A NEW SYNTHESIS OF 7,4′-DIMETHOXY-3-PHENYLCOUMARIN*

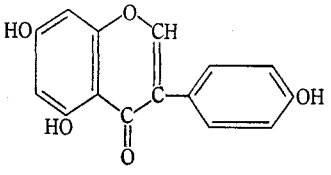
By R. B. Bradbury†

The striking similarity between the naturally occurring *iso*flavones, one of which (genistein, I) has been shown to have oestrogenic properties (Bradbury and White 1951), and 3-phenyl-4-hydroxycoumarin (II), which shows anti-vitamin-K activity, has been stressed by Mentzer (1953). This close relationship is further emphasized when one considers the possibility of addition of water across the double bond of an *iso*flavone (III) to give a 2-hydroxy*iso*flavanone (IV), followed by enolization to a 2,4-dihydroxy*iso*flav-3-en (V). It is well known that 2-hydroxy*iso*flavanones are sufficiently stable to be isolated as intermediates in the formic ester synthesis (Narasimhachari, Rajagopalan, and Seshadri 1953). In order to determine unequivocally the position of the double bond in certain *iso*flavens previously reported (Bradbury and White 1953) 7,4′-dimethoxy-3-phenylcoumarin was prepared as a reference compound for comparison of ultraviolet absorption measurements. The method of synthesis is new and should be generally applicable to compounds of this class. 3-Phenyl-4-alkyl-substituted coumarins can be prepared by the Pechmann condensation (Wawzonek 1951, p. 181), and 7,4′-dimethoxy-3-phenylcoumarin and related compounds by the Perkin reaction (Bhandari, Bose, and Siddiqui 1949), but the yields reported for the last procedure are poor. In the present work, 2,4-dimethoxybenzaldehyde (Adams and Montgomery 1924) was condensed with *p*-methoxybenzyl cyanide in the presence of sodium ethoxide according to the

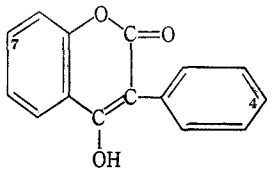
* Manuscript received December 22, 1953.

† Division of Industrial Chemistry, C.S.I.R.O., at Chemistry Department, University of Western Australia; present address: Division of Industrial Chemistry, C.S.I.R.O., Melbourne.

procedure of Niederl and Ziering (1942*a*, 1942*b*) to give 4,2′,4′-trimethoxy-α-cyanostilbene in 85 per cent. yield. Hydrolysis of the nitrile under acid or alkaline conditions proved unsuccessful, but refluxing with aluminium chloride in dry benzene caused demethylation and gave a water-soluble compound containing nitrogen and chlorine. This was evidently the imine-hydrochloride



(I)



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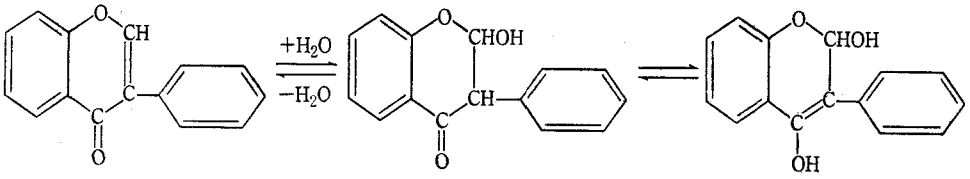
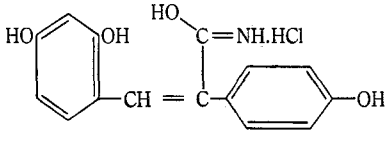


(III) (IV) (V)

(VI), since acetylation and methylation yielded respectively 7,4′-diacetoxy- and 7,4′-dimethoxy-3-phenylcoumarin, having properties in substantial agreement with those reported by Bhandari, Bose, and Siddiqui (loc. cit.) for these compounds. A number of suitably substituted coumarins show fluorescence in solution (Wawzonek 1951, p. 193), and 7,4′-dimethoxy-3-phenylcoumarin shows a characteristic violet fluorescence in alcohol.



(VI)

Experimental

All melting points are corrected. Microanalyses were carried out in the C.S.I.R.O. Microanalytical Laboratory.

(*a*) *4,2′,4′-Trimethoxy-α-cyanostilbene.*—2,4-Dimethoxybenzaldehyde (Adams and Montgomery loc. cit.) (18 g), and *p*-methoxybenzyl cyanide (16 g) were dissolved in ethanol (100 ml) and a solution of sodium ethoxide (from 2·5 g sodium) in ethanol (75 ml) added. After keeping in a water-bath at 50 °C for 1 hr, the cyanostilbene separated as long yellow prisms. Concentrated hydrochloric acid (11 ml) was added, the cyanostilbene brought into solution, the sodium chloride filtered, and the solution cooled. 4,2′,4′-Trimethoxy-α-cyanostilbene (85%; 27·2 g),

m.p. 137 °C, unchanged on recrystallization from benzene was obtained (Found: C, 73·5; H, 5·8; N, 4·9%. Calc. for $C_{18}H_{17}O_3N$: C, 73·2; H, 5·8; N, 4·7%). Attempts to hydrolyse the cyanostilbene by long refluxing with hydrochloric acid, or alcoholic sodium hydroxide, even in the presence of hydrogen peroxide were unsuccessful.

(*b*) *Demethylation and Hydrolysis with Aluminium Chloride.*—4,2′,4′-Trimethoxy-α-cyanostilbene (9·5 g), powdered aluminium chloride (44 g), and dry benzene (100 ml) were refluxed for 16 hr, and poured into 20% aqueous hydrochloric acid cooled in ice. When the excess of aluminium chloride had reacted the mixture was warmed on a water-bath for ¼ hr, and the solid collected (6 g). Recrystallization from water gave yellow needles, m.p. 334 °C (decomp.) (Found: N, 4·3%. Calc. for $C_{15}H_{14}O_4NCl$: N, 4·6%). A qualitative test showed chlorine to be present.

(*c*) *7,4′-Diacetoxy-3-phenylcoumarin.*—The above imine-hydrochloride (0·5 g) and acetic anhydride (10 ml) were refluxed for 2 hr, poured into water, and the product recrystallized from acetic acid. Colourless needles (0·47 g), m.p. 216 °C (Found: C, 67·5; H, 4·2%; mol. wt. (Rast), 347. Calc. for $C_{19}H_{14}O_6$: C, 67·5; H, 4·2%; mol. wt., 338). Bhandari, Bose, and Siddiqui (loc. cit.) report m.p. 213–214 °C.

(*d*) *7,4′-Dimethoxy-3-phenylcoumarin.*—The imine-hydrochloride (0·99 g), dry acetone (100 ml), potassium carbonate (5 g), and dimethyl sulphate (2 g) were refluxed for 3 hr, filtered hot, and the inorganic salts extracted once with hot acetone. The combined filtrate on evaporation gave long colourless needles (0·65 g) which on recrystallization from acetone had m.p. 188–189 °C (Found: C, 72·5; H, 5·1; OMe, 22·0%. Calc. for $C_{17}O_{14}O_4$: C, 72·3; H, 5·0; OMe, 21·8%). Bhandari, Bose, and Siddiqui (loc. cit.) report m.p. 182 °C. The ultraviolet spectrum of this compound has been reported elsewhere (Bradbury and White 1953).

The author is indebted to Dr. D. E. White for advice during the course of this work.

References

Adams, R., and Montgomery, E. (1924).—*J. Amer. Chem. Soc.* **46**: 1521.

Bhandari, P. R., Bose, J. L., and Siddiqui, S. (1949).—*J. Sci. Industr. Res.* B **8**: 189.

Bradbury, R. B., and White, D. E. (1951).—*J. Chem. Soc.* **1951**: 3447.

Bradbury, R. B., and White, D. E. (1953).—*J. Chem. Soc.* **1953**: 871.

Mentzer, C. (1953).—*Angew. Chem.* **65**: 213.

Narasimhachari, N., Rajagopalan, D., and Seshadri, T. R. (1953).—*J. Sci. Industr. Res.* B **12**: 287.

Niederl, J. B., and Ziering, A. (1942*a*).—*J. Amer. Chem. Soc.* **64**: 885.

Niederl, J. B., and Ziering, A. (1942*b*).—*J. Amer. Chem. Soc.* **64**: 2486.

Wawzonek, S. (1951).—"Heterocyclic Compounds." Vol. 2. (Ed. R. C. Elderfield.) (John Wiley & Sons Inc.: New York.)