17. *Chalkones: A New Synthesis of Chrysin, Apigenin, and Luteolin.*

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Kostanecki's first method for the synthesis of flavones involving treatment of *o*-acetoxychalkone dibromides with alcoholic alkali has, hitherto, not been applicable for the synthesis of the numerous natural flavones containing a phloroglucinol nucleus, since the corresponding chalkone dibromides give benzylidenecoumaranones only, on treatment with alcoholic alkali. The observation that *o*-hydroxychalkone dibromides in general give flavones when they are heated above the m. p. or are treated with alcoholic potassium cyanide has enabled the synthesis of chrysin, apigenin, and luteolin to be effected from the corresponding chalkone dibromides.

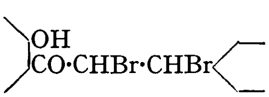
Kostanecki's first method for the synthesis of flavones, which involves the action of hot alcoholic alkali on dibromides (I) of *o*-hydroxy- or *o*-acetoxy-phenyl styryl ketones, is limited in its application, as instead of flavones (II), the isomeric 1-benzylidenecoumaran-2-ones (III) are frequently obtained. The dibromides which give (III) are derived either (A) from *o*-hydroxyphenyl *p*-alkoxystyryl ketones or (B) from chalkones prepared from 2-hydroxy-4 : 6-dialkoxy- or -3 : 4-dialkoxy-acetophenones (Cullinane and Philpott, J., 1929, 1761; Price and Bogert, *J. Amer. Chem. Soc.*, 1934, **56**, 2442). Nadkarni, Warriar, and Wheeler (J., 1937, 1798) showed that with chalkone dibromides of the type (A), the α-bromo-β-alkoxy-β-*p*-alkoxyphenylethyl ketones (IV), formed in the presence of the hot alcohol owing to the mobility of the β-bromine atom in the *p*-alkoxy-compounds, give (III) with alkali, but that the flavone could be obtained from (I; type A) by heating above the m. p. or by treatment with aqueous alkali in presence of acetone. The compound (IV), on the other hand, gave (III) with acetone and aqueous alkali, but the flavone when heated above the m. p. or with pyridine. It has now been found that alcoholic potassium cyanide will convert (I; type A) and (IV) into flavones.

The production of (III) from 2-hydroxy-4 : 6-dialkoxyphenyl styryl ketone dibromides (I; type B) does not depend on the formation of (IV), as the presence of alcohol is found not to be essential; the action of pyridine in some instances or of aqueous alkali in acetone yields (III). Here the phenomena appear to be due to the labile nature of the β-bromine atom in the dibromide: thus Kostanecki and Tambor (*Ber.*, 1899, **32**, 2260) found that the dibromide of 6-bromo-2-acetoxy-4 : 6-dimethoxyphenyl 3 : 4-methylenedioxystyryl ketone was unstable, the β-bromine atom being at once eliminated to give the corresponding α-bromostyryl ketone, which with alkali yields (III). It has now been observed that 5 : 7-dialkoxyflavones can be obtained by heating (I; type B) above the m. p. or with potassium cyanide in alcohol.

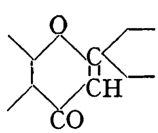
The chalkone dibromides required in the synthesis of many natural hydroxyflavones belong to both (A) and (B) types, being 2-hydroxy-4 : 6-dialkoxyphenyl αβ-dibromo-β-*p*-alkoxyphenylethyl ketones, so direct application of the Kostanecki method failed in the synthesis of some of these flavones (Kostanecki and Tambor, *loc. cit.*; Cullinane and Philpott, *loc. cit.*). The application of the considerations outlined above has now enabled chrysin (5 : 7-dihydroxyflavone), apigenin (5 : 7 : 4′-trihydroxyflavone), and luteolin (5 : 7 : 3′ : 4′-tetrahydroxyflavone) to be synthesised from the corresponding chalkones by the dibromide method. The work has been facilitated by the observation that better yields are obtained in the demethylation of 2 : 4 : 6-trimethoxyacetophenone to 2-hydroxy-4 : 6-dimethoxyacetophenone by the use of cold hydriodic acid in acetic anhydride or of hydrogen bromide in acetic acid in place of anhydrous aluminium chloride hitherto employed (Hutchins and Wheeler, *Current Science*, 1938, **6**, 604).

Bromination of 2-hydroxy-4 : 6-dimethoxyphenyl styryl ketone gave 5-*bromo*-2-*hydroxy*-4 : 6-*dimethoxyphenyl* αβ-*dibromo*-β-*phenylethyl ketone* (V), in which the position of the nuclear bromine is assumed by analogy with the results of previous investigations (cf. Cullinane and Philpott, *loc. cit.*; Nadkarni and Wheeler, *J. Univ. Bombay*, 1937, **6**, ii, 107); this compound, when heated above the m. p. under reduced pressure, gave 6-*bromo*-5 : 7-*dimethoxyflavone*, from which chrysin was obtained by treatment with hydriodic acid. The bromo-flavone was also prepared by heating 5-bromo-2-acetoxy-4 : 6-dimethoxyphenyl αβ-dibromo-β-phenylethyl ketone (VI) (Kostanecki and Tambor, *loc. cit.*). Both (V) and (VI) on treatment with hot pyridine gave 4-bromo-3 : 5-dimethoxy-1-benzylidenecoumaran-2-one, previously prepared by Kostanecki and Tambor (*loc. cit.*) by the action of hot aqueous alcoholic alkali on (VI).

The synthesis of apigenin and luteolin followed similar lines. It may be mentioned, however, that 5-*bromo*-2-*hydroxy*-4 : 6-*dimethoxyphenyl* αβ-*dibromo*-β-p-*anisylethyl ketone* on treatment with hot pyridine eliminated bromine to give 5-*bromo*-2-*hydroxy*-4 : 6-*dimethoxyphenyl* p-*methoxystyryl ketone*. In the synthesis of luteolin it was found advan-



(I.)



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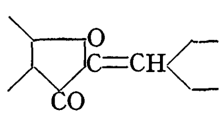
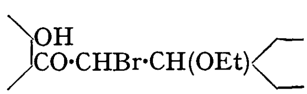


(III.)



(IV.)

tageous to prepare *6-bromo-5 : 7 : 3′ : 4′-tetramethoxyflavone* by heating *5-bromo-2-hydroxy-4 : 6-dimethoxyphenyl αβ-dibromo-β-3 : 4-dimethoxyphenylethyl ketone* with alcoholic potassium cyanide rather than directly above the m. p. under reduced pressure.

Experimental.

Phloroacetophenone 4 : 6-dimethyl ether (4·5 g.) separated from a solution of the trimethyl ether (5 g.) in acetic anhydride (40 c.c.) which had been treated in the cold with hydriodic acid (*d* 1·7; 40 c.c.), kept overnight at room temperature, and poured into aqueous sodium hydrogen sulphite. Demethylation with aluminium chloride (Kostanecki and Tambor, *loc. cit.*) gave 30% less product.

Synthesis of Chrysin.—*5-Bromo-2-hydroxy-4 : 6-dimethoxyphenyl αβ-dibromo-β-phenylethyl ketone*, which remained as a residue after evaporation of the solvent from a solution of 2-hydroxy-4 : 6-dimethoxyphenyl styryl ketone (10 g.) (Kostanecki and Tambor, *loc. cit.*) in carbon disulphide (150 c.c.), which had been treated with bromine (11·5 g.) at 0° and kept at room temperature for 1 hour, separated from carbon tetrachloride (charcoal) in yellow needles (7 g.), m. p. 186° (Found: Br, 45·5. $C_{17}H_{15}O_4Br_3$ requires Br, 45·9%). When this dibromide (V) or its acetyl derivative (VI) (Kostanecki and Tambor, *loc. cit.*) was heated at 195° (oil-bath)/7 mm. until hydrogen bromide ceased to be evolved, it formed 6-bromo-5 : 7-dimethoxyflavone, which, after it had been washed with alcohol–acetone and repeatedly crystallised from chloroform, separated from acetone in yellow needles, m. p. 242° (Found: Br, 22·7. $C_{17}H_{13}O_4Br$ requires Br, 22·2%). A mixture of this bromo-flavone (2 g.), acetic anhydride (40 c.c.), and hydriodic acid (*d* 1·7; 40 c.c.) which had been heated under reflux for 2 hours gave, on being poured into aqueous sodium hydrogen sulphite, a precipitate, which separated from alcohol in needles, m. p. 272—275° (diacetyl derivative, m. p. 185—186°; lit., 185°), not depressed by a specimen of authentic chrysin (m. p. 275°) kindly supplied by Dr. K. Venkataraman. Sublimation under reduced pressure also provided a satisfactory method for the purification of crude chrysin (cf. Seka and Prosche, *Monatsh.*, 1936, **69**, 284).

4-Bromo-3 : 5-dimethoxy-1-benzylidenecoumaran-2-one, m. p. 251° (Found: Br, 22·4. Calc. for $C_{17}H_{13}O_4Br$: Br, 22·2%), separated from an alcoholic suspension of (V) or (VI) which had been treated with hot or cold aqueous sodium hydroxide (10%). Acetone and aqueous alkali gave the same result. The same substance crystallised from a solution of either (V) or (VI) in pyridine, which had been boiled for 5 minutes and diluted with alcohol. Kostanecki and Tambor (*loc. cit.*), who prepared it by the action of hot aqueous alcoholic alkali on (VI), give m. p. 223°.

Synthesis of Apigenin.—*5-Bromo-2-hydroxy-4 : 6-dimethoxyphenyl αβ-dibromo-β-p-anisylethyl ketone*, which separated from carbon tetrachloride–chloroform in yellow needles, m. p. 165° (Found: Br, 43·6. $C_{18}H_{17}O_5Br_3$ requires Br, 43·4%), was prepared by bromination of the corresponding chalkone (Kostanecki and Tambor, *Ber.*, 1904, **37**, 792) in the manner described above for the phenylethyl analogue. When heated above the m. p. at 7 mm., it formed *6-bromo-5 : 7 : 4′-trimethoxyflavone* (Found: Br, 20·4. $C_{18}H_{15}O_5Br$ requires Br, 20·5%), which, after it had been extracted with alcohol and chloroform, crystallised from chlorobenzene in yellow needles, m. p. 250°. It gave apigenin (m. p. 345—346°; lit., *ca.* 347°; triacetyl derivative, m. p. 185—187°; lit., 181—182°, 186°. Found: C, 63·9; H, 4·2. Calc. for $C_{21}H_{16}O_8$: C, 63·6; H, 4·0%) on demethylation and debromination with hydriodic acid in acetic anhydride as described above for chrysin.

4-Bromo-3 : 5-dimethoxy-1-anisylidenecoumaran-2-one separated from an alcoholic suspension of the foregoing bromotrimethoxychalkone dibromide (1 g.) which had been treated with aqueous sodium hydroxide (10%; 2 c.c.). It crystallised from chloroform–methyl alcohol in yellow needles, m. p. 243°; with sulphuric acid it gave a red coloration (Found: C, 55·7; H, 4·1. $C_{18}H_{15}O_5Br$ requires C, 55·2; H, 3·8%). When the same chalkone dibromide was heated with pyridine for 10 minutes, it yielded a product containing halogen, which separated from chloroform–methyl alcohol in orange needles, m. p. 184—185°. It gave a dark coloration with alcoholic ferric chloride, and a yellow coloration with sulphuric acid; analysis and properties showed it to be *5-bromo-2-hydroxy-4 : 6-dimethoxyphenyl p-methoxystyryl ketone* (Found: C, 55·0; H, 4·5. $C_{18}H_{17}O_5Br$ requires C, 55·0; H, 4·3%), side-chain bromine having been eliminated by the action of pyridine.

Synthesis of Luteolin.—*5-Bromo-2-hydroxy-4 : 6-dimethoxyphenyl αβ-dibromo-β-3 : 4-dimethoxyphenylethyl ketone*, which was prepared as described above for the analogous compounds (for parent chalkone, see Kostanecki and Tambor, *loc. cit.*) and separated from chloroform–light petroleum in orange needles, m. p. 165° (Found: Br, 41·7. $C_{19}H_{19}O_6Br_3$ requires Br, 41·2%), gave after it had been heated at 190° under reduced pressure 6-*bromo*-5 : 7 : 3′ : 4′-*tetramethoxyflavone*, which separated from chloroform in yellow needles, m. p. 258° (Found : Br, 18·8. $C_{19}H_{17}O_6Br$ requires Br, 19·0%). This compound was better obtained by heating the tetramethoxychalkone dibromide for 2 hours with excess of alcoholic potassium cyanide and diluting the resulting solution. Debromination and demethylation with hydriodic acid as described above yielded luteolin, which after purification by sublimation under reduced pressure formed yellow needles, m. p. 325—326° (lit., 327—329°; tetra-acetyl derivative, m. p. 225—226°; lit., *ca.* 224°. Found : C, 61·0; H, 4·1. Calc. for $C_{23}H_{18}O_{10}$: C, 60·7; H, 4·0%).

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