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CHALCONE DIHALIDES-VI.[1] GENERALISATION OF THEIR USE IN THE SYNTHESIS OF NATURALLY OCCURRING FLAVONES

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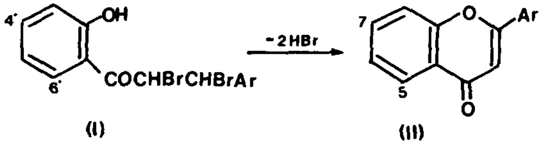
The Emilewicz-von Kostanecki cyclization[2] of 2'-hydroxychalcone dibromides (I) is one of the earliest methods of synthesising flavones (II). It is, perhaps, also the most practical method, having the advantage that in each of the preceding two steps- the condensation of an acetophenone and an aldehyde to form a chalcone and the side-chain bromination of this chalcone - the molecular weight of the substrate is approximately doubled; the large loss of molecular weight at the cyclization stage occurs in an exceptionally clean reaction under the mild conditions of aqueous alcoholic alkali at room temperature.



The procedure has been little used, however, because it was thought[3,4] that flavones (II) with a 5- or 4'-alkoxyl substituent, i.e. the majority of naturally occurring flavones, could not be obtained by this method. The corresponding chalcone dibromides (classes 2A and 2B,[5] respectively) cyclized to aurones - compounds which are much less common in nature.

von Auwers and Anschutz have long since shown[6] that 4'-alkoxyflavones can be obtained in excellent yields from the Emilewicz-von Kostanecki reaction simply by carrying out the cyclization in cold rather than in refluxing alcohol. We have now found that an equally simple change in procedure allows the syntheses of 5-alkoxyflavones in quantitative yields.

If the concentration of alkali used is lowered - to below approximately 0.2M overall - 2'-hydroxychalcone dibromides having a 6'-alkoxyl substituent (class 2A) do not form aurones and the corresponding 5-alkoxyflavones are the sole products. This result follows from our observation that the formation of aurones by these chalcone dibromides decreases with decreasing base concentration.

For example, when a suspension in ethanol (150 ml) of the class 2A chalcone dibromide (1.0 g) most prone to form aurone - 3'-bromo-2'-hydroxy-4',6'-dimethoxychalcone dibromide - was treated with aqueous potassium hydroxide (0.2M; 30 ml) at room temperature for 2 h. and diluted with water, the precipitate (0.7 g) obtained was shown by p.m.r. spectroscopy, thin layer chromatography, and m.p. 256-257° to be pure 8-bromo-5,7-dimethoxyflavone.

The other problem in the synthesis of 5-oxy-substituted flavones by the Emilewicz-von Kostanecki reaction is the incorporation[7] of a bromine atom at the 3'-position during the halogenation of 2'-hydroxy-6'-alkoxychalcones and which results in the eventual formation of an 8-bromo-5-alkoxyflavone. This presents no difficulty when the free hydroxyflavone is required because the nuclear bromine atom is removed if hydriodic acid is employed in the dealkylation of the alkoxyflavone.

In any case, nuclear bromination may be prevented if the corresponding 2'-acetoxy-6'-alkoxychalcones are employed. For example, the careful bromination of 2'-acetoxy-4',6'-dimethoxychalcone in carbon tetrachloride gave[8] 2'-acetoxy-4',6'-dimethoxychalcone dibromide. It was found that this 2'-acetoxychalcone dibromide could be deacetylated to the corresponding 2'-hydroxychalcone dibromide by aqueous alcoholic hydrochloric acid.

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8. Cf. reference 4.