Ring Expansion of 2-Benzylidenecoumaran-3-ones—A Synthesis of Flavones.

By D. M. Fitzgerald, J. F. O'Sullivan, (Mrs.) E. M. Philbin, and
T. S. Wheeler.

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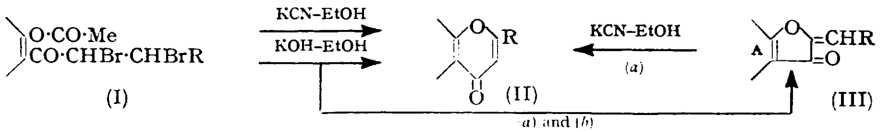
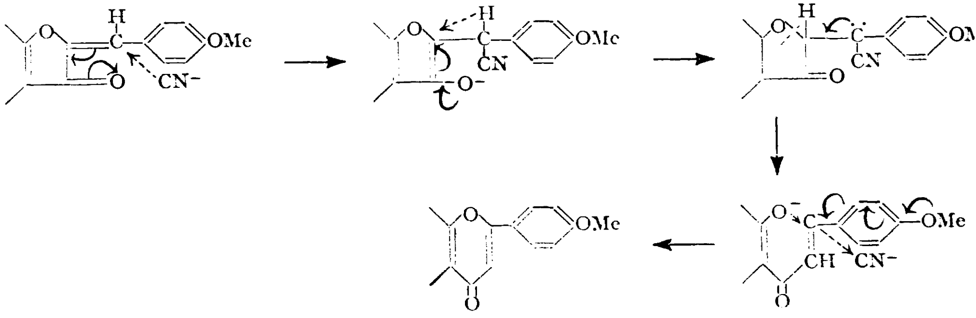
The action of ethanolic potassium cyanide on certain 2-benzylidenecoumaran-3-ones gives the corresponding flavones.

Kostanecki's first synthesis of flavones (II; R = aryl) (Emilewicz and Kostanecki, *Ber.*, 1898, **31**, 696), which involves the action of ethanolic alkali on 2'-acetoxychalkone αβ-dibromides (I; R = aryl), was found by him to be of limited application. 2-Benzylidenecoumaran-3-ones (III; R = aryl) are obtained in two cases : (*a*) when R is *p*-alkoxyaryl (*idem, ibid.*, p. 705; 1899, **32**, 309) and (*b*) when the parent chalkone is derived from phloroacetophenone (Kostanecki and Tambor, *Ber.*, 1899, **32**, 2264). Wheeler and his collaborators (*J.*, 1937—1940, *passim*; Wheeler, *Proc. Nat. Inst. Sci. India*, 1939, **5**, 267; see also Marathey, *Science and Culture*, 1951, **17**, 86; *J. Univ. Poona*, 1952, **1**, 19) devised methods to expand the application of the Kostanecki synthesis; in particular it was shown (Hutchins and Wheeler, *J.*, 1939, 91) that with ethanolic potassium cyanide, the chalkone dibromide (as I) gave the flavone (as II) even in cases (*a*) and (*b*). In an extension of this work, it has now been found that benzylidene compounds of type (*a*) (*i.e.* 2-*p*-alkoxybenzylidenecoumaran-3-ones; III; R = *p*-alkoxyaryl), but not those of type (*b*) (as III; ring A derived from phloroglucinol), when refluxed with excess of ethanolic potassium cyanide undergo ring expansion to form the corresponding 4'-alkoxyflavones (II; R = *p*-alkoxyaryl) in yields of over 50% (Fitzgerald, Philbin, and Wheeler, *Chem. and Ind.*, 1952, 130). Further when a limited quantity of potassium cyanide is employed to treat the chalkone dibromide (I; R = *p*-alkoxyaryl), the corresponding 2-benzylidenecoumaran-3-one (III; R = *p*-alkoxyaryl) and not the flavone (II; R = *p*-alkoxyaryl) is produced, so that in case (*a*), (III) is intermediate in the production of (II) from (I) by Hutchins and Wheeler's method. The thiocoumaran-3-one, 2-benzylidene-2 : 3-dihydro-5-methylthionaphthen-3-one (von Auwers and Arndt, *Ber.*, 1909, **42**, 541), and ω-methoxy-ω-salicylideneacetophenone (Pratt and Robinson, *J.*, 1923, **123**, 747) which has the ·CO·C(O·C)∶CHAr system present in 2-benzylidenecoumaran-3-ones, were unchanged after treatment with ethanolic potassium cyanide. The mechanism of the formation of flavones from 2-benzylidenecoumaran-3-ones is probably :





This synthesis recalls the Auwers synthesis of flavonols from 2-benzylidenecoumaran-3-one dibromides (von Auwers and Pohl, *Annalen*, 1914, **405**, 243), and similarly is of limited application.

EXPERIMENTAL

Ethanol was used for crystallisation if no solvent is mentioned.

Coumaran-3-ones used in the preparation of the 2-benzylidenecoumaran-3-ones were: 5-methylcoumaran-3-one (von Auwers and Müller, *Ber.*, 1908, **41**, 4233); 4 : 6-dihydroxycoumaran-3-one (Shriner and Grosser, *J. Amer. Chem. Soc.*, 1942, **64**, 383); 4 : 5-benzocoumaran-3-one (Ingham, Stephen, and Timpe, *J.*, 1931, 899); and 2 : 3-dihydro-5-methylthionaphthen-3-one (von Auwers and Arndt, *Ber.*, 1909, **42**, 541).

Preparation of 2-*Benzylidenecoumaran*-3-*ones.*—The following 2-benzylidenecoumaran-3-ones (numbered for reference) were prepared as described by the authors cited, or by condensing the appropriate coumaran-3-one and aldehyde by means of acid (method 1; *idem, ibid.*, p. 4238) or alkali (method 2; Sonn, *Ber.*, 1917, **50**, 1266) : 2-*p*-methoxybenzylidenecoumaran-3-one (1) (Herstein and Kostanecki, *Ber.*, 1899, **32**, 319); 2-benzylidene-5-methylcoumaran-3-one (2) (von Auwers and Müller, *loc. cit.*); 2-*p*-methoxybenzylidene-5-methylcoumaran-3-one (3) (method 1), crystallised from methanol in yellow needles, m. p. 152° (Found : C, 77·1; H, 5·1. Calc. for $C_{17}H_{14}O_3$: C, 76·7; H, 5·3%) (von Auwers and Anschütz, *Ber.*, 1921, **54**, 1556, give the same m. p.); 2-3′ : 4′-*dimethoxybenzylidene*-5-*methylcoumaran*-3-*one* (4) (method 1), separated in yellow plates, m. p. 174—176° (Found : C, 72·7; H, 5·2. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%); 5-*methyl*-2-3′ : 4′-*methylenedioxybenzylidenecoumaran*-3-*one* (5) (method 1), crystallised from chloroform–ligroin in yellow needles, m. p. 208—210° (Found : C, 72·8; H, 4·3. $C_{17}H_{12}O_4$ requires C, 72·9; H, 4·3%); 6-methoxy-2-*p*-methoxybenzylidenecoumaran-3-one (6) [Panse, Shah, and Wheeler, *J. Univ. Bombay*, 1941, (3), **10**, 84; *Chem. Abs.*, 1942, **36**, 4507]; 4 : 6-diacetoxy-2-*o*-methoxybenzylidenecoumaran-3-one (7) (Kalff and Robinson, *J.*, 1925, 1969); 4 : 6-*dihydroxy*-2-o-*methoxybenzylidenecoumaran*-3-*one* (8) (method 2), formed yellow plates, m. p. 255—260° (decomp.) (Found : C, 67·6; H, 4·0. $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·2%); 2-3′ : 4′-*dimethoxybenzylidene*-4 : 6-*dihydroxycoumaran*-3-*one* (9) (method 2), separated in yellow needles, m. p. 255—260° (decomp.) (Found : C, 61·2, 61·3; H, 4·7, 4·9. $C_{17}H_{14}O_6,H_2O$ requires C, 61·4; H, 4·8%); 2-p-*methoxybenzylidene*-4 : 5-*benzocoumaran*-3-*one* (10) (method 1), crystallised in yellow needles, m. p. 168° (Found : C, 79·5; H, 4·7. $C_{20}H_{14}O_3$ requires C, 79·5; H, 4·6%); 2-3′ : 4′-methylenedioxybenzylidene-4 : 5-benzocoumaran-3-one (11) (Ingham, Stephen, and Timpe, *loc. cit.*, p. 900); 2-benzylidene-2 : 3-dihydro-5-methylthionaphthen-3-one (12) (von Auwers and Arndt, *loc. cit.*, p. 542).

Preparation of Authentic Samples of Flavones.—The authentic samples of flavones required to confirm the structures of the products of the action of ethanolic potassium cyanide on benzylidenecoumaranones were prepared as shown below. The number after the name of the flavone is that assigned above to the related benzylidenecoumaranone.

4′-*Methoxyflavone* (1). This flavone (m. p. 157—158°) was obtained by cyclisation of *p*-anisoylsalicyloylmethane (Baker and Glockling, *J.*, 1950, 2761) by using acetic acid containing a few drops of mineral acid, and by the method of von Auwers and Anchütz (*Ber.*, 1921, **54**, 1558).

Flavones numbered (3), (4), (5), and (6) were synthesised by the Baker–Venkataraman reaction. In these syntheses the intermediate compounds listed without experimental details were prepared by standard methods.

4′-*Methoxy*-6-*methylflavone* (3). 2-p-*Anisoyloxy*-5-*methylacetophenone*, which was obtained by the pyridine–acid chloride method, crystallised from methanol in plates, m. p. 116° (Found : C, 71·4; H, 5·5. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·6%). The ester was transformed into the diketone by treatment with powdered potassium hydroxide in pyridine in the usual way, and the crude diketone was cyclised to the flavone (m. p. 170°; von Auwers and Anchütz, *loc. cit.*, p. 1556) by the hydrochloric–acetic acid method (Found : C, 76·5; H, 5·1. Calc. for $C_{17}H_{14}O_3$: C, 76·7; H, 5·3%).

3′ : 4′-*Dimethoxy*-6-*methylflavone* (4). 5-*Methyl*-2-*veratroyloxyacetophenone* separated from methanol in plates, m. p. 119° (Found : C, 68·7; H, 5·6. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%). This ester was converted into the flavone through the corresponding diketone which was cyclised in the crude state. The resulting 3′ : 4′-*dimethoxy*-6-*methylflavone* crystallised from ligroin–chloroform (charcoal) in needles, m. p. 190° (Found : C, 72·5; H, 5·3. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·3%). It showed a bright green fluorescence in sulphuric acid solution.

6-*Methyl*-3′ : 4′-*methylenedioxyflavone* (5). 5-*Methyl*-2-*piperonyloyloxyacetophenone* formed plates, m. p. 118—120° (Found : C, 68·6; H, 4·9. $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7%). 5-*Methylsalicyloylpiperonyloylmethane*, obtained from the ester with potassium hydroxide in pyridine, separated in plates, m. p. 103° (Found : C, 68·3; H, 4·5%). 6-*Methyl*-3′ : 4′-*methylenedioxyflavone* crystallised in needles, m. p. 218—220° (Found : C, 72·3; H, 4·3. $C_{17}H_{12}O_4$ requires C, 72·9; H, 4·3%). The fluorescence in sulphuric acid was light blue.

7 : 4′-*Dimethoxyflavone* (6). 2-p-*Anisoyloxy*-4-*methoxyacetophenone* separated from methanol in needles, m. p. 84° (Found : C, 67·8; H, 5·4. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%), and gave by application of the Baker–Venkataraman reaction p-*anisoyl*-4-*methoxysalicyloylmethane* (Found : C, 68·0; H, 5·4%). This compound, which formed yellow needles, m. p. 108—110°, yielded on cyclisation the flavone, which separated from methanol in needles, m. p. 144—146° (Found : C, 72·3; H, 5·2. Calc. for $C_{17}H_{14}O_4$: C, 72·3; H, 5·0%); Tambor (*Ber.*, 1916, **49**, 1710) gives m. p. 143—144°; Anand and Venkataraman (*Proc. Indian Acad. Sci.*, 1947, 26*A*, 284) give m. p. 149—150°.

4′-*Methoxy*-5 : 6-*benzoflavone* (10). The authentic sample of this flavone was prepared as described by Menon and Venkataraman (*J.*, 1931, 2594), who give m. p. 165°. It has now been found to be dimorphic with m. p.s 165° and 171—173° (Found : C, 79·9; H, 4·9. Calc. for $C_{20}H_{14}O_3$: C, 79·5; H, 4·6%).

3′ : 4′-Methylenedioxy-5 : 6-benzoflavone (11). This compound was prepared by Menon and Venkataraman's method (*loc. cit.*, p. 2596).

Preparation of Flavones from Benzylidenecoumaranones.—The corresponding flavones were obtained from benzylidenecoumaranones Nos. 1, 3, 4, 5, 6, 10, and 11 (but not from 2, 7, 8, 9, and 12) by refluxing a mixture of the benzylidenecoumaranone (1 part) and potassium cyanide (1 part) in ethanol for 2—6 hr. The product was cooled, diluted with water, and acidified. The precipitate was crystallised and the purified material (yield over 50%) compared with an authentic sample of the flavone (see above) by the mixed-m. p. method.

Other Experiments.—No useful result was obtained when 2-*p*-methoxybenzylidenecoumaran-3-one was heated with dry pyridine, methanolic sodium methoxide, or ethanolic potassium acetate. Similar negative results were obtained when the same benzylidenecoumaranone in dry pyridine was refluxed with sodium hydride, potassium hydroxide, sodium methoxide, sodium phenoxide, potassium carbonate, or potassium cyanide.

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