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α-HALOGENOKETONES—XIV[1]

STUDIES IN THE CHEMISTRY OF 2'-HYDROXYACRYLOPHENONES

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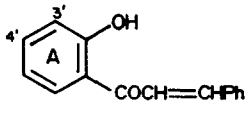
Abstract—An initial study of the side-chain unsubstituted 2'-hydroxyacrylophenone system shows it to have a considerably greater propensity for intermolecular addition than the comparable 2'-hydroxychalcone system, readily undergoing base-catalysed addition of, for example, alcohol and thereby diverting typical chalcone reactions requiring alcoholic alkali. 2'-Acetoxyacrylophenone dibromides and bromoalkoxides cyclize with base to chromone epoxides as do 2'-acetoxy-α-bromoacrylophenones in alcoholic alkali.

The side-chain aryl-substituted acrylophenones, represented by 2'-hydroxychalcone **1**, as precursors in the syntheses of various flavonoid systems, have been intensively studied for many years, particularly their reactions[2] with alkaline hydrogen peroxide (the Algar–Flynn–Oymada reaction) and the reaction[3] of their dibromides with aqueous alcoholic alkali (the Emilewicz–von Kostanecki reaction). Reported here is an initial study of the simple 2'-hydroxyacrylophenone system.

The parent compound, 2'-hydroxyacrylophenone **2**, synthesised via a Mannich reaction on 2'-hydroxyacetophenone, is known.[4] In contrast with 2'-hydroxychalcone **1**, it was now found to readily add methanol across its double bond when treated with aqueous methanolic sodium hydroxide, forming 2'-hydroxy-3-methoxypropiophenone **3**. The conversion of 3 - chloro - 2' - hydroxy - 5' - methylpropiophenone **4** into 2' - hydroxy - 3 - methoxy - 5 - methylpropiophenone **5** by methanolic sodium acetate[5] is probably similar, involving initial dehydrochlorination followed by addition of methanol to the resulting 2'-hydroxyacrylophenone. Bromination of the acetate **6** of 2'-hydroxy-3-methoxypropiophenone gave 2' - acetoxy - 2 - bromo - 3 - methoxypropiophenone **7** which was cleanly cyclized with elimination of hydrogen bromide to form 3 - methoxymethyl - 2 - methylchromone epoxide **8**. This is another example of the recently discovered[1,6,7] synthesis of chromone epoxides from secondary halogeno α-bromoacetophenones. 2' - Acetoxy - 2 - bromo - 3 - methoxypropiophenone **7** was also obtained, though in poor yield, by the reaction of 2'-acetoxyacrylophenone **9** with N-bromosuccinimide in methanol.



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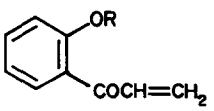
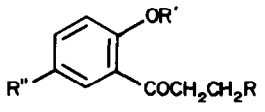
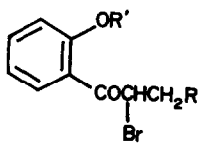


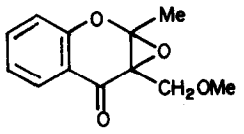
2. R = H
9. R = Ac



3. R = OMe, R' = R'' = H
4. R = Cl, R' = H, R'' = Me
5. R = OMe, R' = H, R'' = Me
6. R = OMe, R' = Ac, R'' = H
20. R = OAc, R' = Ac, R'' = H



7. R = OMe, R' = Ac
10. R = Br, R' = H
21. R = Br, R' = Ac



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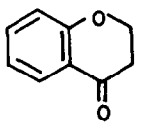

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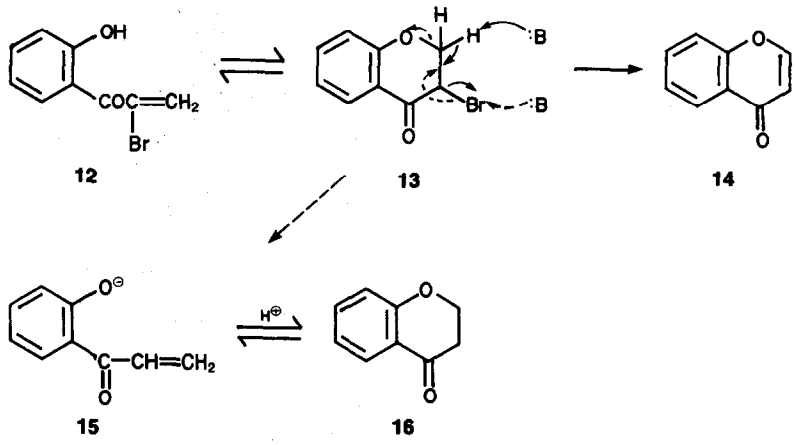
The bromination of 2'-hydroxyacrylophenone **2** gave 2,3 - dibromo - 2' - hydroxypropiophenone **10** but, when treated with aqueous ethanolic sodium hydroxide, this dibromide did not undergo the Emilewicz–von Kostanecki reaction[3] which by analogy with 2'-hydroxychalcone dibromide would have yielded chromone **14**. Instead, chromanone **11** was isolated. Presumably the usual dehydrobromination[3] of the side-chain was replaced by debromination giving 2'-hydroxyacrylophenone **2** which isomerized to chromanone **11**.

Dehydrobromination of the dibromopropiophenone **10** was achieved using sodium acetate in acetate at room temperature and cyclization of the resulting 2 - bromo - 2' - hydroxyacrylophenone **12** with aqueous methanolic sodium hydroxide gave the predictable products, 3-bromochromanone **13** and chromone **14**. The former **13** arises (Scheme 1) by cyclic isomerization of the substrate **12** and the latter **14** by subsequent dehydrobromination. Together with these products there was also isolated chromanone **16**, an abnormal product. It is suggested that chromanone is produced by elimination of bromoaryloxide from 3-bromochromanone **13**, followed by cyclization of the resulting conjugate base **15** of 2'-hydroxyacrylophenone. At least one example of the elimination of bromoalkoxide from 3-bromochromanones is known.[3] When refluxed in methanol with aqueous sodium acetate 2 - bromo - 2' - hydroxyacrylophenone **12** isomerized to 3 - bromochromanone **13**.

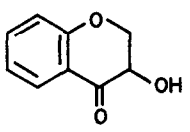
The ease with which 2' - hydroxyacrylophenone **2** added methanol frustrated attempts to carry out the Algar–Flynn–Oyamada reaction[2] on this compound by reacting it with hydrogen peroxide in aqueous methanolic sodium hydroxide. The reaction occurred to a minor



Scheme 1.

extent in the presence of the weaker base, potassium carbonate, producing 3 - hydroxychromanone **17**, but, predictably, the major reaction to occur was the Baeyer–Villiger and the major product isolated was catechol.

The sodium borohydride reduction of 2'- -hydroxyacrylophenone **2** gave 1 - hydroxy - 1 - (2 - hydroxyphenyl)propane **18**. This contrasts with the formation of flav - 3 - enes **19** in the similar reduction[8] of 2' - hydroxychalcones **1**.



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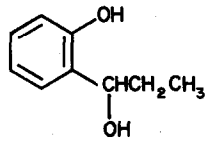

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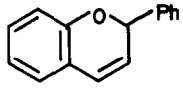

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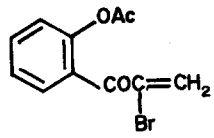

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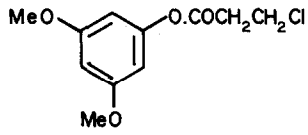
Acetylation of the acrylophenone **2** gave the diacetate, 2',3 - diacetoxypropiophenone **20**, showing again the propensity of this enone system for addition; 2' - acetoxyacrylophenone **9** also was obtained when sodium acetate rather then pyridine was employed as catalyst. The addition of bromine to the monoacetate **9** gave the unstable 2' - acetoxy - 2,3 - dibromopropiophenone **21** which could not be completely purified. Both crystallization and chromatography caused elimination of hydrogen bromide. The dehydrobromination was formally carried out using sodium acetate in acetone. The product, 2' - acetoxy - 2 - bromoacrylophenone **22** cyclized on reacting with sodium methoxide to give 3 - methoxymethyl - 2 - methylchromone epoxide **8**; presumably methoxide attacked the double bond to give 2' - acetoxy - 2 - bromo - 3 - methoxypropiophenone **7** which has been shown above to react with base to give the chromone epoxide **8**. The acrylophenone dibromide **21** was cyclized directly to the chromone epoxide **8** in good yield by aqueous methanolic sodium hydroxide. It is assumed that this reaction involved the initial elimination of hydrogen bromide, followed by the addition of methanol to the resulting 2' - acetoxy - 2 - bromoacrylophenone **22** to give the epoxide precursor 2' - acetoxy - 2 - bromo - 3 - methoxypropiophenone **7**.

Similar general behaviour is observed for 2' - hydroxychalcones variously substituted in the A-ring except[2,3] for those that are also substituted in the 6'-position. A study was made, therefore, of one of the corresponding 2' - hydroxyacrylophenones. 2' - Hydroxy - 4',6' - dimethoxy - acrylophenone **25** was obtained by the dehydrochlorination of 3 - chloro - 2' - hydroxy - 4',6' - dimethoxypropiophenone **24**. The latter was synthesised by esterifying 3,5 - dimethoxyphenol with 3 - chloropropionyl chloride and subjecting the resulting 3 - chloropropionate **23** to a Fries rearrangement. Acetylation of 2' - hydroxy - 4',6' - dimethoxyacrylophenone **25** again resulted in addition to the enone system with the



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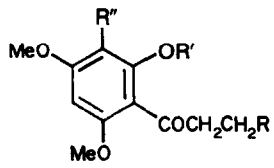
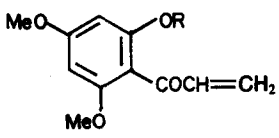
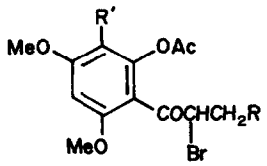


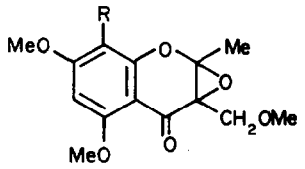
24. R = Cl, R' = R'' = H
26. R = OAc, R' = Ac, R'' = H
34. R = OMe, R' = R'' = H
35. R = OMe, R' = H, R'' = Br
36. R = OMe, R' = Ac, R'' = Br
38. R = Cl, R' = H, R'' = Et



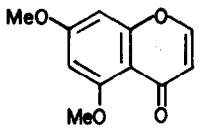
25. R = H
27. R = Ac



28. R = Br, R' = H
31. R = OMe, R' = H
32. R = OMe, R' = Br



29. R = H
33. R = Br



30

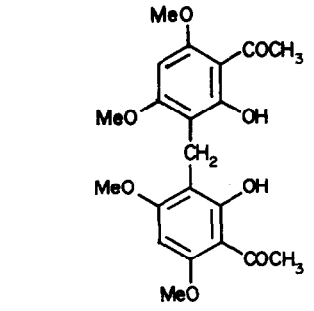
formation of the diacetate 2',3 - diacetoxy - 4'6' - dimethoxypropiophenone **26**. The same product was obtained using either pyridine or sodium acetate as catalyst; the use of an acid catalyst resulted in polymerization. The required monoacetate, 2' - acetoxy - 4',6' - dimethoxyacrylophenone **27**, was obtained in low yield by heating 3 - chloro - 2' - hydroxy - 4',6' - dimethoxypropiophenone **24** in acetic anhydride alone. Its dibromide **28** cyclized to 5,7 - dimethoxy - 3 - methoxymethyl - 2 - methylchromone epoxide **29** in a reaction analogous to that of the simple 2' - acetoxy - 2,3 - dibromopropiophenone **21**; a small quantity of 5,7 - dimethoxychromone **30** (the expected product of an Emilewicz–von Kostanecki reaction[3] of such a dibromoketone) was also obtained.

The supposed intermediate **31** in the above chromone epoxide-forming reaction was not obtained by reacting 2' - acetoxy - 4',6' - dimethoxyacrylophenone **27** with N-bromosuccinimide in methanol. Instead, the nuclear halogenated compound, 2' - acetoxy - 2,3' - dibromo - 3,4',6' - trimethoxypropiophenone **32** was produced which cyclized in aqueous methanolic sodium hydroxide to the chromone epoxide **33**. Because monoacetylation of 2' - hydroxy - 4',6' - dimethoxyacrylophenone **25** is difficult, a better route to this chromone epoxide **33** was to synthesise its precursor, 2' - acetoxy - 2,3' - dibromo - 3,4',6' - trimethoxypropiophenone **32**, by converting 3 - chloro - 2' - hydroxy - 4',6' - dimethoxypropiophenone **24** into 2' - hydroxy - 3,4',6' - trimethoxypropiophenone **34** by reaction with aqueous methanolic sodium hydroxide, brominating this product, acetylating the resulting nuclear halogenated trimethoxypropiophenone **35** and finally brominating this acetate **36**.

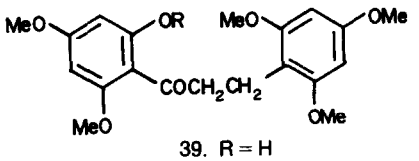
The Algar–Flynn–Oyamada reaction[2] of 2' - hydroxy - 4',6' - dimethoxyacrylophenone **25**, like that of simple 2' - hydroxyacrylophenone **2**, was inhibited by the facility with which this acrylophenone added on methanol in the presence of aqueous sodium hydroxide to form 2' - hydroxy - 3,4',6' - trimethoxypropiophenone **34**. No reaction was observed when potassium carbonate was employed as base.

An attempt to synthesise 2' - hydroxy - 4',6' - dimethoxyacrylophenone **25** via a Mannich reaction on 2' - hydroxy - 4',6' - dimethoxyacetophenone, using paraformaldehyde and dimethlyamine hydrochloride in acidified propanol, resulted in a nuclear Mannich reaction and the formation of bis(3 - aceto - 2 - hydroxy - 4,6 - dimethoxyphenyl)methane **37**. Substitution is assumed to have occurred at the 3'-position of the acetophenone by analogy with the corresponding bromination reaction.[9] Orientation in these cases may, however, be governed by the size of the reactant, e.g. chlorination is now known[10] to occur much more extensively at the 5'-position of this acetophenone than at the 3'-position while bromination occurs exclusively at the latter.

No reaction was observed when an attempt was made to acylate 1,3,5 - trimethoxybenzene with 3 - chloropropionyl chloride in diethyl ether using sulphuric acid as catalyst. The use of aluminium chloride as catalyst gave a low yield of the required 3 - chloro - 2' - hydroxy - 4',6' - dimethoxypropiophenone **24** but when an attempt was made to improve the yield by increasing the amount of this catalyst used, efficient nuclear alkylation was observed and 3 - chloro - 3' ethyl - 2' - hydroxy - 4',6' - dimethoxypropiophenone **38** was obtained. 2' - Hydroxy - 4',6' - dimethoxy - 3 - (2,4,6 - trimethoxyphenyl)propiophenone **39** was isolated as a by-product. The replacement of diethyl ether by carbon disulphide in the above aluminium chloride-catalysed acylations did not give satisfactory results but when the acylation of 1,3,5 - trimethoxybenzene by 3 - chloropropionyl chloride was carried out in carbon disulphide using ferric chloride as catalyst 2',4',6' - trimethoxy - 3 - (2,4,6 - trimethoxyphenyl)propiophenone **40** was obtained in good yield. The reaction of 1,3,5 - trimethoxybenzene with acryloyl chloride in diethyl ether using sulphuric acid as catalyst resulted in alkylation rather than acylation and the formation, in excellent yield, of 3 - (2,4,6 - trimethoxyphenyl)propionic acid **41**.

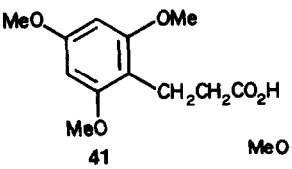


37

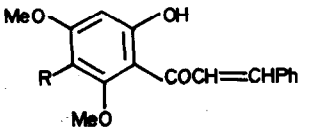


39. R = H
40. R = Me

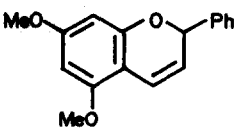
Oxidation of 2' - hydroxy - 4',6' - dimethoxychalcone **42** with m - chloroperbenzoic acid, in an attempt to form[11] the corresponding epoxide, gave instead the known 2',5' - dihydroxy - 4',6' - dimethoxychalcone **43**. Reduction[8] of the former chalcone **42** with lithium aluminium hydride gave 5,7 - dimethoxyflav - 3 - ene **44**.



41



42. R = H
43. R = OH



44

EXPERIMENTAL

^{1}H NMR spectra were obtained at 60 MHz in $CDCl_3$ with TMS as internal reference. Chemical shifts are given in ppm (δ). Hydroxyl signals were identified by deuteriation. M.ps were taken with a Kofler hot-stage apparatus. Solids were crystallized from ethanol unless otherwise stated. Satisfactory analyses (C, ±0.4; H, ±0.2; Hal, ±0.5%) were obtained for new compounds. The usual work-up consisted of diluting the reaction mixture with water, extracting with chloroform, washing the chloroform extract with water, drying the extract over anhydrous sodium sulphate, removing the solvent, and fractionating the residue by thin layer chromatography (tlc) on silica gel.

Reactions of 2'-hydroxyacrylophenone **2**

Aqueous sodium hydroxide (20%; 60 ml) was added slowly to a solution of 2' - hydroxyacrylophenone[4] (12.0 g) in methanol (120 ml) at 0°. After 1h, the solution was acidified with dilute hydrochloric acid. The usual work-up (without tlc) gave 2' - hydroxy - 3 - methoxypropiophenone **3** (8.28 g), b.p. 110–114°/2 torr. NMR 3.26 (t, 2-CH_2; J 5 Hz), 3.40 (s, OMe), 3.83 (t, 3-CH_2), 6.78–7.70 (m Ar), 7.82 (q, 6'-H; J 2 and 8 Hz), 12.30 (s, OH).

A solution of the 3-methoxypropiophenone (3.6 g) in acetic anhydride (10 ml) was heated with sodium acetate (3.6 g) on a steambath for 2 h. The usual work-up (without tlc) gave 2' - acetoxy - 3 - methoxypropiophenone **6** (3.2 g), b.p. 144–8°/2 torr. NMR 2.40 (s, OAc), 3.20 (t, 2-CH_2; J 6 Hz), 3.43 (s, OMe), 3.83 (t, 3-CH_2), 6.95–7.69 (m, Ar), 7.90 (q, 6'-H; J 2 and 8 Hz).

Bromine (2.16 g) in acetic acid (25 ml) was added slowly to a solution of the acetate (3.0 g) in acetic acid (25 ml). The usual work-up (without tlc) gave 2' - acetoxy - 2 - bromo - 3 - methoxypropiophenone **7** (3.1 g), m.p. 49–50°. NMR 2.39 (s, OAc), 3.44 (s, OMe), 3.95 (q, 3-CH; J, 7 and 10 Hz), 4.05 (q, 3-CH; J 7 and 10 Hz), 5.22 (t, 2-CH; J 7 Hz); 7.00–7.70 (m, Ar). This product (0.56 g) was also obtained by adding N-bromosuccinimide (1.57 g) to a solution of 2' - acetoxyacrylophenone (1.53 g) in methanol (40 ml) and working-up after 4 days, using diethyl ether in place of chloroform.

Aqueous sodium hydroxide (0.2 M; 33 ml) was added slowly to a solution of the 2-bromopropiophenone (1.0 g) in methanol (30 ml). After 1 h, and the usual work-up, the product was dissolved in hexane and filtered. Removal of the solvent gave 3 - methoxymethyl - 2 - methylchromone epoxide **8** as an oil (0.26 g). NMR 2.03 (s, 2-Me), 3.49 (s, OMe), 3.66 (d, 3-CH; J 11 Hz), 4.45 (d, 3-CH; J 11 Hz), 6.90–7.88 (m, Ar), 8.03 (q, 5-H; J 2 and 8 Hz).

Bromine (2.16 g) in carbon tetrachloride (40 ml) was added drop-wise to a solution of 2' - hydroxyacrylophenone (2.0 g) in carbon tetrachloride (40 ml). After 1 h, the solvent was removed under reduced pressure, giving 2,3 - dibromo - 2' - hydroxypropiophenone **10** which was obtained from light petroleum (b.p. 40–60°) in yellow crystals (3.5 g), m.p. 42–3°. NMR 3.80 (q, 3-CH; J 4 and 9 Hz), 4.24 (t, 3-CH; J 9.5 Hz), 5.48 (q, 2-CH; J 4 and 10 Hz), 6.78–7.92 (m, Ar), 11.83 (s, OH).

Aqueous sodium hydroxide (1 M; 10 ml) was added to a solution of the dibromide (1.0 g) in ethanol (10 ml). After 1 h, the usual work-up gave chromanone **11** (0.150 g), identical (tlc, NMR) with an authentic sample.[12]

Anhydrous sodium acetate (0.5 g) was added to a solution of the dibromide (1.0 g) in acetone (10 ml). After 12 h, the solvent was removed and the residue was dissolved in diethyl ether. The usual work-up then gave 2 - bromo - 2' - hydroxyacrylophenone **12** as an oil (0.51 g). NMR 6.36 (s, CH_2), 6.80–7.70 (m, Ar), 7.76 (q, 6'-H; J 2 and 8 Hz), 11.45 (s, OH).

Aqueous sodium hydroxide (0.2 M; 15 ml) was added to a solution of the 2 - bromoacrylophenone (0.69 g) in methanol (20 ml). After 1 h, the usual work-up, using diethyl ether in place of chloroform, gave the following products in order of decreasing R_f values. 3 - Bromochromanone **13**, yellow plates (0.04 g) from light petroleum (b.p. 40–60°), m.p. 72–4° (lit.[13] 77–8°); NMR 4.68 (s, 2-CH_2 and 3-CHBr), 6.99–7.82 (m, Ar), 8.02 (q, 5-H; J 2 and 8 Hz). Chromanone[12] **16** (0.026 g). Chromone **14**, colourless crystals (0.11 g) from light petroleum (b.p. 40–60°), m.p. 56° (lit.[14] 57°); NMR 6.42 (d, 3-H; J 6 Hz), 7.30–7.80 (m, Ar), 8.06 (d, 2-H), 8.33 (q, 5-H; J 2 and 8 Hz).

A solution of 2 - bromo - 2' - hydroxyacrylophenone (1.0 g) in methanol (8 ml) and water (2 ml) was heated with sodium acetate (1.0 g) on a steambath for 2 h. After the solvents had been removed under reduced pressure, the residue was extracted with diethyl ether. The extract was worked-up in the usual way (without tlc), giving 3 - bromochromanone[13] **13** in colourless plates (0.69 g), m.p. 72–4°.

Aqueous hydrogen peroxide (26–28% w/w; 3 ml) was added slowly to a solution at 0° of 2' - hydroxyacrylophenone (2.80 g) and potassium carbonate (1.38 g) in methanol (30 ml) and water (10 ml). After 1 h, the usual work-up, using diethyl ether in place of chloroform, gave the following products in order of decreasing R_f values. 3 - Hydroxychromanone **17**, which was obtained from diethyl ether in colourless crystals (0.20 g), m.p. 57–8°; NMR 3.78 (s, OH), 4.16 (q, *trans* - 2 - H, splittings 11 and 15 Hz), 4.54–4.86 (sextet, *cis* - 2 - H and 3-H), 6.97–7.61 (m, Ar), 7.93 (q, 5-H; J 2 and 9 Hz). Catechol (0.67 g), m.p. 100–1° (lit.[15] 104–5°), identical (tlc and NMR) with an authentic sample.

Sodium borohydride (0.255 g) was added to a solution of 2' - hydroxyacrylophenone (1.0 g) in isopropanol (60 ml). After 1 h, the solvent was removed and replaced by water (20 ml). The mixture was heated on a steambath for 0.5 h. The usual work-up, using diethyl ether in place of chloroform and without tlc, gave 1 - hydroxy - 1 - (2 - hydroxyphenyl)propane[16] **18** as an oil (0.42 g). NMR 0.94 (t, Me; J 7 Hz), 1.88 (m, CH_2) 3.00 (s, 1-OH), 4.82 (t, 1-CH; J 7 Hz), 6.80–7.40 (m, Ar), 8.10 (s, 2-OH).

A solution of 2' - hydroxyacrylophenone (10.0 g) in acetic anhydride (30 ml) was heated with anhydrous sodium acetate (10.0 g) on a steambath for 1 h. The usual work-up, using column chromatography in place of tlc, gave the following in order of decreasing R_f values. 2' - Acetoxyacrylophenone **9**, an oil (3.0 g); NMR 2.35 (s, OAc), 6.05 (q, 3-CH; J 2 and 10 Hz), 6.34 (q, 3-CH; J 2 and 18 Hz), 6.98 (q, 2-CH; J 10 and 18 Hz), 7.10–7.70 (m, Ar), 7.80 (q, 6'-H; J 2 and 8 Hz). 2',3 - Diacetoxypropiophenone **20**, an oil (5.0 g); NMR 2.06 (s, 3-OAc), 2.37 (s, 2'-OAc), 3.26 (t, 2-CH_2; J 7 Hz), 4.51 (t, 3-CH_2), 7.08–7.75 (m, Ar), 7.90 (q, 6'-H; J 2 and 8 Hz). 2',3 - Diacetoxypropiophenone **20** was the sole product (0.9 g) isolated when 2' - hydroxyacrylophenone (1.0 g) was acetylated as above but using pyridine (0.2 g) in place of sodium acetate.

Bromine (2.40 g) in carbon tetrachloride (10 ml) was added dropwise to a solution of 2' - acetoxyacrylophenone (2.40 g) in carbon tetrachloride (30 ml). Removal of the solvent under reduced pressure, after 1 h, gave 2' - acetoxy - 2,3, - dibromopropiophenone **21** as an oil (2.72 g). Further purification by attempted crystallization or by chromatography resulted in the elimination of hydrogen bromide. The product was triturated instead with light petroleum (b.p. 40–60°) (Found: C, 38.6; H, 2.9. $C_{11}H_{10}Br_2O_3$ requires: C, 37.7; H, 2.9%). NMR 2.42 (s, OAc), 3.79 (q, 3-CH; J 4 and 9 Hz), 4.23 (t, 3-CH; J 9.5 Hz), 5.42 (q, 2-CH; J 4 and 10 Hz), 7.27–7.78 (m, Ar), 7.96 (q, 6'-H; J 2 and 8 Hz).

Anhydrous sodium acetate (0.46 g) was added to a solution of the dibromopropiophenone (1.0 g) in acetone (10 ml). The solvent was removed under reduced pressure after 12 h. The usual work-up gave 2' - acetoxy - 2 - bromoacrylophenone **22** as an oil (0.54 g). NMR 2.28 (s, OAc), 6.53 (d, 3-CH; J 2 Hz), 6.66 (d, 3-CH), 7.12–7.82 (m, Ar).

Aqueous sodium hydroxide (0.2 M; 26 ml) was added slowly to a solution of the 2 - bromoacrylophenone (0.52 g) in methanol (20 ml). The usual work-up after 1 h gave 3 - methoxymethyl - 2 - methylchromone epoxide **8** as an oil (0.17 g), identical (tlc and NMR) with that previously isolated.

Aqueous sodium hydroxide (0.2 M; 26 ml) was added slowly to a solution of 2' - acetoxy - 2,3 - dibromopropiophenone (0.5 g) in methanol (20 ml). After 1 h, the usual work-up gave 3 - methoxymethyl - 2 - methylchromone epoxide **8** as an oil (0.20 g), identical (tlc and NMR) with that previously isolated.

Reactions of 2' - hydroxy - 4',6' - dimethoxyacrylophenone **25**

A mixture of 3,5-dimethoxyphenol (10.0 g), 3-chloropropionyl chloride (9.0 g), and sulphuric acid (1 drop) was stirred for 1 h and then heated on a steambath for 6 h. The usual work-up, using diethyl ether in place of chloroform and without tlc, gave 3,5-dimethoxyphenyl 3-chloropropionate **23** as an oil (8.5 g), b.p.

168–170°/2 torr. NMR 3.06 (t, 2-CH_2; J 7 Hz), 3.82 (s, 3- and 5-OMe), 3.91 (t, 3-CH_2), 6.40 (s, 2-,4-, and 6-H).

Titanium tetrachloride (5 ml) was added dropwise to a solution of the propionate (10.0 g) in 1,2-dichloroethane (100 ml). After 18 h, ice and dilute hydrochloric acid were added. The usual work-up, using column chromatography in place of tlc, gave 3 - chloro - 2' - hydroxy - 4',6' - dimethoxypropiophenone **24** which crystallized in colourless needles (3.1 g), m.p. 154–5°. NMR 3.60 (t, 2-CH_2; J 6 Hz), 3.94 (s, 4'-OMe), 3.98 (t, 3-CH_2), 4.00 (s, 6'-OMe), 6.06 (d, 3'-H; J 2 Hz), 6.20 (d, 5'-H), 13.82 (s, OH).

A suspension of anhydrous sodium acetate (0.41 g) in a solution of the 3-chloropropiophenone (0.50 g) in acetone (20 ml) was diluted, after 18 h, with water. The usual work-up, using diethyl ether and without tlc, gave 2' - hydroxy - 4',6' - dimethoxyacrylophenone **25** which crystallized from light petroleum (b.p. 60–80°) in yellow needles (0.26 g), m.p. 80–2°. NMR 3.87 (s, 4'-OMe), 3.90 (s, 6'-OMe), 5.80 (q, *cis*-3-CH; J 2 and 10 Hz), 4.01 (d, 3'-H; J 2.5 Hz), 4.18 (d, 5'-H; J 2.5 Hz), 6.46 (q, *trans*-3-CH; J 2 and 17 Hz), 7.55 (q, 2-CH; J 10 and 17 Hz), 14.08 (s, OH).

A solution of the acrylophenone (0.50 g) in acetic anhydride (3 ml), containing either anhydrous sodium acetate (0.2 g) or pyridine (2 drops), was heated on a steambath for 5 h. The usual work-up, using diethyl ether and without tlc, gave 2',3 - diacetoxyl - 4',6' - dimethoxypropiophenone **26** which crystallized from diethyl ether in colourless prisms (0.23 g), m.p. 92–4°. NMR 2.07 (s, 3-OAc), 2.28 (s, 2'-OAc), 3.20 (t, 2-CH_2; J 7 Hz), 3.90 (s, 4'- and 6'-OMe), 4.45 (t, 3-CH_2; J 7 Hz), 6.32 (d, 3'-H; J 2.5 Hz), 6.46 (d, 5'-H; J 2.5 Hz).

A suspension of 3 - chloro - 2' - hydroxy - 4',6' - dimethoxypropiophenone (3.0 g) in acetic anhydride (40 ml) was heated under reflux in a nitrogen atmosphere for 6 h. The usual work-up gave 2' - acetoxy - 4', 6' - dimethoxyacrylophenone **27** as an oil (0.41 g). NMR 2.23 (s, OAc), 3.83 (s, 4'-OMe), 3.85 (s, 6'-OMe), 5.89 (q, *cis*-3-CH; J 2 and 10 Hz), 6.28 (q, *trans*-3-CH; J 2 and 16 Hz), 6.38 (d, 3'-H; J 2 Hz), 6.49 (d, 5'-H; J 2 Hz), 6.88 (q, 2-CH; J 10 and 16 Hz).

Bromine (0.13 g) in carbon tetrachloride (8 ml) was added slowly to a solution of the acetate (0.21 g) in carbon tetrachloride (10 ml). After 1 h, the solvent was removed under reduced pressure, giving 2' - acetoxy - 2,3 - dibromo - 4',6' - dimethoxypropiophenone **28** which crystallized from chloroform-diethyl ether in colourless plates (0.25 g), m.p. 123–5°. NMR 2.32 (s, OAc), 3.78 (q, 3-CH; J 5 and 10 Hz), 3.90 (s, 4'-OMe), 3.95 (s, 6'-OMe), 4.21 (t, 3-CH; J 9.5 Hz), 5.52 (q, 2-CH; J 5 and 9 Hz), 6.40 (d, 3'-H; J 2 Hz), 6.48 (d, 5'-H; J 2 Hz).

Aqueous sodium hydroxide (0.2 M; 18 ml) was added slowly to a solution of the dibromide (0.47 g) in methanol (20 ml). The usual work-up, after 1 h, gave the following products in order of decreasing R_f values. 5,7 - Dimethoxy - 3 - methoxymethyl - 2 - methylchromone epoxide **29**, an oil (0.11 g); NMR 2.08 (s, 2-Me), 3.50 (s, 3-OMe), 3.73 (d, 3-CH; J 11 Hz), 4.00 (s, 7-OMe), 4.34 (d, 3-CH; J 11 Hz), 4.04 (s, 5-OMe), 6.20 (d, 3'-H; J 2 Hz), 6.23 (d, 5'-H; J 2 Hz). 5,7-Dimethoxy-chromone **30**, needles (0.04 g) from water, m.p. 128–130° (lit.[17] 133–4°); NMR 3.94 (s, 7-OMe), 3.98 (s, 5-OMe), 6.25 (d, 3-H; J 6 Hz); 6.40 (d, 8-H; J 2 Hz), 6.50 (d, 6-H; J 2 Hz), 7.66 (d, 2-H; J 6 Hz).

A mixture of N-bromosuccinimide (3.19 g) and 2' - acetoxy - 4',6' - dimethoxyacrylophenone (2.0 g) in methanol (100 ml) was worked-up as usual after 3 days, using diethyl ether in place of chloroform, and gave 2' - acetoxy - 2,3' - dibromo - 3,4',6' - trimethoxypropiophenone **32** (0.91 g), m.p. 93–5°. NMR 2.32 (s, OAc), 3.43 (s, 3-OMe), 3.80 (q, 3-CH; J 7 and 10 Hz), 3.93 (s, 4'-OMe), 3.94 (s, 6'-OMe), 4.05 (q, 3-CH; J 7 and 10 Hz), 5.24 (t, 2-CH; J 7 Hz), 6.45 (s, 5'-H).

Aqueous sodium hydroxide (0.2 M; 7 ml) was added slowly to a solution of the 2-bromopropiophenone (0.30 g) in methanol (10 ml). The usual work-up after 1 h gave 8 - bromo - 5,7 - dimethoxy - 3 - methoxymethyl - 2 - methylchromone epoxide **33** which was obtained as colourless crystals (0.11 g) from chloroform-hexane, m.p. 196–8°. NMR 2.08 (s, 2-Me), 3.50 (s, 3-OMe), 3.73 (d, 3-CH; J 11 Hz), 4.00 (s, 7-OMe), 4.34 (d, 3-CH; J 11 Hz), 4.04 (s, 5-OMe), 6.36 (s, 6-H).

Aqueous sodium hydroxide (10%; 20 ml) was added to a solution of 3 - chloro - 2' - hydroxy - 4',6' - dimethoxypropiophenone (2.30 g) in methanol (30 ml). After 1 h, the mixture was acidified with dilute hydrochloric acid. The precipitate was crystallized, giving 2' - hydroxy - 3,4',6' - trimethoxypropiophenone **34** in colourless prisms (1.57 g), m.p. 116–8° (lit.[5] 120–1°). NMR 3.36 (t, 2-CH_2; J 6 Hz), 3.44 (s, 3-OMe), 3.83 (t, 3-CH_2), 3.86 (s, 4'-OMe), 3.90 (s, 6'-OMe), 6.00 (d, 3'-H; J 2 Hz), 6.40 (d, 5'-H), 13.97 (s, OH).

Bromine (0.95 g) in carbon tetrachloride (10 ml) was added dropwise to a solution of the trimethoxypropiophenone (1.44 g) in carbon tetrachloride (30 ml). The solvent was removed under reduced pressure after 1 h and gave 3' - bromo - 2' - hydroxy - 3,4',6' - trimethoxypropiophenone **35** which crystallized in colourless plates (1.57 g), m.p. 114–6°. NMR 3.35 (t, 2-CH_2; J 7 Hz), 3.44 (s, 3-OMe), 3.83 (t, 3-CH_2), 4.00 (s, 4'- and 6'-OMe), 6.05 (s, 5'-H), 14.50 (s, OH).

A solution of the 3-methoxypropiophenone (1.0 g) in acetic anhydride (5 ml), containing anhydrous sodium acetate (1.0 g), was heated on a steambath for 2 h, cooled, and poured into iced water. The precipitate, 2' - acetoxy - 3' - bromo - 3,4',6' - trimethoxypropiophenone **36** crystallized in colourless plates (0.80 g), m.p. 132–3°. NMR 2.32 (s, OAc), 3.11 (t, 2-CH_2; J 7 Hz), 3.39 (s, 3-OMe), 3.75 (t, 3-CH_2), 3.92 (s, 4'-OMe), 3.99 (s, 6'-OMe), 6.49 (s, 5'-H).

Bromine (0.31 g) in acetic acid (5 ml) was added slowly to a solution of the acetate (0.70 g) in acetic acid (15 ml). After 2 h, the mixture was diluted with water. The precipitate, 2' - acetoxy - 2,3' - dibromo - 3,4',6' - trimethoxypropiophenone **32** crystallized in colourless plates (0.40 g), m.p. 93–5°, identical (tlc and NMR) with that previously isolated.

Aqueous hydrogen peroxide (26–28% w/w; 0.4 ml) was added to a solution of 2' - hydroxy - 4',6' - dimethoxyacrylophenone (0.12 g) in methanol (5 ml) and aqueous sodium hydroxide (10%; 10 ml). The mixture was acidified after 1 h with dilute hydrochloric acid. The precipitate of 2' - hydroxy - 3,4',6' - trimethoxypropiophenone **34** crystallized in colourless plates (0.07 g), m.p. 116–8°, identical (tlc and NMR) with that previously isolated.

A mixture of 2' - hydroxy - 4',6' - dimethoxyacetophenone (2.45 g), paraformaldehyde (0.50 g), and dimethylamine hydrochloride (1.30 g) in propanol (5 ml) containing hydrochloric acid (3 drops) was heated under reflux for 2 h and cooled. Crystalline bis(3 - aceto - 2 - hydroxy - 4,6 - dimethoxyphenyl)methane **37** separated and recrystallized from acetone in yellow needles (0.70 g), m.p. 193–4°. NMR 2.60 (s, Ac × 2), 3.84 (s, 6-OMe × 2), 3.90 (s, 4-OMe × 2 and CH_2), 5.98 (s, 5-H × 2), 14.00 (s, OH × 2).

Reactions of 1,3,5-*trimethoxybenzene*

Aluminium chloride (10.48 g) was added slowly to a solution of 1,3,5-trimethoxybenzene (3.96 g) and 3-chloropropionyl chloride (3.1 g) and dry diethyl ether (38 ml). The mixture was heated under reflux for 5 h; 18 h later, it was decomposed with dilute hydrochloric acid. The usual work-up, using diethyl ether and without tlc, gave 3 - chloro - 2' - hydroxy - 4',6' - dimethoxypropiophenone **24** which crystallized in needles (0.50 g), m.p. 154–5°, identical (tlc and NMR) with that previously isolated.

Aluminium chloride (119.9 g) was slowly added to a solution of 1,3,5-trimethoxybenzene (15.84 g) and 3-chloropropionyl chloride (12.5 g) in dry diethyl ether (152 ml). The mixture was heated under reflux for 15 h; 18 h later, it was decomposed with dilute hydrochloric acid. The usual work-up, using diethyl ether and without tlc, gave 3 - chloro - 3' - ethyl - 2' - hydroxy - 4',6' - dimethoxypropiophenone **38** which was obtained as yellow crystals (9.0 g), m.p. 107–8°. NMR 1.12 (t, Et; J 7 Hz), 2.68 (q, Et), 3.56 (t, 2-CH_2; J 6 Hz), 3.95 (t, 3-CH_2), 3.98 (s, 4'-OMe), 4.00 (s, 6'-OMe), 6.08 (s, 5'-H), 13.70 (s, OH). The ethanolic mother-liquor was concentrated and purified by tlc, givng 2' - hydroxy - 4',6' - dimethoxy - 3 - (2,4,6 - trimethoxyphenyl)propiophenone **39** which was obtained from acetone-light petroleum (b.p. 40–60°) as colourless crystals (0.61 g) m.p. 141–3°. NMR 2.92–3.20 (m, 2- and 3-CH_2), 3.78-3.85 (m, OMe × 5), 5.94 (d, 3'-H; J 3 Hz), 6.03 (d, 5'-H), 6.18 (s, 3- and 5-H), 14.35 (s, OH).

Anhydrous ferric chloride (8.0 g) was added slowly to a solution of 1,3,5-trimethoxybenzene (5.0 g) and 3-chloropropionyl chloride (9.82 g) in carbon disulphide (25 ml). After 24 h, the complex was decomposed with dilute hydrochloric acid. The

usual work-up, using diethyl ether and without tlc, gave 2',4',6' - trimethoxy - 3 - (2,4,6 - trimethoxyphenyl)propiophenone **40** which crystallized in prisms (4.10 g), m.p. 124–6°. NMR 2.93 (s, 2- and 3-CH_2), 3.80 (s, 4'-, 2-, 4-, 6-OMe), 3.84 (s, 2'- and 6'-OMe), 6.18 (s, Ar).

Sulphuric acid (1.7 ml) was added dropwise to a stirred solution of 1,3,5-trimethoxybenzene (5.17 g) and acryloyl chloride (2.79 g) in diethyl ether (15 ml). After 18 h, the mixture was diluted with water and the precipitate, 3 - (2,4,6 - trimethoxyphenyl) propionic acid **41**, crystallized from benzene in colourless plates (4.20 g), m.p. 142–3° (lit.[18] 140°). NMR 2.30–2.70 (m, 2-CH_2), 2.82–3.15 (m, 3-CH_2), 3.82 (s, OMe × 3), 6.20 (s, Ar), 9.80 (s, CO_2H).

Reactions of 2' - hydroxy - 4',6' - dimethoxychalcone

A solution of 2' - hydroxy - 4',6' - dimethoxychalcone (2.5 g) and m-chloroperbenzoic acid (3.66 g) in chloroform (75 ml) was refluxed for 15 h and then worked-up as usual but using column chromatography in place of tlc. The following were isolated in order of decreasing R_f values: Substrate (0.3 g); 3',6' - Dihydroxy - 2',4' - dimethoxychalcone **43** which crystallized in red cubes (0.20 g), m.p. 155–7° (lit.[19] 156–8°). NMR 3.94 (s, 4'-OMe), 3.98 (s, 2'-OMe), 5.45 (s, 3'-OH, 6.42 (s, 5'-H), 7.30–7.80 (m, Ar), 8.02 (s, 6- and 8-H), 13.40 (s, 6'-OH).

Lithium aluminium hydride (2.35 g) was added over 1 h to a solution of 2' - hydroxy - 4',6' - dimethoxychalcone (14.2 g) in tetrahydrofuran (140 ml) at −8°. After 2 h, the usual work-up, but using diethyl ether and column chromatography, gave 5,7-dimethoxyflav-3-ene **44** as an uncrystallizable gum (4.23 g). NMR 3.74 (s, 7-OMe), 3.80 (s, 5-OMe), 5.56 (q, 3-H; J 3.5 and 10 Hz), 5.88 (q, 2-H; J 2 and 3.5 Hz), 6.10 (s, 6- and 8-H), 6.88 (q, 4-H; J 2 and 10 Hz), 7.26–7.67 (m, Ar).

REFERENCES

[1]Part XIII: J. A. Donnelly and D. E. Maloney, *Tetrahedron* **35**, 2875 (1979).
[2]G. Litkei, R. Bognar, Z. Dinya and E. R. David, *Topics in Flavonoid Chemistry and Biochemistry*, p. 110. Akademiai Kiado, Budapest (1975); and refs therein.
[3]D. J. Donnelly, J. A. Donnelly and J. R. Keegan, *Tetrahedron* **33**, 3289 (1977); and refs therein.
[5]A. I. Turbina, V. G. Sinyavskii and M. Y. Romankevich, *Ukr. Khim. Zh.* **31**, 85 (1965).
[5]B. W. Bycroft, J. R. Hatton and J. C. Roberts, *J. Chem. Soc.* (*C*) 281 (1970).
[6]J. A. Donnelly, M. J. Fox and D. E. Maloney, *Tetrahedron Letters* 4691 (1978).
[7]Part XI: J. A. Donnelly, M. J. Fox and T. C. Sharma, *Tetrahedron* **35**, 875 (1979).
[8]J. W. Clark-Lewis and D. C. Skingle, *Aust. J. Chem.* **20**, 2169 (1967).
[9]J. A. Donnelly, *Tetrahedron Letters* No. 19, 1 (1959).
[10]D. J. Donnelly and J. A. Donnelly, this Laboratory, unpublished results.
[11]V. T. Ramakrishnan and J. Kagan, *J. Org. Chem.* **35**, 2898 (1970). L. Main and K. B. Old, *Tetrahedron Letters* 2809 (1977).
[12]A. R. Katritzky and B. Ternai, *J. Heterocyclic Chem.* **5**, 745 (1968).
[13]W. D. Cotterill, J. Cottam and R. Livingstone, *J. Chem. Soc.* (*C*) 1006 (1970).
[14]A. Schonberg and G. Schutz, *Chem. Ber.* **93**, 1466 (1960).
[15]H. D. Dakin, *Org. Synth.* Coll. Vol. I, 149 (1946).
[16]E. Fischer and M. Slimmer, *Chem. Ber.* **36**, 2575 (1903).
[17]N. Narasimhachari, D. Rajagopalan and T. R. Seshadri, *J. Sci. Industr. Res.* **12**, 287 (1953).
[18]N. Nakazawa and S. Matsuura, *J. Pharm. Soc. Japan* **75**, 68 (1955).
[19]S. Rajagopalan and T. R. Seshadri, *Proc. Indian Acad. Sci.* 85 (1948).