43. *The Chemistry of the "Insoluble Red" Woods. Part II. A New Synthesis of 4-Hydroxycoumarins.*

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A convenient method for the synthesis of 4-hydroxycoumarins by the condensation of *o*-hydroxyacetophenones with ethyl carbonate by means of sodium is described. The procedure is illustrated by its application to the preparation of various types of 4-hydroxycoumarin.

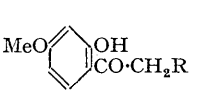
IN the course of experiments on the degradation of homopterocarpin (*J.*, 1940, 787), a product, $C_{15}H_9O_3(OMe)_3$, was obtained which it was considered might possibly be the 4-hydroxycoumarin (II), and during further work on the pterocarpin series and related topics it appeared highly desirable that the structure of this compound should be confirmed by synthesis. For this, a convenient method for the preparation of 4-hydroxycoumarins capable of being applied to the synthesis of 3-phenyl derivatives was required, and an examination of the literature showed that three main synthetical procedures have been described:

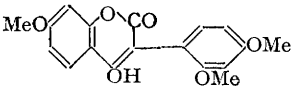
(A) The interaction of *o*-acetoxybenzoyl chlorides with ethyl sodio-malonate and -acetoacetate, yielding products capable of being degraded to the parent 4-hydroxycoumarins (Anschütz, *Ber.*, 1903, **36**, 465; *Annalen*, 1909, **367**, 169 and 289; cf. Heilbron and Hill, *J.*, 1927, 1705).

(B) The condensation of ethyl cyanoacetate with phenols according to the method of Hoesch (Sonn, *Ber.*, 1917, **50**, 1292; Bauer and Schroeder, *Arch. Pharm.*, 1921, **259**, 53).

(C) The cyclisation of suitable *o*-acyloxy-derivatives of benzoic esters with sodium at 160—165° (Pauly and Lockemann, *Ber.*, 1915, **48**, 28).

Of these methods (A) and (B) require the preparation of phenyl-substituted malonic esters for the synthesis of 4-hydroxy-3-phenylcoumarins, and (B) is also limited to the use of *m*-dihydric phenols and their derivatives. Moreover, the hydrolysis of the cyclic ketimines formed as intermediates in (B) is sometimes difficult to effect. On the other hand method (C) involves condensations with sodium at high temperatures and the yields are often erratic. The last procedure, which has been re-investigated by Jensen and Jensen (*Z. physiol. Chem.*, 1942, **277**, 66), who were unable to obtain the yields given by Pauly and Lockemann (*loc. cit.*), has been exhaustively explored by Stahmann, Wolff, and Link (*J. Amer. Chem. Soc.*, 1943, **65**, 2285) who state the optimum temperature for the condensation to be 240—250°.

(I.) 



(II.)

In the present work it has been shown that *o*-hydroxyacetophenones and their ω-substituted derivatives (type I, when R = H, alkyl, or aryl), which are conveniently accessible, readily undergo condensation with absolute ethyl carbonate, or with ethyl carbonate containing 1—2% of alcohol, in the presence of sodium on the water-bath, affording a convenient general method for the synthesis of 4-hydroxycoumarins in good yield. The scope of the reaction is illustrated by its application to a variety of ketones, and as an example of the preparation of the parent hydroxycoumarins of this type from their methyl ethers it has been shown that *4-hydroxy-7-methoxy-3-phenylcoumarin* can be conveniently demethylated by means of boiling hydriodic acid, yielding 4 : 7-*dihydroxy-3-phenylcoumarin*. The *coumarin* (II) has been obtained from the appropriate ketone (type I) by the general method, but it could not be equated with the isomeric oxidation product, $C_{15}H_9O_3(OMe)_3$, from homopterocarpin (*loc. cit.*).

EXPERIMENTAL.

4-Hydroxy-5 : 7-dimethoxycoumarin.—In the following condensations absolute ethyl carbonate or good quality commercial ethyl carbonate containing 1—2% of alcohol was employed.

A mixture of 2-hydroxy-4 : 6-dimethoxyacetophenone (Canter, Curd, and Robertson, *J.*, 1931, 1249) (1·5 g.), ethyl carbonate (40 ml.), and pulverised sodium (2·5 g.) was warmed on the steam-bath and 10 minutes later, when the vigorous reaction had ceased, sufficient methyl alcohol was added to destroy the excess of sodium, followed by ether (100—150 ml.). Extraction of the sodium salt of the product with water (30—40 ml.) and acidification with hydrochloric acid gave the *coumarin* which formed colourless needles (1·4 g.), m. p. 183°, from alcohol (Found: C, 59·3; H, 4·7. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%). Acetylation of the substance (0·2 g.) with acetic anhydride (2 ml.) and pyridine (1 ml.) at room temperature for 4 hours furnished the *acetate* which separated from dilute alcohol in elongated prisms, m. p. 175° (Found in material dried in a high vacuum at 80°: C, 59·3; H, 4·3. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·6%).

4-*Hydroxy*-7-*methoxy*-3-*methyl*- and 4-*hydroxy*-5 : 7-*dimethoxy*-3-*methyl-coumarin* were prepared in the same way from 2-hydroxy-4-methoxy- (1·5 g.) and 2-hydroxy-4 : 6-dimethoxy-propiophenone (*J.*, 1931, 1251) (1·5 g.) respectively. The former compound crystallised from alcohol and then methyl alcohol in small needles (1·5 g.), m. p. 227° (Found : C, 64·3; H, 4·8. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%), and gave an *acetate*, forming prismatic needles, m. p. 131°, from aqueous alcohol (Found : C, 62·8; H, 5·0. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·8%). The latter compound separated from dilute alcohol in a mass of slender needles (1·4 g.), m. p. 176° (Found : C, 60·9; H, 5·2. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%), and yielded an *acetate* in elongated rods, m. p. 166°, from dilute alcohol (Found : C, 60·2; H, 4·9. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·0%).

When the appropriate ketones were employed the same general method gave almost theoretical yields of 4-hydroxycoumarin, m. p. 206° (Anschütz, *Annalen*, 1909, **367**, 162), 4-hydroxy-7-methylcoumarin, m. p. 217° (*ibid.*, p. 219), and 4-hydroxy-7-methoxycoumarin, m. p. 256° (Sonn, *loc. cit.*).

(With W. B. Whalley.) 4-*Hydroxy*-7 : 2′ : 4′-*trimethoxy*-3-*phenylcoumarin* (II).—On being saturated with hydrogen chloride at 0° and then kept at room temperature for 3 days, a solution of 2 : 4-dimethoxybenzyl cyanide (Mitter and Maitra, *J. Indian Chem. Soc.*, 1936, **13**, 236) (2 g.) and resorcinol (3 g.) in ether (50 ml.) containing zinc chloride (2 g.) gave a crystalline ketimine hydrochloride which after being washed with ether and hydrolysed with water (60 ml.) on the steam-bath for 40 minutes yielded 2 : 4-dihydroxyphenyl 2 : 4-dimethoxybenzyl ketone, m. p. 152° after purification; yield of pure material, 1·2 g., the m. p. of which was unchanged after repeated crystallisation (cf. Späth and Schläger, *Ber.*, 1940, **73**, 1, who obtained a poor yield of material, the m. p. of which was stated to be 156°). Methylation of this ketone (2·5 g.) with methyl iodide (0·8 ml.) and potassium carbonate (3 g.) in boiling acetone (50 ml.) during 70 minutes gave ω-2 : 4-dimethoxyphenyl-4-*O*-methylresacetophenone (2·5 g.), m. p. 116° (Found : C, 67·8; H, 6·1. Calc. for $C_{17}H_{18}O_5$: C, 67·5; H, 6·0%), (cf. Späth and Schläger, *loc. cit.*, who give m. p. 114—115°).

Interaction of the foregoing methyl ether (0·5 g.) with ethyl carbonate (50 ml.) and pulverised sodium (0·5 g.) at room temperature and then on the steam-bath for ½ hour gave, on isolation with aid of ether and water, the *coumarin* (II) which formed colourless prisms (0·45 g.), m. p. 200°, from alcohol having a negative ferric reaction (Found : C, 65·8; H, 4·8. $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9%). Methylation of this compound (0·5 g.) with methyl iodide (0·3 g.), and potassium carbonate (1 g.) in boiling acetone (60 ml.) during one hour furnished a quantitative yield of 4 : 7 : 2′ : 4′-*tetramethoxy*-3-*phenylcoumarin* which crystallised from aqueous alcohol in needles, m. p. 152° [Found : C, 66·5; H, 5·4; OMe, 36·8. $C_{15}H_6O_2(OMe)_4$ requires C, 66·7; H, 5·3; OMe, 36·2%]. The O-*acetyl* derivative of (II) formed thick rhombic plates, m. p. 157°, from dilute alcohol (Found : C, 65·1; H, 4·9. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%).

4 : 7-*Dihydroxy*-3-*phenylcoumarin*.—Interaction of (I, R = Ph) (3 g.) with ethyl carbonate (50 ml.) and sodium (2 g.) at room temperature during 14 hours gave rise to 4-*hydroxy*-7-*methoxy*-3-*phenylcoumarin* which separated from benzene in clusters of plates (2 g.), m. p. 204° (Found : C, 71·4; H, 4·6. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%), and on methylation gave 4 : 7-*dimethoxy*-3-*phenylcoumarin*, forming needles, m. p. 105°, from methyl alcohol [Found : C, 72·1; H, 4·9; OMe, 21·4. $C_{15}H_8O_2(OMe)_2$ requires C, 72·3; H, 5·0; OMe, 21·9%]. The *acetate* of the hydroxycoumarin crystallised from methyl alcohol in platelets, m. p. 160° (Found : C, 69·5; H, 4·5. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·5%). Similarly, 2-hydroxy-4-benzyloxyphenyl benzyl ketone (Venkataraman *et al.*, *J.*, 1934, 1121) (1·5 g.) gave 4-*hydroxy*-7-*benzyloxy*-3-*phenylcoumarin*, forming clusters of prismatic needles (1·5 g.), m. p. 259—260° (decomp.), from alcohol (Found : C, 76·4; H, 4·8. $C_{22}H_{16}O_4$ requires C, 76·7; H, 4·7%). This substance, which is sparingly soluble in acetic acid, gave an *acetate*, crystallising in plates, m. p. 153, from dilute alcohol (Found : C, 74·6; H, 4·6. $C_{24}H_{18}O_5$ requires C, 74·4; H, 4·7%).

Demethylation of 4-hydroxy-7-methoxy-3-phenylcoumarin (0·5 g.) with a gently boiling mixture of hydriodic acid (10 ml., *d* 1·7), acetic anhydride (5 ml.), and acetic acid (5 ml.) during 20—25 minutes, and subsequent addition of water (70 ml.) to the cold solution, yielded 4 : 7-*dihydroxy*-3-*phenylcoumarin* which separated from methyl alcohol–chloroform and then methyl alcohol in clusters of elongated prisms, m. p. 284—285° (decomp.), having a negative ferric reaction (Found : C, 70·8; H, 4·2. $C_{15}H_{10}O_4$ requires C, 70·9; H, 3·9%).

The following new 4-hydroxycoumarins and their derivatives have also been prepared by the general method from the requisite ketones in almost theoretical yield :

4-*Hydroxy*-7 : 4′-*dimethoxy*-3-*phenylcoumarin*, prismatic needles, m. p. 219—220°, from alcohol (Found : C, 68·2; H, 4·7. $C_{17}H_{14}O_5$ requires C, 68·4; H, 4·7%), yielding a 4-O-*methyl ether*, irregular plates, m. p. 165°, from alcohol [Found : C, 69·2; H, 5·3; OMe, 28·8. $C_{15}H_7O_2(OMe)_3$ requires C, 69·2; H, 5·1; OMe, 29·8%], and an *acetate*, needles, m. p. 164°, from alcohol (Found : C, 67·1; H, 4·9. $C_{19}H_{16}O_6$ requires C, 67·0; H, 4·7%).

4-*Hydroxy*-7 : 3′ : 4′-*trimethoxy*-3-*phenylcoumarin*, tiny needles, m. p. 212°, from alcohol (Found : C, 65·7; H, 5·0. $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9%), forming an O-*methyl ether*, needles, m. p. 163°. from alcohol [Found : C, 66·3; H, 5·4; OMe, 35·5. $C_{15}H_6O_4(OMe)_4$ requires C, 66·7; H, 5·3; OMe, 36·2%], and an *acetate*, platelets, m. p. 194°, from aqueous alcohol (Found : C, 64·7; H, 5·0. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%).

4-*Hydroxy*-7-*methoxy*-3-(3′ : 4′-*methylenedioxyphenyl*)*coumarin*, needles, m. p. 256°, from methyl alcohol (Found : C, 65·6; H, 3·9. $C_{17}H_{12}O_6$ requires C, 65·4; H, 3·8%), yielding an O-*methyl* derivative, needles, m. p. 186—187°, from alcohol [Found : C, 66·0; H, 4·5; OMe, 17·8. $C_{16}H_8O_4(OMe)_2$ requires C, 66·3; H, 4·3; OMe, 19·0%], and an *acetate*, tiny needles, m. p. 157°, from alcohol (Found : C, 64·2; H, 4·1. $C_{19}H_{14}O_7$ requires C, 64·4; H, 4·0%).

2-*Hydroxy*-4-*methoxyphenyl* 3 : 4-*dimethoxybenzyl ketone* required for the synthesis of the corresponding coumarin was prepared as follows. Condensation of homoveratronitrile (4 g.) with resorcinol (6 g.) in ether (140 ml.) by means of zinc chloride (2 g.) and hydrogen chloride and hydrolysis of the resulting ketimine with water (100 ml.) on the steam-bath for 40 minutes gave 2 : 4-*dihydroxyphenyl* 3 : 4-*dimethoxybenzyl ketone* which crystallised from alcohol in colourless plates (3·2 g.), m. p. 180°, having a cherry-red

ferric reaction in alcohol (Found: C, 66·9; H, 5·7. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%). Methylation of this compound (2 g.) with methyl iodide (0·6 g.) and potassium carbonate (2·5 g.) in boiling acetone (80 ml.) during 70 minutes gave the 4-*O*-methyl ether which separated from light petroleum (b. p. 60—80°) in colourless needles (1·8—1·9 g.), m. p. 118°, having a brown ferric reaction [Found: C, 67·2; H, 6·1; OMe, 30·5. $C_{14}H_9O_2(OMe)_3$ requires C, 67·5; H, 6·0; OMe, 3·07%].

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