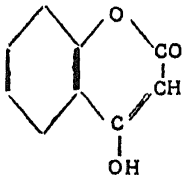
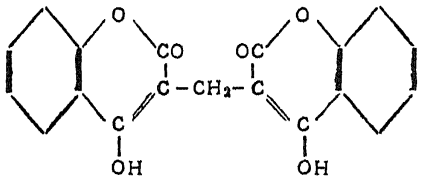
A NEW SYNTHESIS OF 4-HYDROXYCOUMARINS

BY NITY ANAND AND K. VENKATARAMAN, F.A.SC.
(Department of Chemical Technology, University of Bombay)

Received July 29, 1948

RODERICK[1] AND SCHOFIELD[2] noticed a hemorrhagic disease in cattle and showed that it was due to badly cured hay made from sweet clover. Campbell and Link[3] isolated this anticoagulant factor from spoiled sweet clover hay, and determined its structure to be 3 : 3′-methylene-bis-4-hydroxy-coumarin (II) by alkaline degradation and cleavage with phenylhydrazine. The constitution has been confirmed by its synthesis from 4-hydroxy-coumarin (I) and formaldehyde.[4] In view of the anticoagulant properties of


(I)

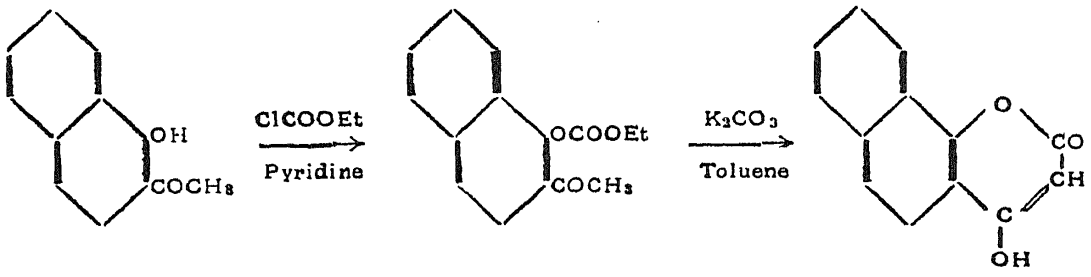

(II)

3-substituted-4-hydroxycoumarins,[5] methods for the synthesis of 4-hydroxy-coumarins (I) have assumed importance.

Three general methods for the synthesis of 4-hydroxy-coumarins have so far been described: (1) *O*-Acetoxybenzoyl chlorides are condensed with malonic ester, cyanacetic ester or acetoacetic ester in presence of sodium, when the corresponding 3-substituted-4-hydroxycoumarins are formed, which are then hydrolysed to 4-hydroxycoumarins.[6] (2) Cyanacetic ester is condensed with phenols[7] according to the method of Hoesch, which is limited to the use of *m*-dihydric phenols. In some cases, the hydrolysis of the intermediate ketimine hydrochloride is difficult. (3) The cyclisation of the *O*-acetyl derivative of an ester of salicylic acid by means of sodium at high temperature[8] gives low yields of 4-hydroxycoumarins.

Earlier work carried out by one of us and others on the transformation of *o*-benzoyloxyacetophenones to dibenzoylmethanes by means of sodamide,[9] potassium carbonate[10] or sodium in toluene,[11] indicate that an application of this reaction to the *O*-carbethoxy-derivatives of *o*-hydroxyacetophenones might lead to a new general method for the synthesis of 4-hydroxycoumarins. We have now examined the scope of this reaction by model experiments on the behaviour of the *O*-carbethoxy derivative (IV) of the readily available

2-acetyl-1-naphthol (III) towards sodamide,[9] anhydrous potassium carbonate,[10] metallic sodium and sodium ethoxide[11] in appropriate solvents.



(III) (IV) (V)

When the ester (IV) was treated with potassium carbonate in toluene, 4-hydroxynaphthocoumarin (V) was obtained in an optimum yield of 45 per cent., but the reaction did not proceed solely in the desired direction.

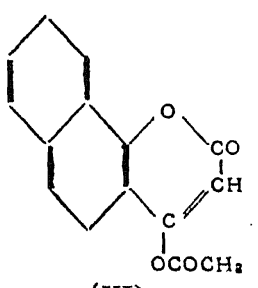
The preparation of the ester (IV), which proved difficult initially due to its instability resulting in hydrolysis to (III), had to be carried out under closely defined conditions. When ethyl chlorocarbonate was added to (III) in pyridine solution in the cold, an instantaneous reaction took place, and by working up the product immediately a quantitative yield of (IV) was obtained. Treatment of (IV) with potassium carbonate in toluene gave a mixture of products (A) and (B), which could be easily separated either by taking advantage of the insolubility of (A) and of the ready solubility of (B) in chloroform, or by extracting with sodium bicarbonate solution in which (A) alone was soluble. The product (A) when obtained in this manner was almost pure, while (B) could only be purified by chromatographic adsorption or by crystallisation from acetic acid. Comparatively lower yields of the products (A) and (B) were obtained when the transformation was carried out with metallic sodium in toluene.

The product (A) crystallised from alcohol or dioxane in small, colourless needles, m.p. 279–80° (decomp.). 4-Hydroxy-naphthocoumarin (V) has been prepared by Anschutz[12] by the condensation of 1-hydroxy-2-naphthoyl chloride with sodio-malonic ester, followed by hydrolysis of the 3-carbethoxy-4-hydroxynaphthocoumarin. He has described this as greyish white crystals, m.p. 256–8°. On repeating Anschutz's work we obtained the intermediate 3-carbethoxy-derivative as yellow needles, m.p. 179° (Anschutz, m.p. 179°). This on hydrolysis gave 4-hydroxynaphthocoumarin as colourless needles, m.p. 279-80°, identical with (A) in all respects. A similar discrepancy in the melting point has been noticed in the case of 3 : 3′-methylene-bis-4-hydroxycoumarin (II), which was first synthesised by Anschutz, who gave the m.p. 260°, and later by Stahmann, *et al.*[4] who gave the m.p. 288–89°; natural dicoumarin has m.p. 288–89°.

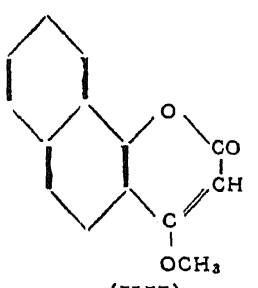
When the intramolecular condensation of the ester (IV) was carried out with sodamide in ether, substance (B) and acetonaphthol (III) were the only products isolated. In a few of the experiments while the product after the sodamide reaction was being worked up, it turned violet on exposure to air; and from the mixture a small quantity of (B), (III) and a violet compound (C) could be isolated by chromatography. The exact conditions for this transformation could however not be ascertained. The condensation of the ester with sodium methoxide in ether gave a 5 per cent. yield of product (B), the rest of the ester being hydrolysed to (III). When sodium ethoxide in alcohol was used, the ester merely underwent hydrolysis to (III).

While this work was in progress Boyd and Robertson[13] described a one-step synthesis of 4-hydroxycoumarins in excellent yields from *o*-hydroxyacetophenones by treatment with ethyl carbonate in presence of metallic sodium. By carrying out the same reaction on (III), a nearly quantitative yield of 4-hydroxynaphthocoumarin (V) could be obtained. For the preparation of 4-hydroxycoumarins, Boyd and Robertson's method is therefore superior to our method *via* the carbethoxy derivatives of *o*-hydroxyacetophenones.

4-Hydroxynaphthocoumarin (V) dissolves in sodium bicarbonate solution with effervescence, and on acidification the hydroxycoumarin is precipitated unchanged. It could be titrated with alkalis using phenolphthalein as indicator. After boiling for 2 to 3 hours with 10 per cent. aqueous or alcoholic alkali, 4-hydroxynaphthocoumarin could be recovered unchanged by acidification. On fusion with caustic potash, it gave a quantitative yield of 1-hydroxy-2-naphthoic acid. It remained unaffected by treatment with cold concentrated sulphuric acid. When heated above its melting point, a mixture of products was obtained, from which 1-acetyl-2-naphthol (III) and an unidentified product (D), m.p. 306–7°, were isolated by chromatography. The hydroxycoumarin (V) gave an acetyl derivative (VI) by long boiling with acetic anhydride, and a methyl ether (VII) by treating its solution in acetone with excess of diazomethane in ether. Coupled with diazotised *p*-nitraniline in aqueous alkaline solution or in alcohol in presence of sodium acetate, (V) gave a yellowish orange dye, 3-*p*-nitrobenzeneazo-4-hydroxynaphthocoumarin (VIII). Huebner and Link[14] have shown that

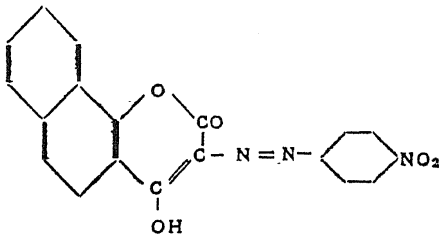


(VI)

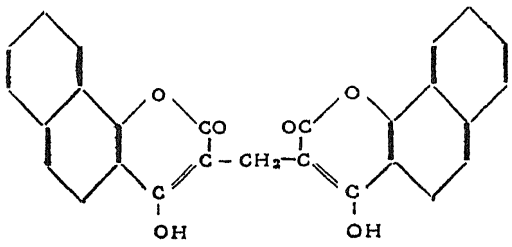


(VII)

4-hydroxycoumarin (I) couples with diazonium salts to give 3-azoderivatives. On treatment of a hot alcoholic solution of (V) with excess of formaldehyde 3 : 3′-methylene-bis-4-hydroxy-naphthocoumarin (IX) was obtained. 4-Hydroxynaphthocoumarin (V) could not be converted into product (B) by treatment with potassium carbonate in toluene.



(VIII)



(IX)

The product (B) crystallised from acetone or acetic acid as greenish yellow, thin elongated plates, m.p. 244–5°. It was phenolic in character and gave a light olive colouration with ferric chloride. It gave a *p*-nitrobenzoate, and an acetate on treatment with acetic anhydride and a drop of pyridine or with acetic acid in presence of hydrochloric acid. It did not form a dinitrophenylhydrazone under the usual conditions. Its yellowish orange alcoholic alkaline solution turned deep red on standing in the cold, and a deep violet compound was isolated by acidification, identical with the product (C) obtained earlier. Treatment with hot alcoholic alkali completely decomposed (B). Fusion of (B) with potassium hydroxide yielded 1-hydroxy-2-naphthoic acid, and a small quantity of a reddish-violet phenolic compound. A deep red dye was obtained by coupling (B) with diazotised aniline, and a yellow crystalline product (E), m.p. 345–50°, was obtained on treatment of product (B) with cold concentrated sulphuric acid. Attempts to convert (B) into (III) were unsuccessful. The analytical data for (B) and its derivatives correspond with the molecular formula $C_{25}H_{16}O_4$. The constitution of this compound will be discussed in a later communication.

Experimental

O-Carbethoxy-2-acetyl-1-naphthol (IV)

To a cooled solution of 2-acetyl-1-naphthol (10 g.) in pyridine (30 c.c.) ethyl chlorocarbonate (15 c.c.) was added drop by drop with shaking, when an instantaneous reaction took place. The reaction mixture was immediately stirred into crushed ice and hydrochloric acid. The precipitate crystallized from alcohol in thin colourless flakes (11 g.), m.p. 76° (Found: C, 70·1; H, 5·7. $C_{15}H_{14}O_4$ requires C, 69·8; 5·4%).

4-Hydroxynaphthocoumarin (V) and product (B)

(i) The compound (IV) (2 g.), toluene (20 c.c.) and freshly ignited potassium carbonate (6 g.) were refluxed under stirring for 12 hours. The potassium salt was filtered from the deep violet coloured toluene solution which on treatment with norit for a long time gave some unconverted (IV). The greyish green potassium salt was decomposed with dilute acetic acid, filtered and treated thrice with hot chloroform, when a part went into solution. The residue (0·8 g.) which was 4-hydroxynaphthocoumarin (V) crystallised from alcohol or dioxane in small colourless needles, m.p. 279–80° (Found: C, 73·1; H, 4·0; M.W. by titration, 225. $C_{13}H_8O_3$ requires C, 73·5; H, 3·9%; M.W. 212).

The chloroform extract on concentration and chromatography gave product (B), which crystallised from acetic acid in greenish yellow long thin plates (0·2 g.), m.p. 244–45° (Found: C, 78·5; H, 4·3. $C_{25}H_{16}O_4$ requires C, 78·9; H, 4·2%).

The separation of 4-hydroxynaphthocoumarin (V) and product (B) could also be very readily effected by macerating the product, obtained after decomposing the potassium salt, with acetic acid, with sodium bicarbonate solution, when (V) could be obtained from the soluble part by acidification, while (B) was obtained as the residue.

(ii) 3-Carbethoxy-4-hydroxynaphthocoumarin, obtained by treating 1-acetoxy-2-naphthoyl chloride in benzene with sodio-malonic ester in benzene for 8 hours at room temperature and for two hours on the water-bath, crystallised from alcohol in yellow needles, m.p. 179° (Anschutz, m.p. 179°). It gave a red colour with ferric chloride and was soluble in aqueous sodium bicarbonate. 4-Hydroxynaphthocoumarin (V) was obtained by hydrolysis of the 3-carbethoxy derivative by refluxing with excess of 1·5 per cent. potassium hydroxide solution for 12 hours, as colourless needles from alcohol, m.p. 279–80° (Anschutz, greyish white needles, m.p. 256–8°), identical with the product obtained by the action of potassium carbonate on (IV).

(iii) 2-Acetyl-1-naphthol (III) (1·5) g.), ethyl carbonate (40 c.c.) and metallic sodium (2·5 g.) were heated on the water-bath for 30 minutes, excess of sodium destroyed by means of methyl alcohol, the sodium salt dissolved in water, acidified, and the light cream coloured precipitate filtered, (1·4 g.). It crystallised from alcohol in thin colourless needles, m.p. 279–80°, identical with 4-hydroxynaphthocoumarin (V).

4-Hydroxynaphthocoumarin (V) gives a light orange colour with ferric chloride. It is very sparingly soluble in chloroform, benzene or toluene.

It dissolves in concentrated sulphuric acid with a brownish orange colour, having a light green fluorescence.

Decarboxylation of 4-hydroxynaphthocoumarin:

When (V) (0·2 g.) was heated at 285° for two minutes, it melted with the evolution of carbon dioxide. The brownish red melt was taken up in chloroform, and the chloroform solution chromatographed through alumina, when it separated into two definite bands. The lesser absorbed yellow band on elution with chloroform gave a phenolic product, which crystallised from alcohol in yellow needles, m.p. 98°, and was identified by mixed m.p. to be 2-acetyl-1-naphthol (III). The column of alumina containing the second band on treatment with hot alcohol gave a non-phenolic product, which crystallised from alcohol in small yellow plates, m.p. 306–7° (with darkening in colour) Product (D). It was too little to be worked up further.

Fusion of (V) with potassium hydroxide

Potassium hydroxide (2 g.) and water (0·5 c.c.) were heated in a nickel crucible till a clear solution was obtained, and (V) (0·5 g.) added. The substance began to go into solution at 240° and gave a clear yellow solution at 280°, at which temperature it was maintained for 15 minutes. On cooling, the yellow product was dissolved in water (20 c.c.) and carbon dioxide passed through the solution till it was no longer alkaline to phenolphthalein. A light brown shining crystalline precipitate separated, which was filtered (0·4 g.) and proved to be a potassium salt. It was dissolved in the minimum quantity of alcohol and precipitated with dilute hydrochloric acid. Crystallised from alcohol, it had m.p. 190–91°, and was identified as 1-hydroxy-2-naphthoic acid. The filtrate, after the separation of the potassium salt, on acidification and ether extraction, yielded a small quantity of a phenolic light brown crystalline substance, m.p. 89–93°; the alcoholic solution gave a green colour with ferric chloride.

4-*Acetoxynaphthocoumarin* (*VI*), obtained by refluxing (V) with acetic anhydride for 2 hours, crystallised from benzene in light yellow shining plates, m.p. 134–35° (Found: C, 70·4; H, 3·9; Acetyl 17·1. $C_{15}H_{10}O_4$ requires C, 70·8; H, 3·9; Acetyl 16·9%). It is insoluble in cold sodium bicarbonate solution, but can be readily hydrolysed by warming with alkalis, or even by hot water or alcohol to the parent 4-hydroxynaphthocoumarin.

4-*Methoxynaphthocoumarin* (*VII*), obtained by treating a solution of (V) (0·2 g.) in dry acetone (20 c.c.) with diazomethane in ether, crystallised from alcohol in thin colourless needles, m.p. 218° (Found: C, 74·4; H, 4·6. $C_{14}H_{10}O_3$ requires C, 74·3; O, 4·4%).

3-*p*-*Nitrobenzeneazo*-4-*hydroxynaphthocoumarin* (*VIII*)

A diazotised solution from *p*-nitraniline (0·3 g.) was added to a solution of (V) (0·2 g.) in sodium hydroxide, and the mixture stirred for one hour, keeping the coupling bath alkaline throughout. The dye, obtained by acidifying the wine-red solution, crystallised from nitrobenzene in yellowish orange needles or from acetic acid in small red shining plates, m.p. 318° (Found: N, 11·5. $C_{19}H_{11}O_5N_3$ requires N, 11·6%). The same dye was also obtained when the coupling was done in alcohol in presence of sodium acetate.

3 : 3′-*Methylene-bis*-4-*hydroxynaphthocoumarin* (*IX*)

To a hot solution of (V) (0·15 g.) in alcohol (4 c.c.), formaldehyde (40 per cent.; 1 c.c.) was added, and the mixture heated when a white crystalline precipitate separated immediately. It was filtered while hot and crystallised from trichlorobenzene in fine thin needles (0·14 g.) melting with decomposition above 300° (Found: C, 73·7; H, 4·0. $C_{27}H_{16}O_6$ requires C, 74·3; H, 3·7%). The substance is insoluble in benzene, toluene, dioxane and chloroform.

Transformation of (*IV*) *with sodamide*

The ester (IV) (2 g.), ether (10 c.c.) and powdered sodamide (2 g.) were shaken at room temperature for 8 hours, and allowed to stand overnight. The yellowish orange coloured solid that separated was filtered and stirred into acetic acid, and the dirty green sticky product thus obtained, solidified after keeping in the refrigerator. It was taken up in hot acetone (norit) and cooled, and the crystalline product that separated was recrystallised from acetic acid. The greenish yellow plates (0·4 g.), m.p. 244–5°, were identical with product (B). The acetone filtrate on evaporation gave 2-acetyl-1-naphthol (III).

Product (B) is very sparingly soluble in alcohol. It gives light olive colour with ferric chloride. It is insoluble in cold sodium carbonate solution and sparingly soluble in cold sodium hydroxide solution, but very soluble in alcoholic alkali giving a reddish yellow solution. It dissolves in concentrated sulphuric acid giving a deep red solution, which when poured over chipped ice gave a bright yellow product (E) crystallising from alcohol in yellow needles, m.p. 345–50°. (with decomp.). (Found: C, 57·1; H, 5·4%.) The substance (E) is soluble in warm sodium carbonate solution and cold caustic soda solution and gives an olive green colouration with ferric chloride. Product (B) on fusion with potassium hydroxide as in the case of

(V), gave 1-hydroxy-2-naphthoic acid and a deep violet product which is being examined.

The *acetate* of product (B), obtained by refluxing with acetic anhydride and a drop of pyridine, crystallised from acetic acid in small light yellow plates, m.p. 234–5° (Found: C, 76·2; H, 4·6; Acetyl 11·0. $C_{27}H_{18}O_5$ requires C, 76·5; H 4·3; Acetyl, 10·0%).

The p-*nitrobenzoate* of (B), prepared by treatment with *p*-nitrobenzoyl chloride in pyridine on the water-bath for 30 minutes, crystallised from acetic acid in small light yellowish brown plates, m.p. 258–60°, after shrinking at 255° (Found: N, 2·6. $C_{32}H_{19}O_7N$ requires N, 2·6%).

When product (B) (0·2 g.), dissolved in 2 per cent. alcoholic alkali, was coupled with diazotised aniline, stirred for 2 hours, a deep red solution was obtained, which on acidification gave a deep red dye. It could not be crystallised, but was purified by precipitation from a benzene solution by petroleum ether (60–80°), when it was obtained as an amorphous powder which decomposed above 180° (Found: N, 5·7. $C_{31}H_{20}O_4N_2$ requires N, 5·4%).

Decomposition of product (B) with alcoholic alkali

Product (B) (0·5 g.) was dissolved in 2 per cent. alcoholic caustic soda solution and the yellowish red solution kept overnight at room temperature. Carbon dioxide was passed through the solution, which had become deep red; but only sodium carbonate was precipitated and the colour of the solution became violet. The violet coloured filtrate was acidified, and the deep violet precipitate collected. The filtrate on evaporation gave a sticky violet-coloured product which could not be crystallised. The precipitate on purification by chromatography through alumina using benzene as solvent gave a violet-coloured compound which crystallised from benzene in greyish violet laminary plates (Product C) (0·2 g.), decomposing at 174–6°. The substance is not soluble in aqueous sodium carbonate or sodium hydroxide solution. It dissolves in hot alcoholic alkali to give a brownish red solution, and dissolves in alcohol to give a violet coloured solution, which gives with ferric chloride a cherry red colouration, and with a drop of hydrochloric acid a reddish brown colour. It gives a brownish orange solution in concentrated sulphuric acid, exhibiting a bright green fluorescence.

Summary

4-Hydroxynaphthocoumarin has been synthesised by the internal condensation of *O*-carbethoxy-2-acetyl-1-naphthol, thus suggesting a new general

method for the synthesis of 4-hydroxycoumarins. The behaviour of 4-hydroxynaphthocoumarin has been studied; its derivatives including the corresponding dicoumarin have been prepared. By the action of potassium carbonate or sodamide on the carbethoxy ester of 2-acetyl-1-naphthol, a second product was obtained, the constitution of which is under examination.

We wish to thank Mr. T. S. Gore for carrying out the microanalyses and the Trustees of the Sir Dorabji Tata Trust for a scholarship awarded to one of us.

References

1. Roderick .. *J. Am. Vet. A.*, 1929, **74**, 314.
2. Schofield .. *Canad. Vet. Rec.*, 1922, **3**, 74.
3. Campbell and Link .. *J. Biol. Chem.*, 1941, **138**, 21.
4. Stahmann, Huebner and Link .. *Ibid.*, 1941, **138**, 513.
5. Overmann *et al.* .. *Ibid.*, 1944, **153**, 5.
6. Anschutz .. *Ber.*, 1903, **36**, 465; *Ann.*, 1909, **367**, 169, 289.
7. Sonn .. *Ber.*, 1917, **50**, 1292.
8. Pauly and Lockemann .. *Ibid.*, 1915, **48**, 28.
9. Mahal and Venkataraman .. *Curr. Sci.*, 1933, **2**, 214; *J.C.S.*, 1934, 1767; *et. sequa.*
10. Baker .. *J.C.S.*, 1933, 1381.
11. Virkar and Wheeler .. *Ibid.*, 1939, 1679.
12. Anschutz .. *Ann.*, 1909, **368**, 48.
13. Boyd and Robertson .. *J. C. S.*, 1948, 174.
14. Huebner and Link .. *J. A. C. S.*, 1945, **67**, 99.