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# CHALCONE DIHALIDES—III*

## CYCLIZATION OF NITRO DERIVATIVES

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**Abstract**—2'-Hydroxy-3',4'-dimethoxy-3-nitrochalcone dibromide and 5'-chloro-2'-hydroxychalcone dibromide, on cyclization with aqueous ethanolic potassium hydroxide, gave the corresponding flavones. The formation of aurones from 2- and 4-nitrochalcone dibromides and flavones from 3-nitrochalcone dibromides is discussed.

OUR interest in the mechanism of ring-closure of chalcone dibromides led us to investigate the anomalous results obtained in the cyclization of certain dibromides. Using aqueous ethanolic sodium hydroxide, Kostanecki and Ludwig[1] found that 5'-bromo-2'-acetoxychalcone dibromide (Ia) cyclized to the corresponding flavone (IIa) whereas Shah and Parikh[2] reported that the closely related compound, 5'-chloro-2'-hydroxychalcone dibromide (Ib), under similar conditions, gave the corresponding aurone (IIIb). It has now been found that 5'-bromo- (Ic) and 5'-chloro- (Ib) 2'-hydroxychalcone dibromides, on treatment with aqueous potassium hydroxide in cold and in hot ethanol, give 6-bromoflavone (IIa) and 6-chloroflavone (IIb), respectively. Pyrolysis of these chalcone dibromides also gave the corresponding flavones.

In 1934, Price and Bogert[3] treated 2'-acetoxy-3',4'-dimethoxy-2-, 3-, and 4-nitrochalcone dibromides (IV, R = OMe) with aqueous ethanolic sodium hydroxide and reported that all three gave the corresponding aurone. In 1959, Reichel and Hempel[4] carried out the same reaction on 2'-acetoxy-2-, 3-, and 4-nitrochalcone dibromides (IV, R = H) and found that, while the 2- and 4-nitrochalcone dibromides gave aurones, the 3-nitrochalcone dibromide gave the corresponding flavone.

In the present work when 2'-acetoxy-3',4'-dimethoxy-3-nitrochalcone was brominated the product, as described by Price and Bogert,[3] was an oil. Two crystalline solids were obtained from this oil having m.ps of 172° and 60°, respectively. The former analyzed correctly for 2'-hydroxy-3',4'-dimethoxy-3-nitrochalcone dibromide (V, R = H) and gave a positive ethanolic ferric chloride test. The low m.p. of the latter suggested that it was the corresponding acetate (V, R = Ac); this was supported by its negative ferric chloride test but not confirmed by analysis. Treatment of either product with aqueous ethanolic potassium hydroxide gave a compound the properties of which were identical with those reported by Price and Bogert for 6,7-dimethoxy-3'-nitroaurone (VI) but, by comparison (mixed m.ps) with authentic samples of 7,8-dimethoxy-3'-nitroflavone (VII) and 6,7-dimethoxy-3'-nitroaurone (VI), was shown to be the flavone (VII).

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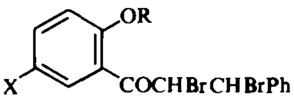
* Part II D. J. Donnelly, J. A. Donnelly and E. M. Philbin, *Tetrahedron*, in press



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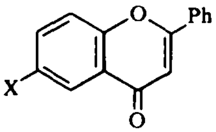

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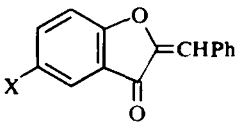
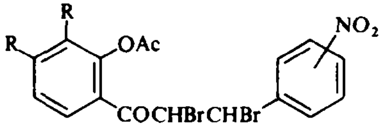


III

a: R = OAc; X = Br
b: R – H; X = Cl
c: R = H; X = Br



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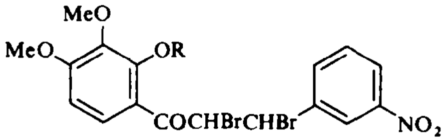

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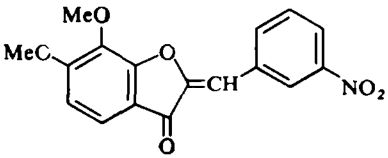

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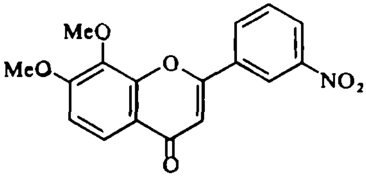

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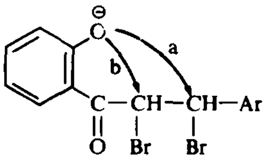

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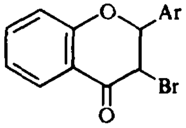

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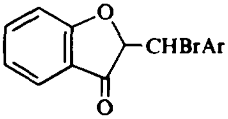

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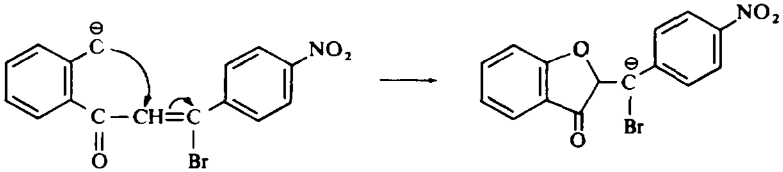
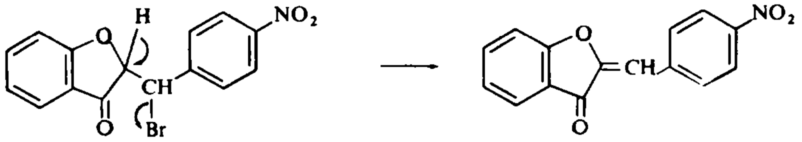
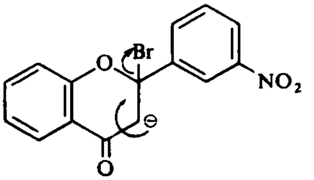


XI XII



XIII XIV



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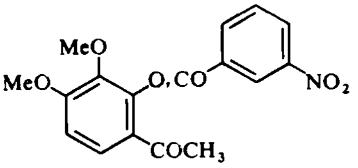
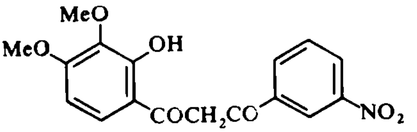


XVI



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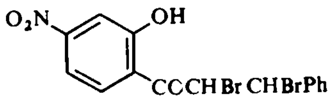
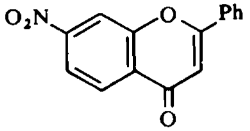


XVIII



XIX

It has been accepted[5] that flavone formation from chalcone dibromides occurs by phenoxide substitution of the β-bromine atom (VIII, path a), followed by elimination of hydrogen bromide from the resulting 3-bromoflavanone (IX). Aurone formation most likely occurs by substitution of the α-bromine (VIII, path b), followed by elimination of hydrogen bromide from the aurone hydrobromide (X) so formed. However, the meta and para Hammett σ-constants[6] of the nitro group (0·710 and 0·778, respectively) are so similar that, if phenoxide substitution of the side-chain halogen is the first step of the reaction, both 3- and 4-nitrochalcone dibromides would be expected to form the same type of intermediate, either IX or X, and, consequently, the same class of product.

The different behaviour of these chalcone dibromides suggests that for the 4-nitro compounds it is the Hammett $\sigma^-$-constant (1·270) that is involved and that here the first step of the reaction is the elimination of hydrogen bromide from the side-chain to form a β-bromochalcone (XI). Production of aurone from a β-bromochalcone requires that addition of phenoxide to the double bond be controlled by the nitro group[*] rather than by the phenoxide-conjugated carbonyl group and results in the formation of XII. It is suggested that this anion is then protonated and that the resulting aurone hydrobromide (XIII) eliminates hydrogen bromide to form an aurone (XIV). The fact that 2-nitrochalcone dibromides form the same class of product as the 4-nitrochalcone dibromides suggests that their mode of cyclization may be similar.

The mechanism of cyclization of 3-nitrochalcone dibromides is still ambiguous. They may ring-close in the normal chalcone dibromide manner to a 3-bromoflavanone before losing hydrogen bromide to form a 3′-nitroflavone or they may eliminate hydrogen bromide from the side-chain to form a β-bromochalcone and then, lacking the large mesomeric effect of a 2- or 4-nitro substituent on the benzal group, cyclize in the normal manner to the conjugate base of a 2-bromoflavanone (XV) before eliminating bromide ion to form a flavone.

The authentic sample of 6,7-dimethoxy-3′-nitroaurone (VI) was prepared by condensing 6,7-dimethoxycoumaranone with 3-nitrobenzaldehyde. 7,8-Dimethoxy-3′-nitroflavone (VII) was synthesized by esterifying 2′-hydroxy-3′,4′-dimethoxyacetophenone with 3-nitrobenzoyl chloride, rearranging the resulting ester (XVI) with potassium hydroxide to the 1,3-diketone (XVII) and, finally, cyclizing this diketone with hydrochloric acid.

The work of Price and Bogert[3] and Reichel and Hempel[4] has demonstrated the anomalous effect of a *para* nitro substituent in the benzyl group on the course of the alkaline cyclization of chalcone dibromides (aurones and not flavones are formed). It has now been found that the introduction of a nitro group into the para position of the benzoyl group has no such dramatic effect. 2′-Hydroxy-4′-nitrochalcone dibromide (XVIII), with aqueous ethanolic potassium hydroxide, gave 7-nitroflavone (XIX); a product also obtained by pyrolyzing the dibromide.

## EXPERIMENTAL

*6-Chloroflavone* (IIb). Aqueous KOH (40%; 1 ml) was added to a suspension or a boiling soln of 2,3-dibromo-5′-chloro-2′-hydroxy-3-phenylpropiophenone (1 g) in EtOH (25 ml). After 2 hr the mixture was diluted with water and the precipitated 6-chloroflavone crystallized from EtOH in needles (0·44 g), m.p. 184–185° (lit.[7] 183–184°). The yellow soln of the product in $H_2SO_4$ showed a blue fluorescence in UV light Pyrolysis of the chalcone dibromide (0·01 g) at 190–200° under reduced pressure also gave 6-chloroflavone.

*6-Bromoflavone* (IIc). $Br_2$ (3·2 g) in $CHCl_3$ (32 ml) was added dropwise to a soln of 5′-bromo-2′-hydroxychalcone (6 g) in $CHCl_3$ (25 ml). After the $CHCl_3$ had evaporated the residual *2,3,5′-tribromo-2′-hydroxy-3-phenylpropiophenone* crystallized from benzene in yellow prisms (6·6 g), m.p. 179–180°. (Found: C, 39·2; H, 2·5; Br, 51·7. $C_{15}H_{11}Br_3O_2$ requires: C, 38·9; H, 2·4; Br, 51·8%). The bromochalcone dibromide (1 g) was treated as above with KOHaq and the product, 6-bromoflavone, crystallized from EtOH in needles, m.p. 192–193° (lit.[8] 192–193°). Pyrolysis of the bromochalcone dibromide (0·01 g) at 190–200° under reduced pressure also yielded 6-bromoflavone.

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[*] We have observed that in basic media 2′-hydroxy-2 methyl-3-(4-pyridyl)acrylophenone cyclizes in this fashion to 2-methyl-2-(4-pyridylmethyl) coumaranone.

*7,8-Dimethoxy-3'-nitroflavone* (VII). $Br_2$ (0·71 g) in $CHCl_3$ (7 ml) was added dropwise to a soln of 2'-acetoxy-3',4'-dimethoxy-3-nitrochalcone[3] (1·4 g) in $CHCl_3$ (20 ml). After the solvent had evaporated the residual oil was triturated with light petroleum (b.p. 40–60°). The solid product, *2,3-dibromo-2'-kydorxy-3',4'-dimethoxy-3-(3-nitrophenyl)propiophenone*, crystallized from benzene in yellow prisms (1·5 g), m.p. 171–172°. (Found: C, 42·3; H, 3·3; Br, 31·0; N, 3·2; OMe, 13·0. $C_{17}H_{15}Br_2NO_6$ requires: C, 41·7; H, 3·1; Br, 32·7; N, 2·9; OMe, 12·7%). An ethanolic soln of the product gave a brown colour with ethanolic $FeCl_3$. In another experiment, carried out as above, the solid product crystallized from benzene/light petroleum (b.p. 40–60°) in needles (1·7 g), m.p. 58–60°. (Found: C, 47·9; H, 3·6; Br, 26·0; N, 2·4. Calc. for $C_{19}H_{17}Br_2NO_7$: C, 43·0; H, 3·2; Br, 30·1; N, 2·6%). An ethanolic soln of the product gave no colour change with ethanolic $FeCl_3$.

Aqueous KOH (40%; 1 ml) was added to a suspension of 2,3-dibromo-2'-hydroxy-3',4'-dimethoxy-3-(3-nitrophenyl) propiophenone (0·7 g) in EtOH (15 ml). After 3 hr the mixture was diluted with water and the product, *7,8-dimethoxy-3'-nitroflavone*, crystallized from EtOH in needles (0·3 g), m.p. 219–220°. (Found: C, 62·8; H, 4·1; N, 4·1; OMe, 18·8. $C_{17}H_{13}NO_6$ requires: C, 62·4; H, 4·0; N, 4·3; OMe, 19·0%). A mixture of this product and a sample of the flavone prepared as below had m.p. 219–220°. 7,8-Dimethoxy-3'-nitroflavone (0·1 g) was also obtained by treating the unknown bromination product (0·5 g) with KOHaq as above.

2'-Hydroxy-3',4'-dimethoxyacetophenone (8·4 g) and 3-nitrobenzoyl chloride (7·8 g) in dry pyridine (50 ml) were heated for 1 hr and poured into dil HCl. The product, *3',4'-dimethoxy-2'-(3-nitrobenzoyloxy)-acetophenone*, crystallized from MeOH in platelets (8·7 g), m.p. 122–123°. (Found: C, 59·5; H, 4·6; N, 3·9; OMe, 18·0%). Powdered KOH (3·2 g) was added to a soln of this ester (6·1 g) in pyridine (35 ml). After 12 hr the mixture was poured into dil HCl and ice. The product, *1-(2-hydroxy-3,4-dimethoxyphenyl)-3-(3-nitrophenyl)propane-1,3-dione*, crystallized from ethanolic acetone in yellow prisms (2·9 g), m.p. 204–205°. (Found: C, 58·7; H, 4·4; OMe, 17·8; N, 3·9; $C_{17}H_{15}NO_7$ requires: C, 59·1; H, 4·4; OMe, 18·0; N, 4·1%). A soln of the diketone (2 g) in AcOH (60 ml) and HCl (1 ml) was heated on a steam-bath for 0·5 hr and poured into water. The product 7,8-dimethoxy-3'-nitroflavone, crystallized from EtOH in needles (1·4 g), m.p. 219–220°.

*6,7-Dimethoxy-3'-nitroaurone* (VI). HCl (1 ml) was added to a hot soln of 6,7-dimethoxycoumaranone[9] (0·6 g) and 3-nitrobenzaldehyde (0·5 g) in EtOH (10 ml) and refluxed for 5 min, *6,7-Dimethoxy-3'-nitroaurone* separated and crystallized from ethanolic acetone in yellow needles (0·8 g), m.p. 217–218°. (Found: C, 62·2; H, 4·3; N, 4·0; OMe, 18·9. $C_{17}H_{13}NO_6$ requires: C, 62·4; H, 4·0; N, 4·3; OMe, 19·0%).

*7-Nitroflavone* (XIX). $Br_2$ (0·7 g) in $CHCl_3$ (7 ml) was added dropwise to a soln of 2'-hydroxy-4'-nitrochalcone[10] (1·2 g) in $CHCl_3$ (120 ml). After the solvent had evaporated the residue, 2,3-dibromo-2'-hydroxy-4'-mitro-3-phenylpropiophenone, crystallized from benzene in yellow needles (1·5 g), m.p. 204–205°. (Found: C, 42·2; H, 2·6; N, 3·6; Br, 36·7. $C_{15}H_{11}Br_2NO_4$ requires: C, 42·0; H, 2·6; N, 3·3; Br, 37·2%). Aqueous KOH (60%; 1 ml) was added to a suspension of the chalcone dibromide (0·65 g) in EtOH (20 ml). After 1 hr the mixture was diluted with water and the product, 7-nitroflavone, crystallized from aqueous AcOH in cream needles (0·3 g), m.p. 238° (lit.[11] 233–234°), pyrolysis of the chalcone dibromide (0·05 g) at 180–190° under reduced pressure gave 7-nitroflavone, m.p. 237–238°.

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