihydroflavonol (**11**) was obtained by reaction of the bromohydrin (**7**) with aqueous potassium acetate in acetone. Despite its protected 2'-oxygen function, the epoxide (**8**) was very reactive and cyclized to *trans*-dihydroflavonol (**11**) when its purification was attempted either by crystallization or chromatography.

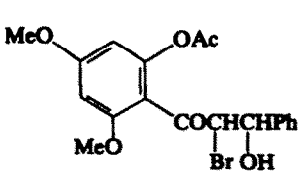
The simple representative of 2A dihydrochalcones (i.e. those substituted in the 6'-position), 2'-acetoxy-α-bromo-β-hydroxy-4',6'-dimethoxy-dihydrochalcone (**12**), was unavailable. The reaction of 2'-acetoxy-4',6'-dimethoxychalcone (**13**) with aqueous t-butanolic NBS gave, mainly, the nuclear halogenated bromohydrin, 2'-acetoxy-α,3'-dibromo-β-hydroxy-4',6'-dimethoxydihydrochalcone (**15**); also isolated were 2'-acetoxy-α,3'-dibromo-4',6'-dimethoxy-β-t-butoxydihydrochalcone (**23**), (Z)- and (E)- 2'-acetoxy-α,3'-dibromo-4',6'-dimethoxychalcone (**16**), 2'-acetoxy-3'-bromo-4',6'-dimethoxychalcone dibromide (**14**), and the bromodeacylated[10] product, 2,6-dibromo-3,5-dimethoxyphenyl acetate.

The bromohydrin (**15**) was cyclized to the chalcone epoxide (**18**) by reaction with potassium carbonate in aqueous t-butanol. This reaction gave as minor products: *cis*- and *trans*-3,8-dibromo-4,6-dimethoxyflavanone (**17**), presumably *via* dehydration of the bromohydrin (**15**) to the α-bromochalcone (**16**) followed by cyclization, and 7-bromo-4,6-dimethoxyaurone (**19**), the product of the Wheeler reaction cyclosubstitution[1] of the α-bromine followed by dehydration of the resulting coumaranone. The same aurone (**19**) was formed in the Wheeler reaction of the α-bromo-β-t-butoxydihydrochalcone (**23**). Also obtained, as a mixture of two diastereomers, was an intermediate, never previously isolated, of this reaction-7-bromo-2-(α-t-butoxybenzyl)-4,6-dimethoxycoumaraone (**20**).

Not unexpectedly,[11] the 2A chalcone epoxide (**18**) reacted atypically with sodium hydroxide in aqueous acetone. No dihydroflavonol was isolated; instead were obtained 7-bromo-4,6-dimethoxyaurone (**19**), 7-bromo-2-(2-hydroxyisopropyl)-4,6-dimethoxycoumaranone (**22**) and benzalacetone (**21**).

There are two reports[9] in the literature regarding the isolation of aurones rather than dihydroflavonols from the Rasoda reaction. Like the present case, both involve dihydrochalcones substituted in the 6'-position but, unlike the present case, the reactions were carried out on 2A chalcone dibromides that also contained 4-alkoxyl substituents; also the intermediate bromohydrins and





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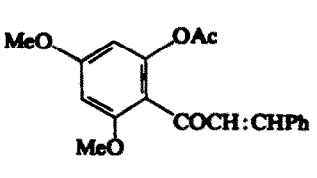

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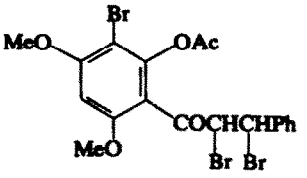

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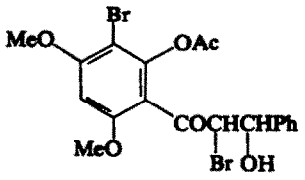

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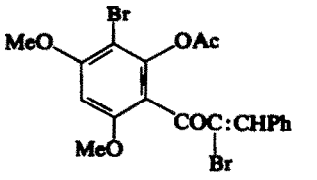

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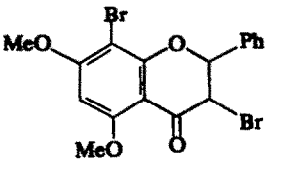

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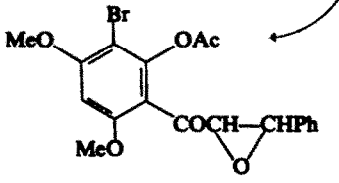

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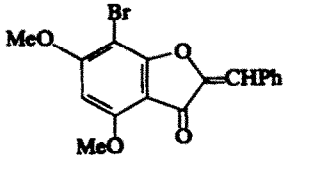

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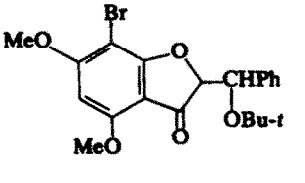

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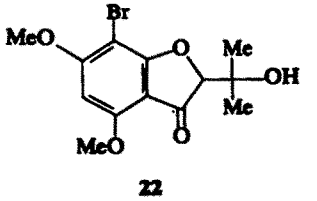

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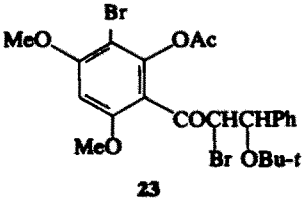

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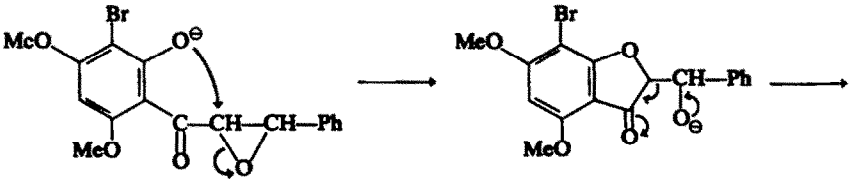

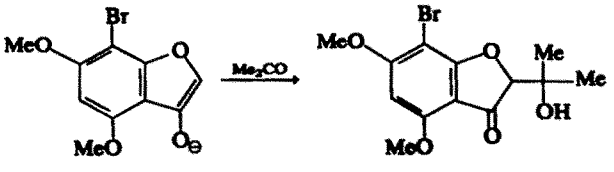

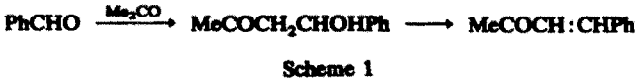

Scheme 1

epoxides were not isolated. 2'-Hydroxychalcones, substituted in the 6'-position, form aurones when treated with alkaline hydrogen peroxide in the Algar–Flynn– Oyamada reaction, supposedly *via* chalcone epoxides.[11] These epoxides have also been postulated[11b] as the aurone-forming intermediates in the Emilewicz–von Kostanecki reaction of 2A chalcone dibromides. It is interesting that the present and the earlier work[9] on the Rasoda reaction show that these epoxides do form aurones and not the dihydroflavonols.

The formation of aurones by 2A dihydrochalcone derivatives has been suggested to be due to the greater proximity[12] of the α-position compared with the β-position, to the 2'-oxygen function in the presence of a 6'-substituent and to the nonbonding interaction between this 6'-substituent and the CO group favouring[13] the smaller heterocyclic ring.

The formation of the isopropylcoumaranone (**22**) and benzalacetone (**21**) possibly arises (Scheme 1) from fragmentation of the chalcone epoxide to benzaldehyde and the conjugate base of coumaranone followed by reaction of both fragments with acetone.

EXPERIMENTAL

^{1}H NMR spectra of all products 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 EtOH (96%). Merck silica gel was used for tlc. Satisfactory analyses (C, ±0.4; H, ±0.2; Hal, ±0.5%) were obtained for new compounds. The usual work-up consisted of diluting the mixture with water, extracting with diethyl ether, washing the ether extract with water and sat NaCl aq, drying the extract over Na_2SO_4 and removing the solvent.

NBS (2.2 g) was added to a soln of 2'-acetoxychalcone (3 g) in t-BuOH (120 ml) and water (90 ml). After 18 hr and the usual work-up the residue was fractionated by tlc and the following products were isolated in order of decreasing R_f values. 2'-Acetoxychalcone dibromide, m.p. 105–7° (lit.[14] m.p. 105–7°). *2'-Acetoxy-2-bromo-3-t-butoxy-3-phenylpropiophenone*, (0.73 g) m.p. 103–4°; pmr, 1.03 (s, OBu-t), 2.43 (s, OAc), 5.06 (d, 3-H), 5.27 (d, 2-H), 7.16–8.14 (m, Ar), J_{23} 10.5 Hz. *2'-Acetoxy-2-bromo-3-hydroxy-3-phenylpropiophenone*, (2.9 g), m.p. 76–8°; pmr, 2.32 (s, OAc), 3.75 (s, OH), 5.26 (s, 2- and 3-H), 7.06–7.99 (m, Ar).

K_2CO_3 (0.45 g) was added to a soln of 2'-acetoxy-2-bromo-3-hydroxy-3-phenylpropiophenone (1 g) in aqueous BuOH (50 ml; 25%). After 1.5 hr, and the usual work-up, the residue was fractionated by tlc and the following products were isolated in order of decreasing R_f values. A mixture (0.05 g) of *cis*- and *trans*-3-bromoflavanones, identified by its pmr spectrum,[15] *cis*-isomer, 4.62 (d, 3-H), 5.51 (d, 2-H), 6.90–8.30 (m, Ar), J_{23} 2 Hz; *trans*-isomer, 5.07 (d, 3-H), 5.66 (d, 2-H), 6.90–8.30 (m, Ar), J_{23} 8.5 Hz. *trans*-3-Hydroxyflavanone (0.55 g), m.p. 186–8° (lit.[16] m.p. 188°).

KOAc (0.24 g) in water (2 ml) was added to a soln of 2'-acetoxy-2-bromo-3-hydroxy-3-phenylpropiophenone (0.55 g) in acetone (25 ml). After 18 hr, and the usual work-up, the residual oil (0.4 g) was identified by its pmr spectrum as *2'-acetoxychalcone epoxide*: 1.98 (s, OAc), 4.05 (d, β-H), 4.16 (d, α-H), 7.02–8.01 (m, Ar), $J_{\alpha\beta}$ 2 Hz. Further purification of the oil for microanalysis by crystallization or chromatography gave *trans*-3-hydroxyflavanone, m.p. 187–8°.

NBS (2.62 g) was added to a soln of 2'-acetoxy-4',6'-dimethoxychalcone (1.6 g) in $CHCl_3$ (20 ml), t-BuOH (80 ml), and water (20 ml). After 1 week, the precipitated 2'-acetoxy-3'-bromo-4',6'-dimethoxychalcone (0.17 g), m.p. 186–8° (lit.[8] m.p. 187–8°) was collected. The mother-liquor was worked up as usual and the residual oil was fractionated by tlc. The following products were isolated in order of decreasing R_f values. 2,6-Dibromo-3,5-dimethoxyphenyl acetate (0.07 g), m.p. 151–3° (lit.[17] 153°). 2'-Acetoxy-2,3,3'-tribromo-4',6'-dimethoxy-3-phenylpropiophenone (0.37 g), m.p. 186° (lit.[4] m.p. 184–6°). A mixture[4] (0.06 g) of (E)- and (Z)- 2'-acetoxy-α,3'-dibromo-4',6'-dimethoxychalcone. *2'-Acetoxy-2,3'-dibromo-3-t-butoxy-4',6'-dimethoxy-3-phenylpropiophenone*, m.p. 214–5°; pmr, 1.03 (s, OBu-t), 2.40 (s, OAc), 3.92 (s, 4'-OMe), 3.98 (s, 6'-OMe), 5.01 (d, 3-H), 5.21 (d, 2-H), 6.50 (s, 5'-H), 7.28–7.61 (m, Ph), J_{23} 10 Hz. *2'-Acetoxy-2,3'-dibromo-3-hydroxy-4',6'-dimethoxy-3-phenylpropiophenone* (1.3 g), m.p. 174–6°; pmr, 2.38 (s, OAc), 3.60 (s, OH), 3.89 (s, 4'-OMe) 3.97 (s, 6'-OMe), 5.32 (s, 3- and 2-H), 6.45 (s, 5'-H), 7.30–7.64 (m, Ph).

K_2CO_3 (0.19 g) in water (20 ml) was added to a soln of 2'-acetoxy-2,3'-dibromo-3-hydroxy-4',6'-dimethoxy-3-phenylpropiophenone (0.67 g) in t-BuOH (80 ml). After 4 days and the usual work-up, the residual oil, on crystallization, gave *2'-acetoxy-3'-bromo-4',6'-dimethoxychalcone epoxide* (0.28 g), m.p. 138–9°; pmr, 2.37 (s, OAc), 3.71 (s, 4'-OMe), 3.98 (s, 6'-OMe), 4.01 (d, β-H), 4.05 (d, α-H), 6.46 (s, 5'-H), 7.48 (s, Ph), $J_{\alpha\beta}$ 2 Hz. The mother-liquor was fractionated by tlc and the following products were isolated in order of decreasing R_f values. *trans*-3,8-Dibromo-5,7-dimethoxyflavanone (0.031 g). m.p. 182–4° (lit.[10] m.p. 183–4°). *cis*-3,8-Dibromo-5,7-dimethoxyflavanone (0.059 g), m.p. 232–3° (lit.[18] 232–3°). 7-Bromo-4,6-dimethoxyaurone (0.062 g), m.p. 256–9° (lit.[4] m.p. 258–9°). Further 2'-acetoxy-3'-bromo-4',6'-dimethoxychalcone epoxide (0.046 g).

NaOH (0.073 g) in water (2 ml) was added to a soln of 2'-acetoxy-α,3'-dibromo-β-t-butoxy-4',6'-dimethoxydihydrochalcone (0.3 g) in t-BuOH (150 ml). After 0.5 hr and the usual work-up, the residual oil was fractionated by tlc and the following products were isolated in order of decreasing R_f values. *7-Bromo-2-(α-t-butoxybenzyl)-4,6-dimethoxycoumaranone*; a mixture (3:2) of two isomers which could not be separated but which gave a correct elemental analysis; pmr (1st isomer), 1.00 (s, OBu-t), 3.93 (s, 6-OMe), 4.02 (s, 4-OMe), 4.86 (d, α-H), 5.20 (d, 2-H), 6.16 (s, 5-H), 7.10-7.74 (m, Ph), $J_{\alpha 2}$ 2.5 Hz: pmr (2nd isomer), 1.15 (s, OBu-t), 3.97 (s, 6-OMe), 4.02 (s, 4-OMe), 4.64 (d, α-H), 5.13 (d, 2-H), 6.04 (s, 5-H), 7.10-7.74 (m, Ph), $J_{\alpha 2}$ 2.5 Hz. 7-Bromo-4,6-dimethoxyaurone (0.101 g).

NaOH (0.024 g) in water (1 ml) was added to a soln of 2'-acetoxy-3'-bromo-4',6'-dimethoxychalcone epoxide (0.25 g) in acetone (25 ml) and water (5 ml). After 0.5 hr and the usual work-up, the residue was fractionated by tlc and the following products were isolated in order of decreasing R_f values. Benzalacetone (0.005 g); the pmr spectrum of which was identical with that of an authentic sample. 7-Bromo-4,6-dimethoxyaurone (0.045 g). *7-Bromo-2-(2-hydroxyisopropyl)-4,6-dimethoxycoumaranone* (0.12 g), m.p. 160-2°; pmr, 1.25 (s, Me), 1.40 (s, Me), 3.35 (s, OH), 4.03 (s, 6-OMe), 4.07 (s, 4-OMe), 4.49 (s, 2-H), 6.20 (s, 5-H).

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