Tetrahedron Vol 33, pp 3289 to 3294 Pergamon Press 1977 Printed in Great Britain

CHALCONE DIHALIDES—IX[1]

THE MODES OF CYCLIZATION OF 4-NITROCHALCONE DIBROMIDES AND α-BROMO-4-NITROCHALCONES

D. J. DONNELLY, J. A. DONNELLY* and J. R. KEEGAN
Chemistry Department, University College, Dublin 4, Republic of Ireland

(*Received in UK 8 June 1977; Accepted for publication 28 June 1977*)

Abstract—The (E) and (Z) isomers of α-bromo-2'-hydroxy-4-nitrochalcone both exhibited the unusual ability to undergo nucleophilic addition to the α-position of the double bond. They differed markedly, however, in their preferred mode; the former favoured α-addition, the latter β-addition. It is proposed that these isomers are intermediates in the Emilewicz-von Kostanecki cyclization of 2'-hydroxy-4-nitrochalcone dibromide to a mixture of aurone and flavone.

The Emilewicz-von Kostanecki reaction—the cyclization of 2'-hydroxychalcone dihalides (e.g. **1**) or their acetates by base—is an excellent general synthesis[2] of flavones. Dihalides having certain substitution patterns and known[3] collectively as class 2 dihalides, while forming flavones exclusively[2,4] under mild conditions, form the 5-membered heterocycles, aurones (e.g. **4**), to some extent when these conditions are altered.

The first group of these exceptional dihalides (class 2A) is characterised by a substituent, usually an ether, in the 6'-position of the A-ring. At relatively high base concentrations these dihalides (**1**) form,[4] to some extent, α-halogeno-β-hydroxyl dihydrochalcones (**3**) (via α-halogenochalcones (**2**)), the cyclization of which to aurones (**4**) is a reflection on the leaving-group abilities of the side-chain substituents. Class 2B chalcone dihalides (**5**) are characterised by an ether substituent in the *o*- or *p*-position of the B-ring and, if their cyclization[6] is carried out in *warm* alcohol, this substituent facilitates prior displacement of the nearer halogen by solvent. The cyclization of the resulting α-halogeno-β-alkoxyl dihydrochalcone (**6**), like that of the analogous intermediate (**3**) from class 2A dihalides above, results in the formation of aurones (**7**). The mode of cyclization of the remaining aurone-forming group of dihalides (class 2C) is the subject of the present study.

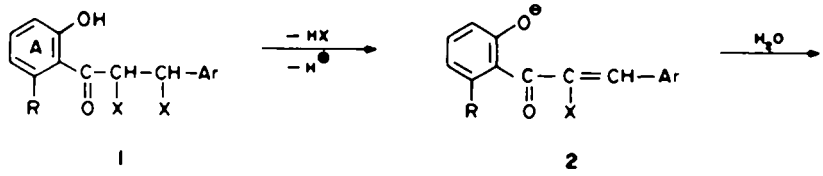
Chalcone dihalides of class 2C (**8**) contain an *o*- or *p*-nitro group in the B-ring and have been reported[7,8] to yield only aurones (**11**). In contrast, 3-nitrochalcone dihalides cyclize[8,9] to 3'-nitro*flavones*. This dichotomy in the reactions of B-ring nitrochalcone dihalides has led[9] to the suggestion that aurone-formation occurs not via direct cyclosubstitution of the α-halogen but via prior elimination of hydrogen halide to form a β-halogenochalcone (**9**), followed by cycloaddition to the α-position of the double bond—both the elimination and the cycloaddition steps being controlled by the nitro group rather than by the phenoxide-deactivated CO group.

It has now been found that 2'-hydroxy-4-nitrochalcone dibromide (**8**) does not exclusively form aurone (**11**). It yielded (Table 1) nearly half as much flavone as aurone. Also, unlike class 2A dihalides,[4] the aurone-to-flavone ratio (A/F) was not significantly affected by the concentration of the added base. Other chalcone dibromides with substituents having positive Hammett σ constants in the 4-position gave flavones alone and, therefore, belong[1] to class 1: 4-bromo-2'-hydroxychalcone dibromide (**12**, X = Br) and 4-chloro-2'-hydroxychalcone dibromide (**12**, X = Cl) gave 4'-bromoflavone (**13**, X = Br) and 4'-chloroflavone (**13**, X = Cl), respectively. It was found that 2'-hydroxy-3-nitrochalcone dibromide, like its acetate,[8] cyclizes exclusively to 3'-nitroflavone.

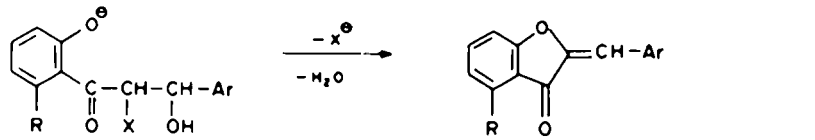
It has been possible to prepare the (Z) and (E) isomers of a monobromochalcone by the reaction of 2'-hydroxy-4-nitrochalcone dibromide (**8**) with ethanolic potassium acetate. These isomers are believed to be the aurone- and flavone-forming intermediates in the Emilewicz–von Kostanecki reaction of this chalcone dibromide. They were only obtained, however, in small quantities; the main products being aurone (**11**) and substrate(**8**). They were more readily prepared indirectly from 2'-acetoxy-4-nitrochalcone dibromide (**14**). This acetate eliminated hydrogen bromide on reaction with potassium acetate and the (Z)- (**15**) and (E)- (**16**) isomers of 2'-acetoxy-α-bromo-4-nitrochalcone were isolated in the approximate

Table 1. Products (%) from the reaction of 2'-hydroxy-4-nitrochalcone dibromide (**8**) with aqueous ethanolic potassium hydroxide

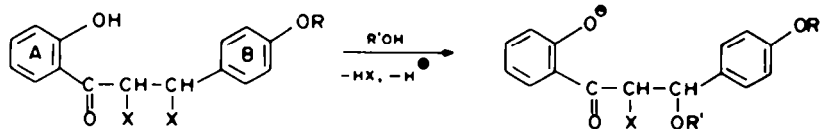
Added base conc.	4'-Nitroaurone	4'-Nitroflavone	A/F
0.2M	59.4	26.3	2.26
0.2M	58.8	28.9	2.03
1.0M	62.9	27.6	2.28
1.0M	55.9	23.4	2.39



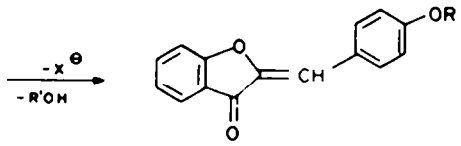
1 2



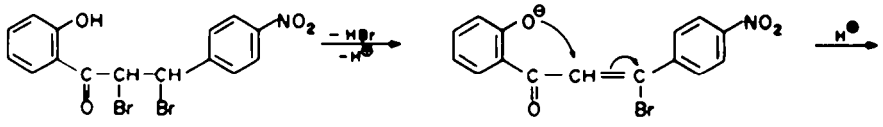
3 4



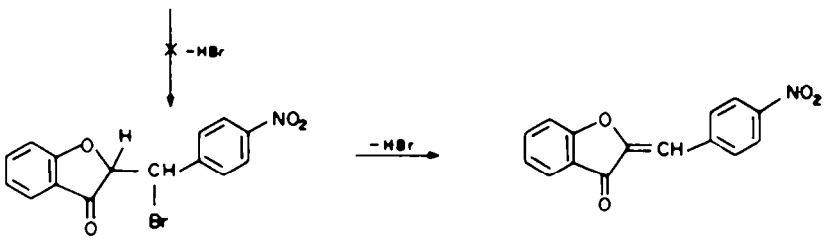
5 6



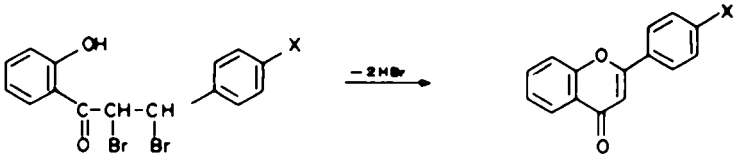
7



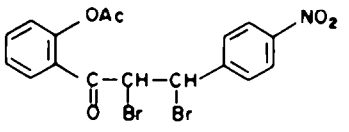
8 9



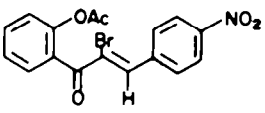
10 11



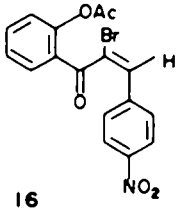
12 13



14



15



16

ratio of 2:1. Some 4'-nitroaurone (**11**) and a small amount of an unknown bromo-ethoxyl compound were also isolated.

The assignment of the bromine of the monobromochalcones (**15**, **16**) to the α-rather than to the β-position is based on the observations of Agoff and Cabaleiro who found[10] that β-acetoxy-α-bromo-4-nitrodihydrochalcone (**17**) eliminated acetic acid rather than hydrogen bromide on reaction with ethanolic sodium acetate. The possibility that the products are an α- and a β-bromochalcone is excluded by the interconversion (see below) of their derivatives.

(Z)-2'-Acetoxy-α-bromo-4-nitrochalcone (**15**) was deacetylated by aqueous ethanolic hydrogen chloride and gave (Z)-α-bromo-2'-hydroxy-4-nitrochalcone (**19**). The (E)-acetate (**16**), similarly treated, gave both (E)- (**18**) and (Z)- (**19**) α-bromo-2'-hydroxy-4-nitrochalcone. The latter was photoisomerised to the (E)-isomer by sunlight irradiation. These isomers of α-bromo-2'-hydroxy-4-nitrochalcone were identical with the above-mentioned monobromochalcones (NMR; tlc) obtained directly from 2'-hydroxy-4-nitrochalcone dibromide (**8**). Their proposed intermediacy in the cyclization of the dibromide to aurone and flavone was tested by subjecting them to typical Emilewicz-von Kostanecki reaction conditions. The results are shown in Table 2.

While both isomers exhibited the ability to undergo cycloaddition to both ends of the double bond, they differed markedly in their preferred mode. (E)-α-bromo-2'-hydroxy-4-nitrochalcone (**18**) gave predominantly aurone (**21**) on cyclization while its (Z)-isomer (**19**) yielded mostly flavone (**22**). If the cyclization of 2'-hydroxy-4-nitrochalcone dibromide occurs entirely through these α-bromochalcone isomers, it follows from the data in Table 2 that they would have to be formed in the ratio of 30:70 approximately in order that the A/F ratio of the chalcone dibromide products be that observed (Table 1).

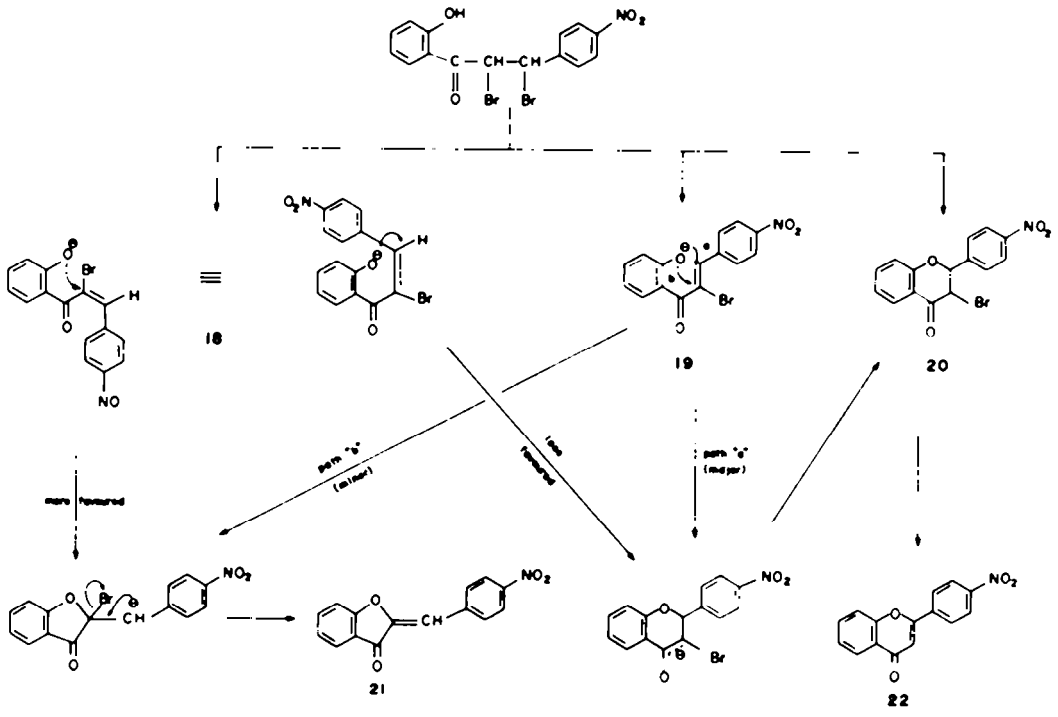
No data are available for the elimination of one mole of hydrogen bromide from 2'-hydroxy-4-nitrochalcone dibromide (**8**) by potassium hydroxide because of more rapid further reactions. However, NMR data on the isomer composition of the products of hydrogen bromide elimination from 2'-acetoxy-4-nitrochalcone dibromide (**14**) by potassium acetate indicate an (E)/(Z) ratio of 25:75 which is not significantly different from that required for the Emilewicz-von Kostanecki reaction, considering the ease of interconversion of these isomers and that the data are not from 2'-hydroxy-4-nitrochalcone dibromide but from its acetate.

The dichotomy in the predominant mode of cyclization of these α-bromochalcones may be a consequence of the nonbonding interaction of the aromatic nuclei in the transition state for the cyclization of the (E)-isomer (**18**) to flavone (**22**), resulting in preferential formation of aurone **21** (Scheme 1). No such interaction occurs in the cyclization of the (Z)-isomer (**19**) with the consequent production mainly of flavone (**22**). Nucleophilic addition to the α-position of the double bond of an α,β-unsaturated CO group is unusual[11] and is attributed here to the counter effects of the 4-nitrophenyl group to the phenoxide-conjugated ketone. Scheme 1 shows the suggested routes to aurone and flavone from 4-nitrochalcone dibromide (class 2C).

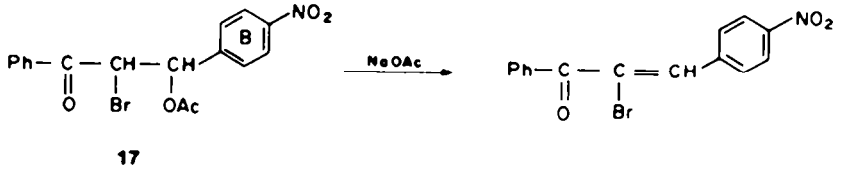
The unknown bromoethoxyl minor product, isolated from the reaction of 2'-acetoxy-4-nitrochalcone dibromide (**14**) with ethanolic potassium acetate, analysed for $C_{17}H_{14}BrNO_5$ and gave 4'-nitroflavone (**22**) when treated with ethanolic potassium hydroxide. A likely structure appeared to be 3-bromo-2-ethoxy-4'-nitroflavanone (**23**). However, unlike the parent compound, 3-bromo-2-ethoxyflavanone (**24**), it could not be prepared from the corresponding flavone (**22**) and its one-proton singlet occurred at δ6.10 as against δ4.47 for the 3-H of the parent flavanone (**24**). Also, the parent compound (**24**) yielded not flavone (**26**) but 3-bromoflavone (**25**) when treated with ethanolic potassium hydroxide. Only with the soft base, dimethyl-sulphox-

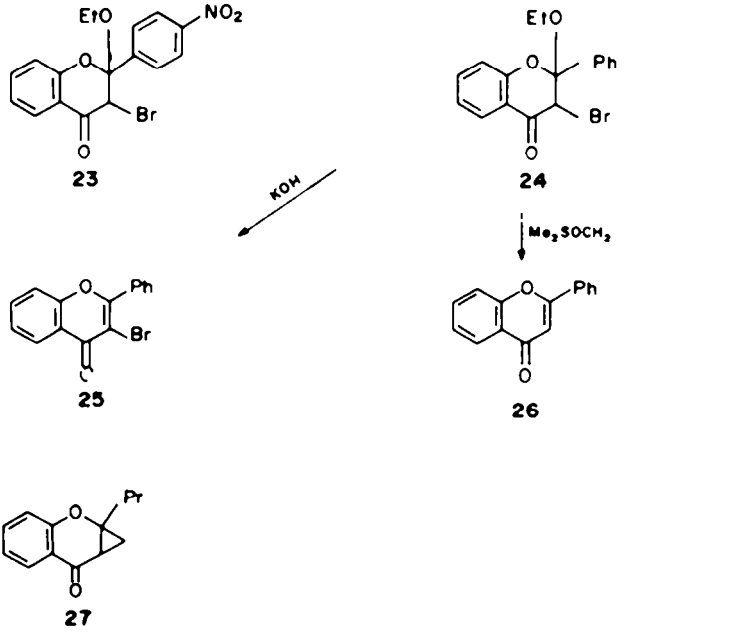
Table 2. Products (%) from the reaction of α-bromo-2'-hydroxy-4-nitrochalcones with aqueous ethanolic potassium hydroxide (1.0 M)

Substrate	4'-Nitroaurone	4'-Nitroflavone	A/F
(E)-α-Bromochalcone (**18**)	86.0	13.0	6.6
(E)-α-Bromochalcone (**18**)	74.3	13.0	6.7
(Z)-α-Bromochalcone (**19**)	39.1	65.1	0.6
(Z)-α-Bromochalcone (**19**)	33.9	63.8	0.5



Scheme 1.





onium methylide, did 3-bromo-2-ethoxyflavanone (**24**) form flavone (**26**) (together with 2,3-methanoflavanone (**27**), the product of a secondary reaction between flavone (**26**) and the ylide).

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. Merck silica gel $PF_{254+366}$ was used for tlc. Unless otherwise stated, all solid products were crystallized from EtOH.

A soln of 2' - acetoxy - 2,3 - dibromo - 3 - (4 - nitrophenyl)-propiophenone[8] (2 g) in aqueous EtOH (50%; 200 ml) and HClaq (10%; 50 ml) was refluxed for 5 hr and diluted with water (200 ml) to give a yellow ppt of *2,3-dibromo-2'-hydroxy-3-(4-nitrophenyl)propiophenone* (1.4 g) m.p. 197–8°. (Found: C, 41.5; H, 2.6; H, 2.6; Br, 37.5; N, 3.2. $C_{15}H_{11}Br_2NO_4$ requires: C, 42.0; H, 2.6; Br, 37.2; N, 2.5%). P m.r.: 5.78 (d, 3-H), 5.98 (d, 2-H), 11.80 (s, OH), $J_{2,3}$ 12 Hz.

Similar treatment of 2' - acetoxy - 2,3 - dibromo - 3 - (3 - nitrophenyl)propiophenone[8] (2 g) gave 2,3 - *dibromo* - 2' - *hydroxy* - 3 - (3 - *nitrophenyl)propiophenone* (1.3 g), m.p. 188–9°. (Found: C, 42.5; H, 2.7; Br, 36.6; N, 3.2. $C_{15}H_{11}Br_2NO_4$ requires: C, 42.0; H, 2.6; Br, 37.2; N, 3.3%). PMR: 5.79 (d, 3-H), 6.01 (d, 2-H), 11.75 (s, OH), $J_{2,3}$ 12 Hz.

Bromine (2.3 g) in chloroform (10 ml) was added to a soln of 4-bromo-2'-hydroxychalcone[12] (4 g) in chloroform (100 ml). Removal of the solvent gave 2,3 - *dibromo* - 2' - *hydroxy* - 3 - (4 - *bromophenyl)propiophenone* (3.4 g), m.p. 180–1°. (Found: C, 38.5; H, 2.2; Br, 52.4. $C_{15}H_{11}Br_3O_2$ requires: C, 38.9; H, 2.4; Br, 51.8%). PMR: 5.68 (d, 3-H), 5.88 (d, 2-H), 11.83 (s, OH), $J_{2,3}$ 12 Hz.

Similar addition of bromine (2.5 g) to 4 - chloro-2'-hydroxychalcone[13] (4 g) gave 2,3 - *dibromo* - 2' - *hydroxy* - 3 - (4 - *chlorophenyl)propiophenone* (3.4 g), m.p. 180–181°. (Found: C, 42.8; H, 2.7; Br, 39.2; Cl, 8.1. $C_{15}H_{11}Br_2ClO_2$ requires: C, 43.0; H, 2.6; Br, 38.2; Cl, 8.5%). PMR 5.71 (d, 3-H), 5.93 (d, 2-H), 11.85 (s, OH), $J_{2,3}$ 12 Hz.

KOHaq (0.2 M; 17.5 ml) was added to a suspension of 2,3 - dibromo - 2' - hydroxy - 3 - (3 - nitrophenyl)propiophenone (500 mg) in EtOH (30 ml). After 2 hr at 25°, the suspension was diluted with water (30 ml) to precipitate 3'-nitroflavone[8] (232 mg), m.p. 203–4°. PMR: 7.05 (s, 3-H).

Similar addition of KOHaq (0.2 M; 17.3 ml) to 2,3 - dibromo - 2' - hydroxy - 3 - (4 - bromophenyl)propiophenone (500 mg) gave 4'-bromoflavone[12] (310 mg), m.p. 173–4°. PMR: 6.88 (s, 3-H).

The addition of KOHaq (0.2 M; 18 ml) to 2,3 - dibromo - 2' - hydroxy - 3 - (4 - chlorophenyl)propiophenone (500 mg) gave 4'chloroflavone[14] (240 mg), m.p. 183–4°. PMR: 6.86 (s, 3-H)

The ppt from the reaction of KOHaq (0.2 m; 17.5 ml) with 2,3 - dibromo - 2' - hydroxy - 3 - (4 - nitrophenyl)propiophenone (500 mg), as above, was fractionated by tlc and gave 4'-nitroaurone[8] (175 mg), m.p. 206–7° (PMR: 7.00 (s, β-H)) and 4'-nitroflavone[8] (82 mg), m.p. 239–240° (PMR: 7.03 (s, 3-H)). This reaction, when repeated, gave 4'-nitroaurone (183 mg) and 4'-nitroflavone (90 mg).

When the above reaction was carried out using KOHaq (1.0 M; 3.5 ml), the products were 4'-nitroaurone (196 mg) and 4'-nitroflavone (86 mg). When repeated, this reaction gave aurone (174 mg) and flavone (93 mg).

A mixture of 2,3 - dibromo - 2' - hydroxy - 3 - (4 - nitrophenyl)propiophenone (400 mg) and anhyd KOAc (91 mg) in EtOH (25 ml) was stirred at room temp for 24 hr, diluted with water, and extracted with chloroform. This extract was fractionated by tlc and gave substrate (46 mg), 4'-nitroaurone (36 mg), (E) - α - *bromo* - 2' - *hydroxy* - 4 - *nitrochalcone* (32 mg), m.p. 128–129° and (Z) - α - *bromo* - 2' - *hydroxy* - 4 - *nitrochalcone* (59 mg), 114–5°. PMR of (E)-isomer: 6.8–8.3 (m, aromatic and β H's), 11.54 (s, OH). (Found: C, 52.0; H, 3.0; Br, 22.2; N, 3.9. $C_{15}H_{10}BrNO_4$ requires: C, 51.7; H, 2.9; Br, 23.0, N, 4.0%). PMR of (Z)-isomer: 6.9–8.5 (m, aromatic and β H's), 11.38 (s, OH). (Found: C, 51.4; H, 2.8; Br, 22.9; N, 3.9. $C_{15}H_{10}BrNO_4$ requires: C, 51.7; H, 2.9; Br, 23.0; N, 4.0%).

A soln of 2' - acetoxy - 2,3 - dibromo - 3 - (4 - nitrophenyl)propiophenone (3.0 g) and anhyd KOAc (0.72 g) in EtOH (200 ml) was refluxed for 2 hr, diluted with water (200 ml), and extracted with chloroform. The chloroform extract was fractionated by tlc and gave 4'-nitroaurone (120 mg), an unidentified oil (90 mg), (E) - 2' - *acetoxy* - α - *bromo* - 4 - *nitrochalcone* (800 mg), m.p. 105–7° and (Z) - 2' - *acetoxy* - α - *bromo* - 4 - *nitrochalcone* (1.62 g), m.p. 90–3°. PMR of (E)-isomer: 2.40 (s, OAc), 7.1–8.2 (m, aromatic and β H's). (Found: C, 51.9; H, 2.9; Br, 20.6; N, 3.6. $C_{17}H_{13}BrNO_5$ requires: C, 52.3; H, 3.1; Br, 20.5; N, 3.6%). PMR of (Z)-isomer: 2.26 (s, OAc), 7.3–8.4 (m, aromatic and β H's). (Found: C, 52.1; H, 2.9; Br, 20.4; N, 3.4. $C_{17}H_{13}BrNO_5$ requires: C, 52.3; H, 3.1; Br, 20.5; N, 3.6%). PMR of unknown oil: 1.50 (t, CH_3), 4.18 (q, CH_2) J 6 Hz, 6.10 (s, one H), 6.8–8.4 m, eight H's). (Found: C, 52.5; H, 3.5; Br, 20.5; N, 4.4 $C_{17}H_{14}BrNO_5$ requires: C, 52.6; H, 3.6; Br, 20.4; N, 3.6%).

A soln of (E)-**16** (400 mg) in EtOH (100 ml) and HClaq (10%; 20 ml) was refluxed for 5 hr, diluted with water (200 ml), and extracted with chloroform. This extract was fractionated by tlc and gave (E)-**18** (340 mg), m.p. 128–9° and its (Z)-isomer (20 mg), m.p. 114–5°.

(Z)-**15** (400 mg), similarly treated, gave (Z)-**19** (380 mg), m.p. 114–5°.

KOHaq (1.0 M; 1 ml) was added to a suspension of (E)-**18** (100 mg) in EtOH (25 ml). After 2 hr at 25°, the suspension was diluted with water (50 ml), and extracted with chloroform. This extract was fractionated by tlc and gave 4'-nitroaurone (66 mg), m.p. 206–7° and 4'-nitroflavone (10 mg), m.p. 239–240°. This reaction, when repeated, gave 4'-nitroaurone (59 mg) and 4'-nitroflavone (10 mg).

The ppt from the reaction of KOHaq (1.0 M; 1 ml) with (Z)-**19** (100 mg), as above, gave 4'-nitroaurone (30 mg) and 4'-nitroflavone (50 mg). This reaction, when repeated, gave aurone (26 mg) and flavone (49 mg).

Sunlight irradiation of a soln of (Z)-**19** (50 mg) in pentane (250 ml) for 4 hr followed by fractionation by tlc, gave (E)-**18** (20 mg), m.p. 128–9° and substrate (20 mg).

Br_2 (0.83 mg) was added to a suspension of AgOAc (0.90 g) in a soln of flavone (1.16 g) in chloroform (50 ml) and EtOH (1 ml). After 1 hr the mixture was filtered and the solvent removed, giving 3 - *bromo* - 2 - *ethoxyflavanone* (0.83 g), m.p. 123–4°. (Found: C, 58.4; H, 4.5; Br, 22.4. $C_{17}H_{15}BrO_3$ requires: C, 58.8; H, 4.4; Br, 23.0%). PMR: 0.91 (t, CH_3), 3.34 (q, CH_2), J 7.5 Hz, 4.47 (s, 3-H).

KOHaq (6.5 M; 2 ml) was added to a soln of 3 - bromo - 2 - ethoxyflavanone (0.97 g) in EtOH (30 ml). After 15 min the mixture was diluted with water (500 ml) and the resulting ppt was crystallized from aqueous EtOH giving 3-bromoflavone[15] (0.65 g), m.p. 126–7°. Treatment of 3 - bromo - 2 - ethoxyflavanone (5.10 g) in dimethylsulphoxide with dimethylsulphoxonium methylide[16] (from NaH (1.1 g) and trimethylsulphoxonium iodide (13.3 g)) in dimethylsulphoxide, followed after 5 min by dilution with water (700 ml), extraction into diethyl ether, and removal of solvent, gave an oil which was fractionated by tlc to give flavone (2.1 g), m.p. 95–97° and 2,3-methanoflavanone[17] (0.91 g), m.p. 64–65°.

KOHaq (1.0 M; 1 ml) was added to a soln of the unknown, $C_{17}H_{14}BrNO_5$, oil (50 mg) in EtOH (5 ml) and gave a ppt of 4'-nitroflavone (20 mg), m.p. 239–240°.

Acknowledgements—We wish to express our indebtedness to Professor E. M. Philbin. One of us (D.J.D.) thanks Bristol Laboratories, Syracuse, New York for financial support.

REFERENCES

[1]Part VIII: J. A. Donnelly and H. H. Doran, *Tetrahedron* **31**, 1791 (1975).
[2]J. A. Donnelly and H. J. Doran, *Tetrahedron Letters*, 4083 (1974).
[3]J. A. Donnelly, H. J. Doran and J. J. Murphy, *Tetrahedron* **29**, 1037 (1973).

[4]K. von Auwers and L. Anschutz, *Ber. Dtsch. Chem. Ges.* **54**, 1543 (1921).
[5]J. A. Donnelly and H. J. Doran, *Tetrahedron* **31**, 1565 (1975).
[6]S. M. Nadkarni, A. M. Warriar and T. S. Wheeler, *J. Chem. Soc.* 1798 (1937).
[7]D. Price and M. T. Bogert, *J. Am. Chem. Soc.* **56**, 2442 1934).
[8]L. Reichel and G. Hempel, *Liebigs Ann.* **625**, 184 (1959).
[9]D. J. Donnelly, J. A. Donnelly and E. M. Philbin, *Tetrahedron* **28**, 1867 (1972).
[10]J. M. Agoff and M. C. Cabaleiro, *Tetrahedron Letters* 3527 (1974); J. M. Agogg, M. C. Cabaleiro and A. B. Chopa, *Anal. Assoc. Quim. Argent.* **63**, 105 (1975).
[11]For other examples see: D. J. Donnelly, J. A. Donnelly and E. M. Philbin, *Proc. Roy. Irish Acad.* **73**, 129 (1973).
[12]F. Chen and C. Yang, *J. Taiwan Pharm. Assoc.* **3**, 39 (1951).
[13]R. Polanowski and M. Krajewska, *Acta Pol. Pharm.* **24**, 567 (1967).
[14]W. Baker, J. B. Harbourne and W. D. Ollis, *J. Chem. Soc.* 1294 (1952).
[15]H. de Diesbach and H. Kramer, *Helv. Chim. Acta* **28**, 1399 (1945).
[16]E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.* **87**, 1353 (1965).
[17]P. Bennett and J. A. Donnelly, *Chem. Ind.* 783 (1969).